Semester-III

18CHU304A PHARMACEUTICAL CHEMISTRY3H 3C

Instruction Hours/week:L:03 T:0 P:0Marks: Internal:40External: 60 Total:100

End Semester Exam:3hrs.

Course Objectives

The course enables the students to

1. Understand the drug discovery process.
2. Understand the synthesis of analgesic, antipyretic, anti-inflammatory agents
3. Understand the synthetic process of Central Nervous System and cardiovascular drugs.
4. Understand the fermentation process
5. Know to prepare antibiotics and related compounds.

Course Outcome

The students understood the

1. Knowledge about drug discovery
2. Procedures to prepare analgesic, antipyretic, anti-inflammatory agents
3. Synthesis of Central Nervous System and cardiovascular drugs.
4. Fermentation process and preparation of antibiotics.

UNIT 1

Drug discovery, design and development; Basic Retrosynthetic approach.ADMET proprtties,Lipinski's rule of five, Cheminformatics tools,Synthon,FGI.

UNIT II

Synthesis of therepresentative drugs of the following classes: analgesic agents, antipyretic agents, anti-inflammatory agents (Aspirin, paracetamol, lbuprofen); antibiotics (Chloramphenicol);antibacterial and antifungal agents (Sulphonamides; Sulphanethoxazol, Sulphacetamide,Trimethoprim); antiviral agents (Acyclovir),

UNIT III

Synthesis of therepresentative drugs of the following classes: Central Nervous System agents (Phenobarbital,Diazepam),Cardiovascular (Glyceryl trinitrate), antilaprosy (Dapsone), HIV-AIDS relateddrugs (AZT- Zidovudine).Blood Brain Barrier(BBB).

UNIT IV

Fermentation

Aerobic and anaerobic fermentation. Production of Ethyl alcohol and citric acid,

UNIT V

Production of (i) Antibiotics; Penicillin, Cephalosporin, Chloromycetin and Streptomycin, (iii) Lysine,Glutamic acid, Vitamin B2, Vitamin B12 and Vitamin C.

Suggested Readings

1. Patrick, G.L.(1995). *Introduction to Medicinal Chemistry*.65. UK: Oxford University Press
2. Hakishan, V.K. Kapoor,(1996). *Medicinal and Pharmaceutical Chemistry*, New Delhi: Vallabh Prakashan. Pitampura.
3. William O. Foye, Thomas L., Lemke & David A. William.(2008).*Principles of MedicinalChemistry*. New Delhi: B.I. Waverly Pvt. Ltd.

Karpagam Academy of Higher Education
(Established Under Section 3 of UGC Act,1956)
Coimbatore – 641021

Department of Chemistry

Lecture Plan

Incharge Staff: Dr. E. Yamuna

II B.Sc. Chemistry

Title: Pharmaceutical Chemistry Subject code:18CHU304A

Total hours: 36

UNIT-I **Hour's required-8**

S.No	Lecture Hour	Topics	Support Material
1	1	Drug discovery-Introduction	T1:189
2	1	Drug design	T1:215
3	1	Drug development	T1:215
4	1	Basic Retrosynthetic approach	R1:863-864
5	1	Synthons	R2:695
6	1	Examples of retrosynthesis	R1:863-864
7	1	Functional group interconversions	R2:699
8	1	Recapitulation and discussion of important questions	

UNIT-II **Hours required-7**

S.No	Lecture Hour	Topics	Support Material
1	1	Synthesis of analgesic agent- Aspirin Synthesis of antipyretic agent-Paracetamol	T2-174-175,178 T5: 101
2	1	Synthesis of anti-inflammatory agent-Ibuprofen	T5: 104
3	1	Antibiotics- Chloramphenicol	T2-252-253
4	1	Antibacterial agents: Sulphonamides,	T2-135-137 T2-1064
5	1	antifungal agents: Sulphamethoxazol	T5: 30,47, 49

6	1	Sulphacetamide and Trimethoprim Antiviral agents -Acyclovir	T3-46, T1:420 T1:472
7	1	Recapitulation and discussion of important questions	

UNIT-III **Hours required-6**

S.No	Lecture Hour	Topics	Support Material
1	1	Central nervous system agents: Synthesis of Phenobarbital	T1:166 T5: 116
2	1	Synthesis of central nervous system agents-Diazepam	T1:261
3	1	Cardiovascular (Glyceryl trinitrate)	T1:207
4	1	Antilaprosy (Dapsone)	T1:462
5	1	HIV-AIDS relateddrugs (AZT-Zidovudine)	T1:478
6	1	Recapitulation and discussion of important questions	

