CHAPTER 10

PHARMACEUTICAL INDUSTRY

CHAPTER 10 OBJECTIVES

- INTRODUCTION
- DISCOVERYAND DEVELOPMENT OF DRUGS
- CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS
- INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY
- MANUFCTURING OF PHARMACEUTICAL PRODUCTS
- QUALITY CONTROL IN PHARMMCEUTICAL INDUTRY

INTRODUCTION

- The pharmaceutical industry is one of the most important sectors of health care worldwide.
- Pharmaceutical materials are all manufactured in very small quantities relative to other types of compounds, but their dollar value is exceedingly high.
- Changes in health care systems are having a profound impact on drug purchasing.
- The nearly US $300 billion worldwide market for various drugs is expected to grow about 6-12% per year through 2005.

DISOVERY AND DEVELOPMENT OF DRUGS
Introduction

- The development of a new drug is a long, tedious and expensive process.
- It takes about 8 to 12 years from the time a new drug substance is discovered until a marketing authorization is obtained.
- The starting point is always connected to the health problem that needs a cure. This is the main target.
- The next step is to find a chemical substance that shows promising activity against the target disease.
- New leads are sometimes discovered incidentally and more often they are the results of long-term observation of nature.

DISOVERY AND DEVELOPMENT OF DRUGS
Introduction

- The drug discovery and early development phase is followed by the pre-clinical phase, during which the route of synthesis, the safety and general properties of a drug substance are established.
- This is a pre-requisition before it can enter the clinical phase and the testing on humans.
- A well-known drug Aspirin™ can demonstrate the various stages in the life of a drug substance.
- It was known since ancient times that the bark and leaves of the willow tree can relief pain and fever.

DISOVERY AND DEVELOPMENT OF DRUGS
Introduction

- In 1832 the German chemist Piria isolated salicylic acid as the active substance in the plant material. Salicylic acid became the lead substance for further development.
- Salicylic acid was used as a pain remedy, but because of its high acidity it has severe side effects when applied orally.
- In 1987 Felix Hoffmann, a chemist at Bayer AG, realized that the ester form of the acetylsalicylic acid (acetylsaylicylic acid) had less side effects and was even more efficacious than the free acid.

DISOVERY AND DEVELOPMENT OF DRUGS
Introduction

- The Bayer Company marketed the ester under the trade name Aspirin, which became soon the number one selling drug worldwide and is still today a synonym for pain reliever.
- However, the story was not over. About 80 years after the introduction of Aspirin as a pain reliever, it was established that acetylsaylicylic acid prevents heart attacks and strokes and reduces the risk of death during a suspected heart attack.
- In 1982 John R. Vane was awarded the Nobel Prize for medicine for discovering the basic mechanism of action of acetylsaylicylic acid.

DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development

- As shown in the Aspirin example, the first step is to define a target disease, for which a remedy is to be developed.
- Next step is the design of a suitable screening model. It is not possible to use patients for screening of unknown substances.
- The model can be a cell culture, for instance bacteria, or a laboratory animal, usually a mouse, in which the disease is artificially induced.
- In classical drug discovery, two sources of possible new drugs are used: natural products and chemical compounds, which were synthesized for this purpose.

DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development

- These compounds are tested on the models and those that show a positive effect are selected as hits and the others are shelved.
- This requires further research work in order to confirm the result in a second test and also to investigate that the substance has no deleterious toxic effects on mammals. A confirmed hit is called a ***lead***.
- The lead compound serves as a model for further development. Similar substances are synthesized and compared to the lead.
- The chemical structure is elucidated and carefully analyzed in order to determine which part of the molecule is responsible for the pharmacological effect. It is called the ***pharmacophore.***

DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development

- The original lead compound can be modified to change its physical and physiological properties, but the pharmacophore remains the same.
- The modified substances must be again tested, modified, tested – and so on, until an optimal drug substance is obtained.
- The synthesis of a new substance by classical means takes about one to two weeks, its biological testing another 2 to 4 weeks in each optimization step.

DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development

TABLE 10.5. Tasks in drug discovery and early development

Discovery and early development	*Classical approach*	*High throughput approach*
target identification	Based on medical symptoms	Based on receptor binding
screening	Using laboratory animals or cell cultures	Using receptor binding assays with fast detection techniques
hit confirmation => lead	Use of second animal species	Use of second assay type
lead optimization	Classical synthesis of 10 to 20 similar compounds, testing on laboratory animals	High throughput synthesis of 1000 to 100000 compounds tested with HTS receptor binding assays.

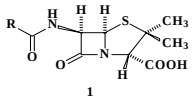
DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development

- The most famous example of such an incidental discovery of a new lead drug is the story of penicillin by Alexander Fleming.
- Penicillin is so important because it opened the route to a whole new class of highly active antibiotics. The molecule contains the characteristic β-lactic group, which is the lead structure for other substances.
- The simplest modification is changing the side chains of the molecule leading to other penicillins, **1**.

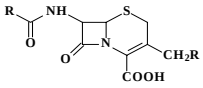
DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development

- The replacement of the 5-membered thiazolidine ring to an analogous 6-membered ring leads to cephalosporin, **2**, structure.
- The structure can be simplified even further to give clavulanic acid, **3**, and norcardicin, **4**, which are both powerful antibiotics although they are no longer used as penicillins.

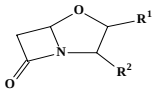
DISOVERY AND DEVELOPMENT OF DRUGS
Classical drug discovery and early development



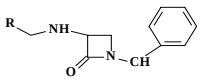
1
R=PhOCH$_2$, Penicillin V;
R=CH$_2$Ph, Penicillin G



2, Cephalosporin



3, Clavulanic acid



4, Norcaradicine

DISOVERY AND DEVELOPMENT OF DRUGS
Modern drug discovery

- Today pharmaceutical companies apply computerized robotic systems in drug discovery. Starting point is a chemical library. This library does not contain books but chemicals.
- The size of the library is increased continuously using high throughput synthesis.
- The concept of *Combinatorial Chemistry* is applied, meaning that available analogues of starting material A are combined with analogues of B.

DISOVERY AND DEVELOPMENT OF DRUGS

Modern drug discovery

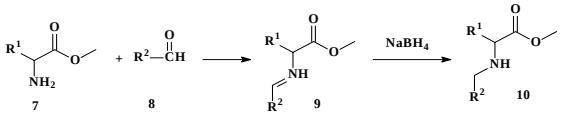
- This leads to a very large number of reactions requiring handling by robotic systems. Let as assume there are 3 analogues of A (A1, A2, A3) and 3 analogues of B (B1, B2, B3); then the following combinations are possible:

A1 + B1 => X1, A1 + B2 => X2, A1 + B3 => X3
A2 + B1 => X4, A2 + B2 => X5, A2 + B3 => X6
A3 + B1 => X7, A3 + B2 => X8, A3 + B3 => X9

DISOVERY AND DEVELOPMENT OF DRUGS

Modern drug discovery

- The reaction between amino acid esters, **7**, and aldehydes, **8**, may serve as an example of a real combinatorial reaction, which was used to produce N-alkylated-α-amino methyl esters **10** via the intermediate **9**.



DISOVERY AND DEVELOPMENT OF DRUGS

Modern drug discovery

- The combinatorial library can be reagent based, that means all available reagents of types A and B are combined with each other, or based on Structure–Activity Relationship (***SAR***).
- ***SAR*** can be used to select starting compounds with chemical structures that are known to have pharmacological activity.
- If ***SAR*** is applied, the library is product based, that means it is more focused than a random library.

DISOVERY AND DEVELOPMENT OF DRUGS
Pre-clinical testing

- The objective of the preclinical phase is to assure that new substances are safe for humans before they are tested in patients.
- First a few kilogram of the test substance must be synthesized to have enough material for further testing.
- The purity and the impurities are determined by spectroscopic and chromatographic techniques and basic physical chemical properties are established, especially water solubility and stability.

DISOVERY AND DEVELOPMENT OF DRUGS
Pre-clinical testing

Table 10.6 Tasks in Pre-clinical Development

Pre-clinical Phase	Typical tasks
route of synthesis	Development of a industrial synthesis method
properties and stability	Identification of impurities, physicochemical properties, stability upon storage
toxicity	Acute toxicity in rat & mice (single dose application) 4 week up to 2 years repeated dose toxicity in rat and dog Genetic toxicity *in-vitro* and *in-vivo*, e.g. mutagenicity Reproductive toxicity in rat and rabbit
pharmacokinetics and metabolism (ADME)	Absorption into blood circulation Distribution in body Metabolism (= chemical reactions) of drug in the body Elimination of drug from body
development of drug formulation	Development of tablets, syrups, injectables etc. containing the drug substance.

DISOVERY AND DEVELOPMENT OF DRUGS
Pre-clinical testing

- The toxicity testing starts in parallel to analytical studies.
- Single application of different doses of the test substance to rats or mice gives an indication of the acute oral toxicity.
- Another type of studies is described by the term ADME (Absorption, Distribution, Metabolism, and Elimination).
- The rate of absorption and describes how fast the drug substance enters the blood stream and is a measure for the bioavailability.

DISOVERY AND DEVELOPMENT OF DRUGS
Pre-clinical testing

- The distribution is the body is measured to confirm that the substance reaches the target organ and that it does not accumulate in other organs.
- The metabolism is the chemical conversion of the substance in the body to other compounds and elimination describes how fast and by which route the substance and its metabolites are eliminated from the body.
- The distribution of the substance in the body is often studied with substances that have carbon-14 as a radioactive label in the molecule.
- The labeled substance must be specifically synthesized, but it allows a direct visualization of the distribution in the animal body.

DISOVERY AND DEVELOPMENT OF DRUGS
Clinical testing

- After 3 to 5 years of research and development, the new drug substance can be applied to humans.
- Commonly three clinical phases and the post marking monitoring are distinguished.
- Since clinical studies are conducted with humans, they are directed by physicians.
- Nevertheless clinical and analytical chemistry plays an important role in monitoring of the results of the test.

DISOVERY AND DEVELOPMENT OF DRUGS
Clinical testing

Table 10.7. Tasks in Clinical Development and Post Marketing Research

Clinical testing	Description of work
Phase 1	Testing of pharmacokinetics and side effects in healthy human volunteers
Phase 2	Proof of concept and efficacy in small group of human patients
Phase 3	Testing of efficacy and long-term effects in large groups of patients in different countries
Post-marketing research	Development of new indications and formulations

DISOVERY AND DEVELOPMENT OF DRUGS
Clinical testing

- In phase I, the substance is applied to healthy human volunteers, starting with a very low dose and then slowly increasing until the planned pharmaceutical dose is reached.
- The purpose of the test is two fold:
  - The clinical parameters are monitored to detect any side effect, which may not have been observed in the animal tests.
  - The second is to establish the pharmacokinetics in humans.
- For this purpose blood samples are taken at predetermined intervals and analyzed for drug substance concentration usually by LC-MS-MS.