UNIT-IV **Hour's required-6**

S.No	Lecture Hour	Topics	Support Material
1	1	Aerobic fermentation	T4:258-259
2	1	Glycolysis	T6: 245
3	1	Citric acid circle	T6: 254
4	1	Anaerobic fermentation	T4:258-259
5	1	Production of Ethyl alcohol Production of citric acid	R1-493 R1-641
6	1	Recapitulation and discussion of important questions	

UNIT-V **Hours required-9**

S.No	Lecture Hour	Topics	Support Material
1	1	Production of Antibiotics-Penicillin	T1:-255-259
2	1	Cephalosporin and Chloromycetin	T4: 37 T2-261-263
3	1	Streptomycin	T5: 44
4	1	Lysine and Glutamic acid	T6: 46, 368 T6: 369

5	1	Vitamin B2	T2-143
6	1	Vitamin B12	T2-146
7	1	Vitamin C	T2-146-147
8	1	Recapitulation and discussion of important questions	
9	1	Previous year ESE question paper discussion	

Supporting Materials:

Text Books

T1: Patrick, G.L (1995). Introduction to Medicinal Chemistry. 65. UK: Oxford University Press.

T2. Jayashree Ghosh (2015). A Text Book of Pharmaceutical Chemistry, S. Chand & Company Ltd. Ram Nagar, New Delhi.

T3. V.K. Ahluwalia, (2010). Drugs, Ane Books Pvt.Ltd, NewDelhi-110002.

T4. L.E. Casida, JR. (2005), Industrial Microbiology, New Age International (P) Ltd. Publishers, NewDelhi.

T5: G.L. David krupadanam (2001). Drugs, Universities Press (India) Limited, Hyderabad-29.

T6: U. Sathyanayana and U Chakrapani (2013). Biochemistry, Books and Allied Pvt. Ltd., Kolkatta.

Reference Books

R1. M.K.Jain and S.C.Sharma (2012). Modern organic chemistry, 4thEdition,vishal publishing Co, New Delhi.

R2: Jonathan Clyden (2012). Organic Chemistry, Second Edition, Oxford University Press.

KARPAGAM ACADEMY OF HIGHER EDUCATION

Class: II B.Sc Chemistry **Course Name: Pharmaceutical Chemistry**
Course Code: 18CHU304A **Unit: I** **Batch-2018-2021**

S.no	Question	A	B	C	D	answer
1.	The branch of biology which one is provide scientific data for the treatment of disease	Pharmacology	Pharmacokinetics	Molecular pharmacology	Pharmacodynamics	Pharmacology
2.	The drug is responsible for the physiological effect is called	Pharmacophore	Pharmacy	Medicinal chemistry	Pharmacology	Pharmacophore
3.	The study of pharmacological action of a drug is called	Pharmacokinetics	Pharmacodynamics	Molecular pharmocology	Pharmaceutical chemistry	Molecular pharmocology
4.	Which is the major site of absorption of most drugs?	kidney	stomach	small intestine	liver	liver
5.	Which of the following statements is true?	Drugs and drug targets generally have similar molecular weights	Drugs are generally smaller than drug targets.	Drugs are generally larger than drug targets.	There is no general rule regarding the relative size of drugs and their targets.	Drugs are generally smaller than drug targets.
6.	What is meant by a binding site?	The area of a macromolecular target that is occupied by a drug when it binds.	The portion of the drug to which a drug target binds.	The functional groups used by a drug in binding to a drug target.	The bonds involved in binding a drug to its target.	The area of a macromolecular target that is occupied by a drug when it binds.
7.	Which of the following binding interactions is likely to be the most important *initial* interaction when a drug enters a binding site?	van der Waals interactions	hydrogen bond	ionic	induced dipole-dipole interactions	ionic
8.	Which of the following strategies will increase the polarity and water solubility of a drug?	Removing polar functional groups	Adding extra alkyl groups	Replacing an aromatic ring with a nitrogen containing heterocyclic ring	Replacing an alkyl group with a larger alkyl group	Replacing an aromatic ring with a nitrogen containing heterocyclic