DISOVERY AND DEVELOPMENT OF DRUGS
Clinical testing

- When a drug is administered orally as a tablet, it takes some time before it dissolves in the stomach and transferred to the blood circulation.
- During this absorption phase the level of the drug increases with time and reaches a maximum after about 1 to 2 hours.
- As soon as the drug reaches the circulation, it is also metabolized, mainly in the liver. The drug is slowly eliminated from the body and as a consequence the blood level and also the effect of the drug decrease.

CHAPTER 10 OBJECTIVES

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- CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS
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CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- Analgesics represent an important class of drugs that is used primarily for the relief of severe pain. They are classified as ***narcotic*** and ***non-narcotic***.
- The opiates are perhaps the oldest drugs known to man. Opium contains a complex mixture of almost twenty-five alkaloids.
- The principle alkaloid in the mixture, and the one responsible for analgesic activity, is morphine, **11**. The pure morphine is especially good for treating dull, constant pain, and periodic pain.
- **11** has a large number of side-effects which include the depression of respiratory center, excitation, nausea, euphoria, dependence and others.

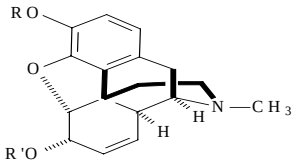
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- Codeine, **12**, is the methyl ether of morphine and also present in opium. Codeine is used for treating moderate pain and coughs.
- The analgesic activity drops drastically by methylation of morphine; codeine is only 0.1 percent as active as morphine.
- A free phenolic group is crucial for analgesic activity. The heroin, **13**, a morphine analogue, is more active than morphine by a factor of two.

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics



11; R = R'= H Morphine

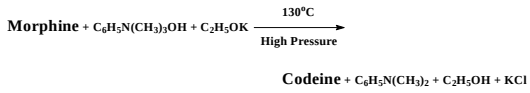
12; R = CH_3, R' = H Codeine

13; R = R' = $CH_3C(=O)$ Heroin

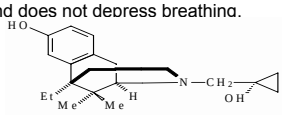
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- The codeine **12** is produced from morphine by the alkylation reaction in presence of a quaternary nitrogen alkylating agent such as phenyl trimethyl ammonium hydroxide.



- A newer compound (**14**, bremazocine) has a longer duration, is 200 times the activity of morphine, appears to have no addictive properties, and does not depress breathing.



14, Bremazocine

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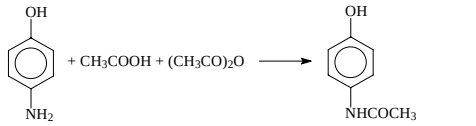
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- The non-narcotic analgesics are widely used as nonprescription drugs. They are also efficient for the relief of mild pain and symptoms of rheumatoid arthritis.
- For example, acetaminophen, **15**, sold under the trade name Tylenol, is a widely used non-prescriptive drug.
- Acetaminophen is usually prepared by reacting p-aminophenol with a mixture of glacial acetic acid and acetic anhydride.



15, Acetaminophene

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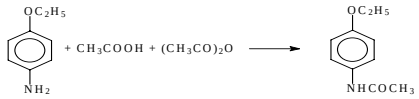
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

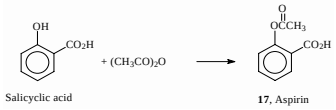
The Analgesics

- Phenacetin, **16**, is also a non-prescription drug, which represents the ethyl ether of acetaminophen and it is prepared from p-ethoxyaniline.



16, Phenacetin

- Aspirin, **17**, is an old analgesic known as a methyl acetyl ester derivative of salicylic acid.



Salicyclic acid

17, Aspirin

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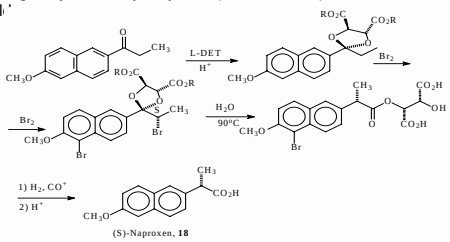
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- (S)-Naproxen, **18**, and S-ibuprofen, **19**, are important and widely used analgesics.
- The use of R,R-tartaric acid as chiral auxiliary was demonstrated in the Zambon Process for S-Naproxen manufacture.
- In this process, the diastereoselective bromination is followed by bromine hydrogenolysis and hydrolysis to produce S-Naproxen in 75% overall yiel

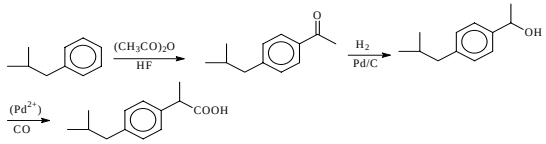


(S)-Naproxen, **18**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- Ibuprofen, **19**, was developed by Hoechst-Celanese. This method involves two steps: catalytic hydrogenation and catalytic carbonylation.