						ring
9.	Some drugs containing an ester group are inactive *in vitro*, but are active once the drug has been absorbed *in vivo*. What term is used for such drugs?	postdrugs	predrugs	metabolites	prodrugs	prodrugs
10.	Some peptides and proteins have been used as drugs. Which of the following statements is untrue?	Protein drugs suffer a disadvantage in that they could produce an immune response.	Peptides and proteins generally show poor bioavailability.	Peptide drugs are susceptible to peptidase enzymes.	Peptide drugs are susceptible to metabolic enzymes but not to digestive enzymes.	Peptide drugs are susceptible to metabolic enzymes but not to digestive enzymes.
11.	Pharmacokinetics is:	The study of biological and therapeutic effects of drugs	The study of absorption, distribution, metabolism and excretion of drugs	The study of mechanisms of drug action	The study of methods of new drug development	The study of absorption, distribution, metabolism and excretion of drugs
12.	Retrosynthetic analysis is a technique for solving problems in the planning of	organic synthesis	inorganic synthesis	analytical	pericyclic synthesis	organic synthesis
13.	The goal of retrosynthetic analysis is	structural simplification	functional simplification	position simplification	none of these	structural simplification
14.	In which step involving the breaking of a bond to form two (or more) synthons	Retrosynthetic	organic synthesis	inorganic synthesis	pericyclic	Retrosynthetic
15.	Which analysis is not a synthesis form of organic chemistry, but an analytical approach based on the desired product	Retrosynthetic	organic synthesis	inorganic synthesis	pericyclic	Retrosynthetic
16.	Drug design, often referred to as	rational drug design	ligand drug design	structural drug design	direct drug design	rational drug design
17.	Drug design frequently but not necessarily relies on computer modeling techniques. This type	computer-aided drug design	wet lab drug design	direct drug design	indirect drug design	computer-aided drug design

	of modeling is referred to as					
18.	The phrase "drug design" is to some extent a	misnomer	isomer	stereomer	dimer	misnomer
19.	Ligand-based drug design is otherwise called as	indirect drug design	direct drug design	structure based drug design	computer based drug design	indirect drug design
20.	Structure-based drug design is otherwise called as	direct drug design	indirect drug design	structure based drug design	computer based drug design	direct drug design
21.	Which one of the drugs have been discovered by accident	penicillin	morphine	aspirin	cocaine	penicillin
22.	How long does the FDA take to approve a drug?	10 years	20 years	30 years	40 years	10 years
23.	QSAR stands for	qualitative structure–activity	Quantitative structure–activity relationship	Quantitative structure–activity region	Qualitative structure–activity region	Quantitative structure–activity relationship
24.	SAR stands for	structure–activity region	shape activity relationship	shape activity region	structure–activity relationship	structure–activity relationship
25.	ADME stands for	adsorption, distribution, metabolism, and excretion	adsorption, distraction, metabolism, and excretion	adsorption, distribution, mutation, and excretion	absorption, distribution, metabolism, and excretion	absorption, distribution, metabolism, and excretion
26.	What is the first satge to identify the structure based drug design	Binding site	scoring function	molecular recognition	hydrogen bonding	Binding site
27.	Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying the principles of	Binding site	molecular recognition	scoring function	hydrogen bonding	molecular recognition
28.	The molecular formula of ethanol is	C_2H6	$C_2H_5O_2$	C_3H_60	C_2H_5O	C_2H_5O
29.	Ethanol is used at industry level for the	production of vinega	production of cosmetics	production of plastics	leather treatment	production of vinega
30.	Carbon dioxide (CO_2) is removed in alcoholic fermentation from	pyruvic acid	nitric acid	sulphuric acid	hydrochloric acid	pyruvic acid

31.	Alcoholic fermentation is carried by yeast known as	wilmot cerevisiae	saccharomyces cerevisiae	lactobacillus	lactobacillus cerevisiae	saccharomyces cerevisiae
32.	Pyruvic acid in alcoholic fermentation reduced to acetaldehyde which further reduced into	carbon dioxide	methanol	ethanol	methane	ethanol
33.	Pyruvic acid in alcoholic fermentation leads to	glucose	lactose	lactic acid	acetaldehyde	acetaldehyde
34.	which of the folowing enzymes is converts glucose and fructose into ethyl alcohol	zymase	diastase	maltase	invertase	zymase
35.	which of the folowing enzyme is converts sucrose into glucose and fructose	zymase	diastase	maltase	invertase	invertase
36.	Rectified spirit is	95% alcohol	90% alcohol	100% alcohol	85% alcohol	95% alcohol
37.	Ethanol is obtained by hydration of ethylene in presence of	H3PO4	H2SO4	PCl5	PCl3	H3PO4
38.	Azeotropic mixture of alcohol is	ethylalcohol 95% + water 5%	ethylalcohol 90% + water 10%	ethylalcohol 85% + water 15%	ethylalcohol 80% + water 20%	ethylalcohol 95% + water 5%
39.	Who first isolated & crystallized Citric acid?	Louis Pasteur	Alexander Fleming	Robert Koch	Carl Wilhelm Scheele	Carl Wilhelm Scheele
40.	sulphonamides are	amides of nitic acid	amides of iodic acid	amides of sulphonic acid	amides of phophoric acid	amides of sulphonic acid
41.	Suulphanilamide is	4-aminobenzenesulphonamide	3-aminobenzenesulphonamide	2-aminobenzenesulphonamide	3,5-aminobenzenesulphonamide	4-aminobenzene sulphonamide
42.	Formulation of drugs deals by	pharmacology	pharmacy	pharmacophore	molecular pharmacology	pharmacy
43.	The study of the action of drugs at the molecular level is	molecular pharmacology	pharmacy	pharmacophore	paharmacology	molecular pharmacology
44.	The study of absorption, distribution, metabolism and excretion is known as	Pharmacology	pharmacy	pharmacokinetics	pharmacophore	pharmacokinetics
45.	Which of the following statements best describes	The reaction conditions required	A strategy used to design a synthesis	The design of a synthetic scheme	The design of reaction	A strategy used to design