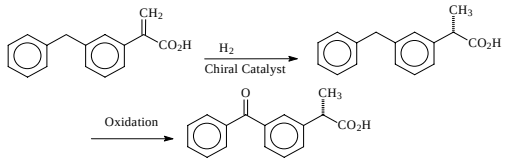


Ibuprofen, **19**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

The Analgesics

- (S)-Ketoprofen, **20**, is also an important analgesic used to relief strong to mild pain. It is produced by asymmetric hydrogenation followed by oxidation.

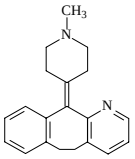


(S)-Ketoprofen, **20**

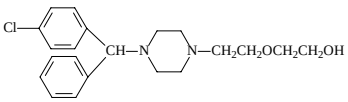
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiallergy and Antiasthmetic Drugs

- The antihistamines such as Claritin, Hismanal, and Zyrtec, are used to relieve the seasonal hay fever and other forms of allergies by counteracting the effect of histamines in the body.
- The first generation of antihistamines known as Piperadines include Azatadine, **21**, Hydroxyzine HCl, **22**, and others.



Azatadine, **21**

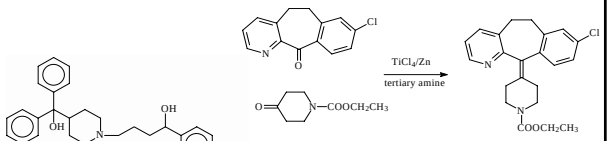


Hydroxyzine HCl, **22**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiallergy and Antiasthmetic Drugs

- The second generation of antihistamines includes strong drugs that are involved in the inhibition of the release of histamine and other inflammatory mediators from several cell types.
- Examples include Terfenidine, **23,** and Loratadine, **24**. Loratadine (Claritin), **24**, is prepared in good yield by the following reaction:



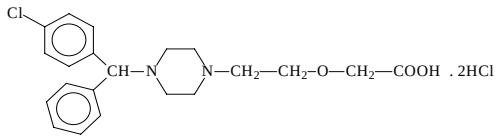
Terfenadine, **23**

Loratadine, **24**
(Claritin)

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiallergy and Antiasthmetic Drugs

- Cetirizine, **25**, is sold as Zyrtec and is widely used as antillergic and is most effective against rash/hives.

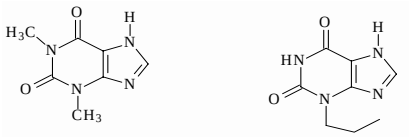


Cetrizine (Zyrtec), **25**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiallergy and Antiasthmetic Drugs

- Antiasthmatic and Bronchodilators (Singulair, Flovent, Ventrolin, Spiropent) prevent the effects of asthma by treating the underlying causes of airway inflammation.
- Also provide symptomatic relief, and contain agents that expand the bronchial airways by relaxing the bronchial muscles.
- Xanthine derivatives, such as theofylline, **26**, and enprofylline, **27**, were found to possess the property of effecting smooth muscle relaxation.



Theofylline, **26**

Enprofylline, **27**

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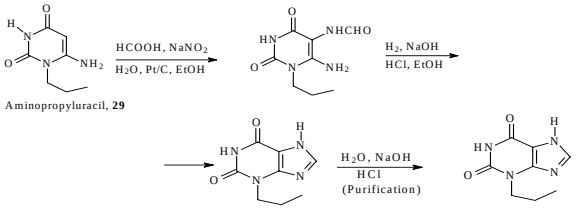
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiallergy and Antiasthmetic Drugs

- Enprofylline, **28**, is produced in a multistep process of conversion of aminopropyluracil, **29**.



Aminopropyluracil, **29**

Enprofylline, **28**
(Pure)

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CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

- Sulfonamides (known as sulfa drugs) represent the best example of antibacterial agents before the discovery of penicillin.
- In 1935, a red dye called Prontosil, **30**, was discovered to have antibacterial properties in vitro (i.e. when given to laboratory animals).
- No antibacterial effect was observed in vitro (i.e. prontosil could not kill bacteria grown in a test tube).
- This result remained a mystery until it was discovered that prontosil was not in fact the antibacterial agent.

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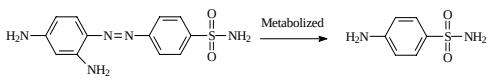
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

- Instead, it was found that the prontosil was metabolized by bacteria present in the small intestine of the test animal, and broken down to give a product called sulfanilamide, **31**.

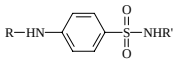


Prontosil, **30** Sulfanilamide, **31**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

- The synthesis of a large number of sulfonamide analogues **32** lead to the following conclusions:



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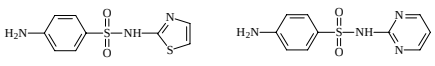
1. The p-amino group is essential for the activity and must be unsubstituted (R=H)
2. The aromatic ring and the sulfonamide group are both needed.
3. The aromatic ring must be *para*-substituted only.
4. The sulfonamide nitrogen must be secondary.

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

- It is interesting to observe that certain nationalities are more susceptible to one type of sulfonamides then others.
- For example, the Japanese and Chinese metabolize sulfathiazole, **33**, more quickly than the Americans.
- The solubility problem of sulfathiazole could be solved by replacing the thiazole ring with a pyrimidine ring to give sulfadiazine, **34**.

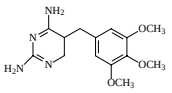


Sulfathiazole, **33** Sulfadiazine, **34**

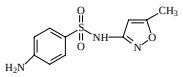
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

- Sulfonamides maintain a significant role because they are often used in combination with other antibacterials.
- For example, trimethroprim, **35**, is a diaminopyrimidine structure which has proved to be a highly selective, orally active, antibacterial and antimalarial agent.
- Trimethroprim is combined to sulfamethoxazole, **36**, for the treatment of bacterial respiratory tract infections and gastrointestinal infections.



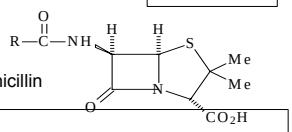
Trimethroprim, **35**



Sulfamethoxazole, **36**

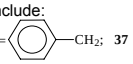
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

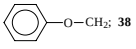


General structure of Penicillin

- The penicillin derivatives include:

1) Benzyl Penicilin (PEN G); R =  **37**

Penicillin G is a non-toxic drug. It is not active over a wide range of bacteria and ineffective when taken orally. Penicillin G can only be administered by injection.

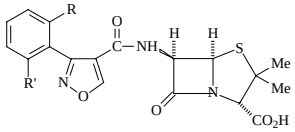
2) Phenoxy-methyl penicillin (PEN V); R =  **38**

Penicillin V has an electronegative oxygen on the acyl side-chain with the electron withdrawing effect required. The molecule has better stability than penicillin G and is stable enough to survive the acid in the stomach. Thus, it can be given orally.

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

- Oxacillin, **39**, Cloxacillin, **40**, and Flucloxacillin, **41**, are acid-resistant and penicillinase-resistant.

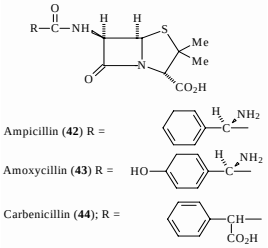


Oxacillin (R = R'= H) (**39)**
Cloxacillin (R = Cl; R'= H) (**40)**
Flucloxacillin (R = Cl, R' = F) (**41)**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antibacterials and Antibiotics

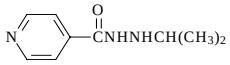
- There are two classes of such broad-spectrum antibiotics and both have an alpha-hydrophilic group.
- In one class the hydrophilic group is an amino function as in ampicillin, **42**, or amoxicillin, **43**, while in the other the hydrophilic group is an acid group as in carbenicillin, **44**.



CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antidepressant

- The new era of therapeutics for the treatment of depression began in the late 1950s with the introduction of both the monoamine oxidase (MAO) inhibitors and the tricyclic antidepressants.
- The first MAO inhibitor was iproniazid, **49**, which initially was used as an antituberculosis drug until it was observed that patients taking it exhibited excitement and euphoria.

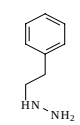


Iproniazid, **49**

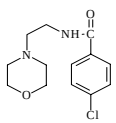
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antidepressant

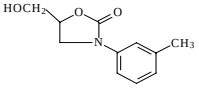
- Some of the major drugs in the category of MAOs include phenelzine, **50**, moclobemide, **51**, toloxatone, **52**, and others.



Phenelzine, **50**



Moclobemide, **51**

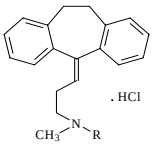


Toloxatone, **52**

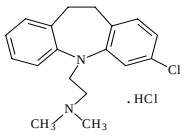
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antidepressant

- Other tricyclic antidepressants such as amitriphyline, **55**, nortriptyline, **56**, and clomipramine, **57**, are used for the treatment of obsessive-compulsive disorders.



R = CH_3; Amitriptyline, **55**
R = H; Nortriptyline, **56**

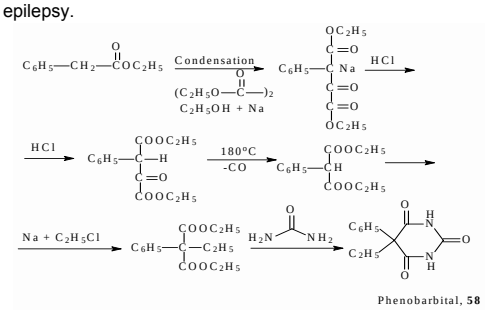


Clomipramine, **57**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiepilepitcs

- Epilepsy is a disease that is characterized by recurring convulsive seizures. Phenobarbital, **58**, possesses specific usefulness in epilepsy.

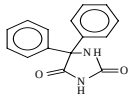


Phenobarbital, **58**

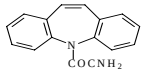
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiepilepitcs

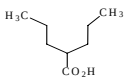
- Other drugs used for the treatment of the epilepsies: phenytoin, **59**, carbomazepine, **60**, and valproic acid, **61,** hat are well-known anticonvulsants.