	retrosynthesis?	to convert the product of a reaction back to the original starting materials	of a target molecule by working back from the target to simple starting materials	using cheap, traditional reagents, rather than expensive modern reagents	conditions such that an equilibrium reaction is pushed towards the products rather than the starting materials.	a synthesis of a target molecule by working back from the target to simple starting materials
46.	Which of the following statements best describes a synthon?	A synthetic reagent used in a reaction	A key intermediate in a reaction sequence	A transition state involved in a reaction mechanism	A hypothetical structure that would result in a given reaction if it existed	A hypothetical structure that would result in a given reaction if it existed
47.	Which of the following statements best describes a disconnection in retrosynthesis?	A disconnection involves a theoretical disconnection of a bond in a target structure in order to identify simpler structures that could be linked through the formation of that bond	A disconnection involves identifying stages where a bond is split in the corresponding synthesis.	A disconnection identifies retrosynthetic stages which would not be feasible in the corresponding synthesis	A disconnection describes the reaction conditions required to split a target structure into simpler molecules.	A disconnection involves a theoretical disconnection of a bond in a target structure in order to identify simpler structures that could be linked through the formation of that bond
48.	Amides of sulphonic acid is	anti bacterial agent	anti viral agent	anti diabetic agent	anti cancer agent	anti bacterial agent
49.	The study of pharmacological action of a drug is called	Pharmacokinetics	Pharmacodynamics	Molecular pharmocology	Pharmaceutical chemistry	Molecular pharmocology
50.	Formulation of drugs deals by	pharmacology	pharmacy	pharmacophore	molecular pharmacology	pharmacy
51.	ADME stands for	adsorption,	adsorption,	adsorption,	absorption,	absorption,

		distribution, metabolism, and excretion	distraction, metabolism, and excretion	distribution, mutation, and excretion	distribution, metabolism, and excretion	distribution, metabolism, and excretion
52.	Retrosynthetic analysis is a technique for solving problems in the planning of	organic synthesis	inorganic synthesis	analytical	pericyclic synthesis	organic synthesis
53.	Willow bark plant contains	salicylic acid	pyruvic acid	acetic acid	citric acid	salicylic acid
54.	Who was found the salicyclic acid in willow bark tree	Flemming	Edward stone	Louis pasteur	Antonie van leeuwenhoek	Edward stone
55.	Which of the following drugs was not isolated from a natural source?	quinine	morphine	isoniazid	artemisinin	isoniazid
56.	What is the term used for small molecules that bind to different regions of a binding site?	epimers	isomers	isotopes	epitopes	epitopes
57.	Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying the principles of	Binding site	molecular recognition	scoring function	hydrogen bonding	molecular recognition
58.	Which of the following binding interactions is likely to be the most important *initial* interaction when a drug enters a binding site?	van der Waals interactions	hydrogen bond	ionic	induced dipole-dipole interactions	ionic
59.	SAR stands for	structure–activity region	shape activity relationship	shape activity region	structure–activity relationship	structure–activity relationship

UNIT I
Syllabus

Drug discovery & Retrosynthetic approach
Drug discovery, design and development; Basic Retrosynthetic approach.

Glossary of Common Terms used in Drug Discovery

Drug:

A drug is a molecule that interacts with a biological molecule triggering a physiological effect. Drugs for the treatment of "illnesses" produce positive effects relating to the condition.

ADME(T):

Absorption, distribution, metabolism, excretion (and toxicology).

Array synthesis:

Form of parallel synthesis in which the reaction vessels are maintained in a specified spatial distribution, e.g. the "wells" of a 96-well plate

Bead:

A particle, normally spherical, of a microporous polymeric material used as a support to attach reagents or substrates. Used in sold-phase organic chemistry.

Biosistere

Bioisosteres are substituents or groups with similar physical or chemical properties that impart similar biological properties to a chemical compound. In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.