Phenytoin, **59**



Carbamazepine, **60**

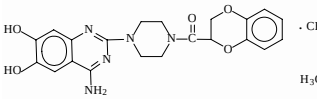


Valproic acid, **61**

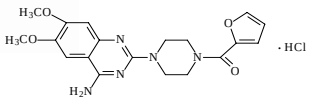
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antihypertensives

- Antihypertensive drugs are grouped into four main categories that include:
  - adrenergic blockers (e.g. cardura, **62** minizide, **63**),
  - adrenergic stimulants (e.g. aldoclor, clorpres),
- Most of these agents have a very low incidence of side-effects and are used with patients with moderate hypertension.



Cardura, **62**

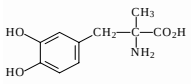


Minizide, **63**

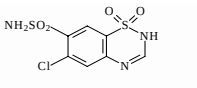
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antihypertensives

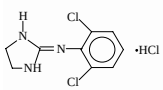
- Aldocolor combines methyldopa, **64**, and chlorthiozide, **65**. Clorpes is a combination of clonidine hydrochloride (a centrally acting antihypertensive agent), **66**, and chlorthalidone (a diuretic), **67**.



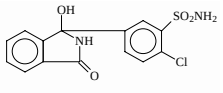
Methyldopa, **64**
(antihypertensive)



Chlorothiozide, **65**
(diuretic and antihypertensive)



Clonidine, **66**

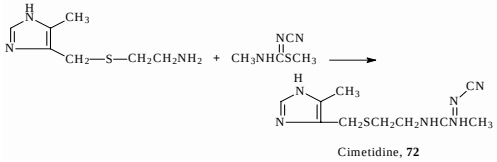


Chlorthalidone, **67**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiulcers

- Ulcers are localized erosions of the mucous membranes of the stomach. It is not known how these ulcers arise, but the presence of gastric acid (HCl), released by cells in the stomach, aggravates the problem and delays recovery.
- In the 1960s, sodium bicarbonate or calcium carbonate was used to neutralize gastric acid.
- Later, cimetidine, 72, was used as an antiulcer medication. Cimetidine, 72, acts by blocking the histamine molecules in the stomach from signaling.

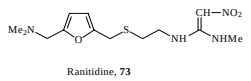


Cimetidine, **72**

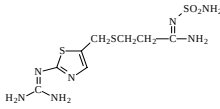
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antiulcers

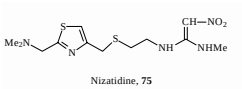
- Ranitidine, **73,** with a furan ring, has fewer side-effects than cimetidine, lasts longer, and is 10 times more active.
- Famotidine, **74**, and nizatidine, **75**, are more active antiulcers than cimetidine in vitro. Omeprazole, **76**, is also an active antiulcer agent.



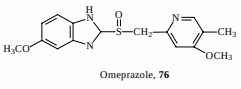
Ranitidine, **73**



Famotidine, **74**



Nizatidine, **75**

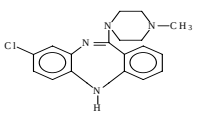


Omeprazole, **76**

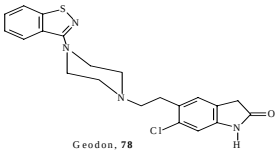
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Antipsychotic Agents

- These drugs are usually used to treat patients with psychotic or other serious related illnesses.
- Clozaril, **77,** is the most active drug with almost 1% incidence of agranulocytosis.
- Other antipsychotics agents such as geodon, **78,** is also widely used as antipsychotic drugs.



Clozaril, **77**



Geodon, **78**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

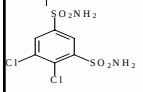
Diuretics

- Diuretics are highly efficient drugs for the treatment of edema associated with congestive heart failure.
- They are also used to increase the volume of urine excreted by the kidneys.
- For example, duranide, **81**, a dichlorinated benzene disulfonamide, is an oral carbonic anhydrous inhibitor. Duranide reduces intraocular pressure by partially suppressing the secretion of aqueous humor.
- Diuril, **82**, has an antihypertensive activity and is issued to control blood pressure.

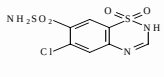
CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Diuretics

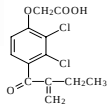
- Edecrin, **83**, is an unsaturated ketone derivative of an aryloxyacetic acid. Edecrin is used in the treatment of the edema associated with congestive heart failure, renal disease, and cirrhosis of the liver.
- Amiloride, **84**, is also used as an adjunctive treatment with thiazide diuretics in congestive heart failure hypertension.



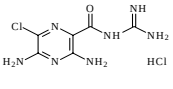
Diranide, **81**



Diuril, **82**



Edecrin, **83**

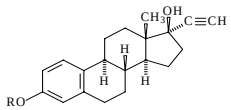


Amiloride Hydrochloride, **84**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

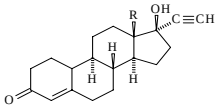
Contraceptives

- The most common type of oral contraceptive is a combination of a synthetic estrogen such as mestranol, **85**, or ethinylestradiol, **86**, and a progestin such as levonorgestrel, **87**, or norethynodrel, **88**.



R = CH_3; Mestranol, **85**

R = H; Ethinyl estradiol, **86**



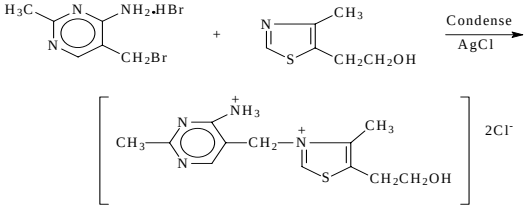
R = CH_2CH_3; Levonorgestrel, **87**

R = CH_3; Norethynodrel, **88**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Vitamins

- Vitamin B1, **89**, is essential for daily growth and the prevention of beriberi.

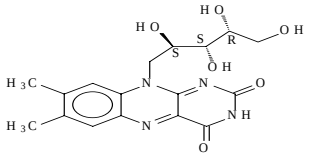


Thiamine Chloride
Vitamine B_1, **89**

CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS

Vitamins

- Riboflavin (vitamin B2), **90**, is an important and necessary element of most living cells. Riboflavin is added on a large scale to bread, flour and other dietary and pharmaceutical preparations.



Riboflavin, **90**
(Vitamin B_2)

CHAPTER 10 OBJECTIVES

- INTRODUCTION
- DISCOVERYAND DEVELOPMENT OF DRUGS
- CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS
- INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY
- MANUFCTURING OF PHARMACEUTICAL PRODUCTS
- QUALITY CONTROL IN PHARMMCEUTICAL INDUTRY

INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY

Research and Development

- The research and development of new drugs include four phases:
  - Pre-clinical research and development.
  - Clinical research and development.
  - New drug application (NDA)
  - Post-marketing surveillance.

INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY

Research and Development

- The pre-clinical research and development starts after the discovery and the isolation of a promising compound in the laboratory.
  - The biological activity and safety is extensively studied in the laboratory and tested on animals. This phase is usually completed in six years.

INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY

Research and Development

- The clinical research and development is typically conducted in three phases, with each phase involving progressively more people.
  - The aim of the first phase is to establish the safety of the drug. It involves a small number of health volunteers and lasts about one year.
  - The effectiveness of the drug is determined in the second phase, which lasts about two years.
  - In the third phase, the drug is used in clinics and hospitals. Scientists must confirm the results of earlier tests. The clinical research and development phase take about six years.

INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY

Chemical Manufacturing

- Bulk pharmaceutical substances consist of complex organic chemical compounds, which are used in the manufacture of the dosage form of drugs. These substances are usually manufactured by:
  1. Chemical synthesis
  2. Fermentation
  3. Isolation/recovery from natural sources

CHAPTER 10 OBJECTIVES

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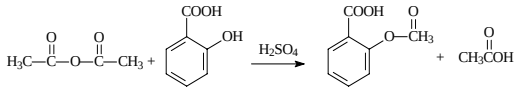
- INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY
- MANUFCTURING OF PHARMACEUTICAL PRODUCTS
- QUALITY CONTROL IN PHARMMCEUTICAL INDUTRY

Manufacturing of pharmaceutical products

The Manufacturing of Aspirin

- The commercial process for the production of aspirin (or acetyl salicylic acid) involves a one-pot acylation reaction.
- Acetic anhydride reacts with salicylic acid in the presence of a small amount of sulfuric acid to produce acetyl salicylic acid and acetic acid.

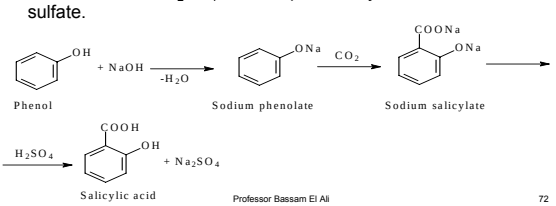


Acetic anhydride | Salicylic acid | Acetyl salicylic acid | Acetic acid

Manufacturing of pharmaceutical products

The Manufacturing of Aspirin

- The synthesis of salicylic acid involves the combination of several reactants.
- Sodium hydroxide (NaOH) reacts with phenol (C_6H_5OH) to give sodium phenolate and water. Sodium phenolate reacts with carbon dioxide (CO_2) to obtain sodium salicylate. The subsequent acidification with H_2SO_4 leads to pure salicylic acid and sodium sulfate.



Phenol | Sodium phenolate | Sodium salicylate

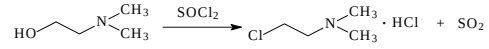
Salicylic acid

Manufacturing of pharmaceutical products

The Manufacture of Pyribenzamine

- The production of pyribenzamine (or tripelennamine) takes place in four steps (Figure 10.7).
- Dimethylaminoethanol reacts with thionyl chloride in toluene as a solvent. The mixture is heated in the reactor at the boiling point to complete the reaction. Sulfur dioxide gas is evolved and absorbed in the scrubber.

  The mixture is cooled to promote crystallization of 2-chloro-N,N-dimethylethylamine as the intermediate product.

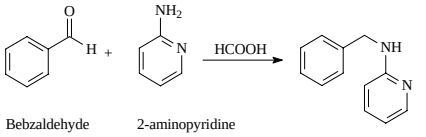


Dimethylaminoethanol 2-chloro-N,N-dimethylethylamine

Manufacturing of pharmaceutical products

The Manufacture of Pyribenzamine

- The second step involves the reaction of 2-amino-pyridine with benzaldehyde and formic acid. The mixture is acidified by the addition of aqueous HCl. The second intermediate product 2-benzyl-aminopyridine is separated by centrifuging after a normal workup of the reaction.