Chemical diversity libraries

A library of chemical compounds may be small (e.g. a few compounds) or large (e.g. thousands or even millions of compounds), and it may focus on a narrow or wide range of "diversity space." These libraries offer unprecedented opportunities for the rapid identification of small molecules with significant physiological effects.

Combinatorial Chemistry

Using a combinatorial process to prepare sets of compounds from sets of building blocks. In the early 1990's it was believed that combinatorial chemistry would revolutionize the drug discovery industry. Ten years later the route from design and synthesis of compound libraries to identification of lead structures is still long and costly. Synthesis of an almost unlimited number of organic compounds covering as much of "chemistry space" as possible is no longer the most cost effective and time saving approach to hit identification. Creating libraries, using biological target structure to inform chemical design, facilitated by quantum advances in structural genomics and computational capabilities, is a smarter, more efficient way to produce good initial leads. Considering solubility, permeability and other drug-like properties early in library design and introducing both target and lead structural constraints in lead development are further ways to ensure more compounds make it to trial.

Enzymes:

Enzymes are catalytic proteins that increase the rate of chemical reactions in the body.

Hit:

A "hit" is colloquial term used for a compound whose biological activity exceeds a predefined, statistically relevant threshold or a molecule with robust dose response activity in 2 a primary screen and known, confirmed structure. The precise definition of the following terms varies widely between drug discovery companies.

Hormones:

Chemicals released onto the bloodstream, they produce their physiological effect in tissues possessing specific hormone receptors.

Lead compound:

A lead compound is a representative of a compound series with sufficient potential (as measured by potency, selectivity, pharmacokinetics, physicochemical properties, absence of toxicity and novelty) to progress to a full drug development programme. The precise definition of the following terms varies widely between drug discovery companies.

Lead discovery:

Lead discovery is the process of identifying active new chemical entities (NCEs), which by subsequent modification may be transformed into a clinically useful drug.

Lead optimization:

The synthetic modification of a biologically active compound, to fulfil all stereoelectronic, physicochemical, pharmacokinetic and toxicological properties required for clinical usefulness. The new lead optimization paradigm demands that companies move to parallel processes that evaluate binding affinity, ADME, drug properties, etc. earlier in the process in order to cut the time and costs lost in failed leads.

Pharmacophore:

Ehrlich described a pharmacophore as "a molecular framework that carries (phoros) the essential features responsible for a drug's (=pharmacon's) biological activity". This definition was updated by Gund (1977) to "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity".

Pharmacodynamics:

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of drug action and the relationship between drug concentration and effect. It is often

summarily stated that pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug.

Pharmacokinetics:

Pharmacokinetics is a branch of pharmacology dedicated to the study of the time course of substances and their relationship with an organism or system.

Prodrug:

A prodrug is drug which is given (taken) in an inactive form. Once administered, the prodrug is metabolised by the body into a biologically active compound.

QSAR:

Structure-activity relationship (SAR) is a process by which chemical structure is correlated with a well defined process, such as biological activity or chemical reactivity. For example, biological activity can be expressed quantitatively as in the concentration of a substance required to give a certain biological response. Additionally, when physiochemical properties or structures are expressed by numbers, one can form a mathematical relationship, or 3 quantitative structure-activity relationship (QSAR), between the two. The mathematical expression can then be used to predict the biological response of other chemical structures. Receptor Most drugs produce their effects by acting on specific protein molecules, usually located in the cell membrane. These proteins are called receptors and are normally activated by endogenous chemicals in the body (transmitter substances or hormones). For example acetyl choline is a transmitter substance release from motor nerve endings. It activates receptors on the skeletal muscle initiating a sequence of events that result in the contraction of smooth muscle.

SAR Structure-activity relationship. Structure-based screening: Structure- based screening combines the power of NMR spectroscopy, automatic docking, and X-ray crystallography and provides the means to apply structural information (NMR, modelling, and X-ray) early in the projects to identify hits, select targets, and optimize the hits in terms of their affinities and specificities.

Target validation:

Target validation is the determination that a molecular target is critically involved in a disease process and a potentially valuable point of intervention for new drugs.

Transmitter substances:

Transmitter substances are chemicals released from nerve terminals which diffuse across the synaptic cleft and bind to receptors. This activates the receptors (presumably by changing their conformation (shape) and triggers a series of events such as muscle contraction or glandular secretion. After release the transmitter is inactivated by either enzymatic degradation or re-uptake.

Drug discovery

In the fields of medicine, biotechnology and pharmacology, **drug discovery** is the process by which new candidate medications are discovered. Historically, drugs were discovered through identifying the active ingredient from traditional remedies or by serendipitous discovery. Later chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that have a desirable therapeutic effect in a process known as classical pharmacology. Since sequencing of the human genome which allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets which are hypothesized to be disease modifying in a process known as reverse pharmacology. Hits from these screens are then tested in cells and then in animals for efficacy.

Drug Discovery and Development

- The discovery phase:
    - Serendipity (penicillin, chlorpromazine/Thorazine, sildenafil/Viagra)
    - Screening (statins, HMG CoA reductase inhibitors)
    - Design (HIV protease inhibitors, COX2-specific inhibitors)

- Addressing the challenges a useful compound must endure to be a useful drug
- Drug development phase: target evaluation, design and implementation of clinical trials
- Genomic evaluation is key for future discovery and development of drugs.

Serendipity

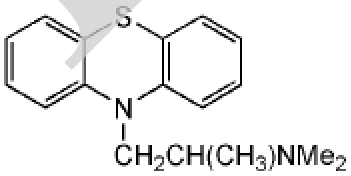
- Several drugs were discovered while looking for other drugs, or not looking for drugs at all.
- An intuitive understanding of biochemical systems is necessary to make serendipitous use of unexpected observations.

Penicillin Discovery

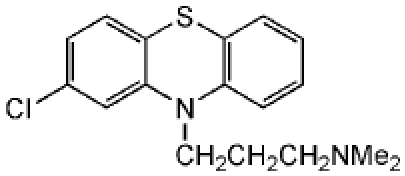
- Fleming observed in 1928 that colonies of *S. aureus* died when they were adjacent to *Penicillium* mold colonies. Fleming realized that a substance was produced in the mold spores capable of killing bacteria.
- Flory and Chain developed a powder form of penicillin in the 1940s, which allowed for large-scale production and chemical synthesis of derivatives.
- Strominger and Park elucidated the mechanism of action in 1965.

Thorazine Discovery

- In 1952, a physician was using chlorpromazine to mitigate shock in surgical patients. However, he observed that every patient was remarkably calm after surgery.
- Because of this, it was used in schizophrenia for years. Its large number of side effects had deprecated its use.



Promethazine



Chlorpromazine

Willow bark and salicylic acid

Rev Edward Stone (1760s) searched along a riverbank (i.e. a cold and wet place) for a plant-based cure for the fevers associated with influenza. Found that the bark of the willow was effective in reducing fever. Native Americans used willow bark for such purposes for centuries. willow bark contains salicin metabolized in vivo to the active agent salicylic acid salicylic acid and more tolerable "prodrug" aspirin made in late 19th century mechanism of action not discovered until the 1970s.

High-Throughput Screening

- A target (enzyme, receptor, etc.) for drug intervention is identified through basic research.
- A source of the target (tissue homogenate or purified target, animal or human) is evaluated against thousands or millions of synthetic or natural compounds and peptides (potential lead compounds) from "screening libraries".

Statin Development

- Cholestorol synthesis was decided as a target for inhibition, since slowing cholesterol synthesis would lower serum cholesterol levels.
- An mild inhibitor of an enzyme in the cholesterol synthesis pathway was discovered in a screening against a natural-products library.
- Statin drugs were developed from this initial natural compound.

Structure-Based (Rational) Drug Design: HIV Protease Inhibitors

HIV Protease Inhibitor Design

- Two sets of promising inhibitors were discovered with high potency but poor solubility and bioavailability.
- X-ray crystallography and molecular modeling suggested a hybrid molecules may have the good qualities or each, and be optimized with regards to solubility and bioavailability.

COX2-Specific Inhibitors

- COX2 was not known until the 1980s, and was found to be induced only by inflammatory stimuli.
- A COX2-specific inhibitor may reduce inflammation without producing other side effects (such as aspirin's stomach irritation).
- X-ray crystallography revealed an extension of the binding pocket in COX2, indicating that inhibitors which bound at this domain should be specific to COX2.
- Several such compounds (Vioxx and Celebrex) were designed, tested, modified, and released.

Challenges to Developing a Useful Drug

- Just because a compound is a good inhibitor, it's not necessarily a good drug.
- Drug targets are usually receptors or enzymes. The drug needs to bind a sufficient number of target proteins at a reasonable dose. Strength of binding aids in determining effectiveness and is monitored by a Michaelis-Menten model.
- ADME (absorption, distribution, metabolism, and excretion) characteristics favourable to effectiveness under physiological conditions are what separate mere compounds from drugs.
- Drugs should be easily administerd.
- Drugs should be easily absorbed by the intestinal system (orally bioavailable).
    - This is measured as the ratio of the peak serum drug concentration when orally administered to the peak serum drug concentration when injected intravenously.
    - Lipinski's rules for poor absorption:
    - Molecular weight greater than 500
    - More than five hydrogen-bond donors
    - More than ten hydrogen-bond acceptors
    - Partition coefficient, log(P), of lipid membrane solubility greater than five
    - IC50 is the inhibitor concentration required to reduce enzyme activity to 50% of maximum.
    - Log(P) is the measure of the tendency of a molecule to dissolve in membranes, which is correlated to its ability to dissolve in organic solvents.