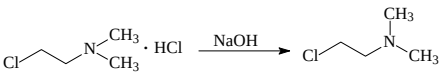


Bebzaldehyde 2-aminopyridine 2-benzylaminopyridine

Manufacturing of pharmaceutical products

The Manufacture of Pyribenzamine

- The 2-chloro-N,N-dimethylethylamine hydrochloride formed in first step is added to 30% NaOH. The lower aqueous is eliminated, and the organic phase is dried.

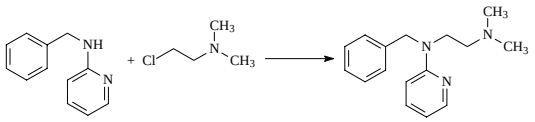


2-chloro-N,N-dimethylethylamine

Manufacturing of pharmaceutical products

The Manufacture of Pyribenzamine

- The last step of the process includes the reaction of 2-chloro-N,N-dimethylethylamine with 2-benzylaminopyridine in toluene as a solvent. Tripelennamine is separated by concentrating the filtrate under reduced pressure.



Tripelennamine

Manufacturing of pharmaceutical products

Formulation, Mixing and Compounding

- The conversion of the manufactured bulk substances into its final form represents the main objective of mixing, compounding, or formulation.
- The most common dosage forms of pharmaceutical products include tablets, capsules, liquids, creams, ointments, as well as aerosols, patches and injectable dosages.

Manufacturing of pharmaceutical products

Tablets

- Tablets represent the most popular type of dosage form that offers convenience, stability, accuracy and precision, and bioavailability active ingredients.
- Tablets are prepared by combining the active pharmaceutical ingredient with a filler, such as sugar or starch, and a binder, such as corn syrup or starch.
- The filler is added to ensure that the active pharmaceutical ingredient is diluted to the correct concentration.
- A binder is needed to bind tablet particles together. In addition, a lubricant, such as magnesium stearate or polyethylene glycol, may be added to facilitate equipment operation, or to slow disintegration or dissolution of the active ingredient.

Manufacturing of pharmaceutical products

Capsules

- The most common solid oral dosage form after tablets is the capsule.
- There are two forms of capsules:
- Soft-gelatin capsules that contain glycerol as well as gelatin maintain plasticity even when dried.
- Hard capsules are formed by dipping metals pins into a solution of gelatin of a specific temperature.
- Hard capsules are made in two sections, cap and body, which are then filled.
- Soft-gelatin capsules have their shell formed and filled in succession in one manufacturing procedure. Soft-gelatin capsules are generally filled with nonaqueous solutions.

Manufacturing of pharmaceutical products

Liquid Dosage Forms

- The liquid products are prepared by dissolving the ingredients in the appropriate solvent systems.
- Dyes, flavors, sweeteners, and antimicrobial preservatives are added to mask unpleasant taste or appearance, and to prevent mold and bacterial growth.
- The final products are stored in large tanks before final packaging.
- Quality-control analysis is then performed. If the liquid will be used for injection or ophthalmic use, sterilization is required.
- Solutions for external or oral use do not require sterilization but generally contain antimicrobial preservatives.

Manufacturing of pharmaceutical products

Creams, Ointment and Pastes

- Creams are semisolid emulsions and are either oil-in-water or water-in-oil.
- Generally, the ingredients of the two phases are heated separately to 70-80°C while they are mixed and stirred vigorously to achieve emulsification.
- A solid ingredient can be added to the appropriate phase before emulsification or may be dispersed at some point after the emulsification step.
- Ointments are prepared by melting together the active ingredient with a base, such as petroleum derivative or wax.
- The powdered drug components are added with stirring and the mixture is cooled. The product then is passed through a roller mill to achieve the particle size range desired for the dispersed solid.

Manufacturing of pharmaceutical products

Suppositories

- Suppositories are semirigid and plastic dosage forms designed to be delivered to body cavities, such as the rectum, vagina, or urethra.
- They either melt at body temperature (cocoa butter) or dissolved in the fluid of the cavity (polyethylene glycols or glycerogelatin).
- Suppositories can be used for systemic therapy (rectal suppositories) or for local treatment.
- Cocoa-butter-based suppositories can be prepared manually by pharmacists by mixing the ingredients to a pliable consistency in a mortar.

CHAPTER 10 OBJECTIVES

- INTRODUCTION
- DISCOVERYAND DEVELOPMENT OF DRUGS
- CLASSIFICATION AND THE CHEMISTRY OF PHARMACEUTICAL PRODUCTS
- INDUSTRIAL PROCESSES IN PHARMACEUTICAL INDUSTRY
- MANUFCTURING OF PHARMACEUTICAL PRODUCTS
- QUALITY CONTROL IN PHARMMCEUTICAL INDUTRY

Quality Control

- Various chemical, physical and biological tests are provided to ensure the required high standards of safety, purity, and effectiveness of drugs.
- The drug agencies monitor the levels of quality control through its good-manufacturing practices and factory inspections. For example, tablets and capsules are examined for the following properties:
  1. Identity.
  2. Content of active drug.
  3. Size.
  4. Physical appearance.
  5. Disintegration and/or dissolution time.
  6. Friability (mechanical stability of tablets).
  7. Variability in weight.

Quality Control

- All injectable solutions are tested for sterility and the absence of pyrogens.
- Various spectroscopic techniques, such as high performance liquid chromatography (HPLC), and other analytical techniques are used in the quality control laboratory to determine the purity and the amount of the active drug present in the different dosage forms.

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