- C_{max} is the maximal serum concentration of a compound present, as a measure of bioavailability.

- Drugs should pass into the bloodstream. Many compounds bind to carrier proteins and distribute throughout body compartments. Many drugs, though, do not pass the blood-brain barrier from tight junctions between endothelial cells in the brain and spinal cord.
- Drugs are metabolized via oxidation and conjugation and influences its effectiveness. These reactions aid in excretion by increasing water solubility.
- Toxicity limits a drug's effectiveness, and is usually tested early in the development plan, to preclude wasted effort developing a drug which has toxic effects.

Drug Development

- The FDA regulates drug candidates to demonstrate efficacy and safety before being used in humans on a large scale.
- More side effects are acceptable for drug candidates intended to treat significantly ill patients.
- Clinical trials test the effectiveness and potential side effects of a drug.

Phases of Drug Development

- **Phase I**: Safety. A small number (10-100) of healthy volunteers are given a range of doses and are monitored for signs of toxicity. Efficacy is not yet evaluated.
- **Phase II**: Safety, efficacy, dosage. Efficacy of the drug is tested in a small number of persons who may benefit from the use of the drug. Usually, they are controlled and double-blinded.
- **Phase III**: Safety, efficacy, side effects. Similar to phase II, except with a large population. This will detect any side effects that may develop in a small percentage of patients. Thousands usually participate in double-blind controlled studies.

Geneome Analysis

- Genome analysis is the future of drug discovery.

- The human genome encodes about 23,000 proteins, plus additional plice variants and post-translationally-modified proteins, many of which (especially enzymes and receptors) are drug targets.
- Bacterial and viral genomes have been sequenced and are being mined for potential targets.
    - New antibiotics are needed against resistant strains of bacteria.
    - The SARS virus was isolated in a month, and weeks later, the genome was sequenced, a protease was revealed, and an inhibitor started development.
- Many drugs are not effective in everyone. Pharmacogenetics/genomics is the design of drugs which act more consistently or are tailored to people with specific genotypes.
- Beta adrenergic receptors have two gene variants common in the American population. This receptor is a target for the anti-hypertensive *metoprolol*. Homozygotes for the variant allele are non-responsive to metoprolol, and heterozygotes are only moderately-responsive. Only homozygotes for the common allele are fully-responsive to metoprolol. Genotyping can help design cost-effective treatment strategies.

Modern drug discovery

Key stages:

• Programme selection (choosing a disease to work on)
• Identification and validation a drug target
• Assay development
• Identification of a “lead compound”
• Lead optimization
• Identification of a drug candidate
• Clinical trials
• Release of the drug
• Follow-up monitoring Some of these areas will not be covered in any detail, and some will be covered in other lecture courses.

Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development prior to clinical trials. One or more of these steps may, but not necessarily, involve computer-aided drug design.

Generally, the "target" is the naturally existing cellular or molecular structure involved in the pathology of interest that the drug-in-development is meant to act on.

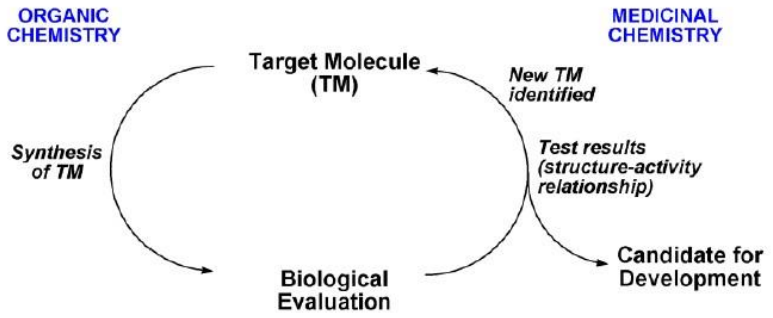
The process of finding a new drug against a chosen target for a particular disease usually involves high-throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to modify the target.

It is often observed that several compounds are found to have some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can then be developed. At this point, medicinal chemists will attempt to use structure-activity relationships (SAR) to improve certain features of the lead compound:

- increase activity against the chosen target
- reduce activity against unrelated targets
- improve the druglikeness or ADME properties of the molecule.

Once a lead compound series has been established with sufficient target potency and selectivity and favourable drug-like properties, one or two compounds will then be proposed for drug development. The best of these is generally called the lead compound,

The start of a drug discovery project relies on a "make and test" cycle.



To make meaningful progress, a quick entry into this cycle must be gained through identification of a "lead compound" with some of the desired biological activity.

Drug targets

Drug targets are most often proteins, but nucleic acids may also be attractive targets for some diseases.

TARGET - MECHANISM

• Enzyme Inhibitor - reversible or irreversible

• Receptor* Agonist or antagonist

• Nucleic acid Intercalator (binder), modifier (alkylating agent) or substrate mimic.

• Ion channels* Blockers or openers

• Transporters* Uptake inhibitors *present in the cell membranes

Retrosynthetic analysis or retrosynthesis

It is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures without assumptions regarding starting materials. Each precursor material is examined using the same method.

Retrosynthesis is thinking backwards from relatively complex molecules to simpler ones through the disconnection approach.i.e. the process of WORKING BACKWARDS from the TM in order to devise a suitable synthetic route (or routes) on paper.

Target molecule (TGT) the molecule to be synthesized Retrosynthetic analysis or retrosynthesis the process of mentally breaking down a molecule into a starting material Disconnection an imaginary bond cleavage corresponding to a reverse of a real reaction Transform the exact reverse of a synthetic reaction Retron structural subunit on the target that enables a transform to operate Synthon idealized fragment resulting from a disconnection, which is related to possible synthetic operations Umpolung reversal of normal polarization of a molecule or synth Reagent a real chemical compound used as the equivalent of a synthon Target molecule (TGT) the molecule to be synthesized Retrosynthetic analysis or retrosynthesis the process of mentally breaking down a molecule into a starting material Disconnection an imaginary bond cleavage corresponding to a reverse of a real reaction Transform the exact reverse of a synthetic reaction Retron structural subunit on the target that enables a transform to operate Synthon idealized fragment resulting from a disconnection, which is related to possible synthetic operations Umpolung reversal of normal polarization of a molecule or synth Reagent a real chemical compound used as the equivalent of a synthon

Note: $\Longrightarrow$ denotes disconnection of TM to its most immediate precursor.

Multiple steps are required so this needs to be repeated.

TM $\Longrightarrow$ 1st Precursor $\Longrightarrow$ 2nd Precursor $\Longrightarrow$ Starting compounds - readily available

Definitions

Reagent:

A compound which reacts to give an intermediate in the planned synthesis or to give the target molecule itself.

The synthetic equivalent of a synthon.

Synthon:

A generalized fragment, usually an ion, produced by a disconnection. (some people also use synthon for a synthetic equivalent).

Synthonis an idealised fragment, usually a cation or anion, resulting from a disconnection.

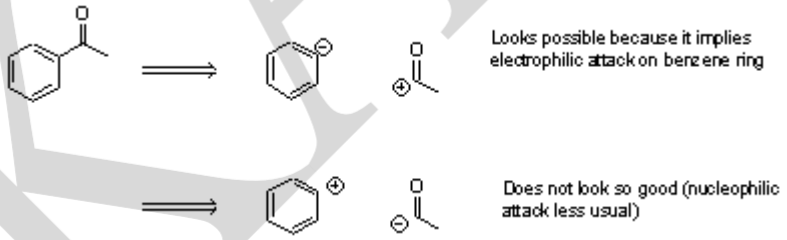
$X^+ Y^-$

$X^{\bullet} Y^{\bullet+}$

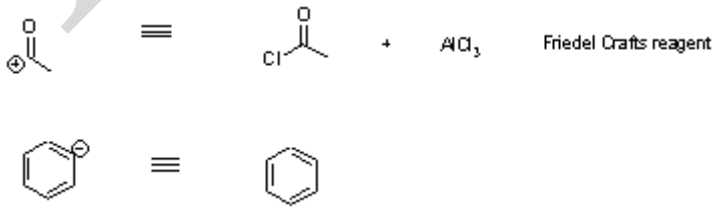
X Y

Usually synthons don't exist as such, but help in the correct choice of

reagent. In our example:



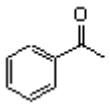
Synthetic Equivalent : the actual compounds used to function as synthons.



A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable.

Target Molecule:

The molecule whose synthesis is being planned.



methylphenyl ketone
(acetophenone)

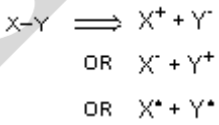
After writing possible routes we would need to evaluate each one before deciding which to follow.

Readily Available Starting Materials (RASM) : cheap, commercially available compounds.

Disconnection:

An analytical operation, which breaks a bond and converts a molecule into a possible starting material.The reverse of a chemical reaction.Symbol ⇒ and a curved line drawn through the bond being broken.

Disconnection: a paper operation involving an imagined cleavage of a bond (yielding synthons) to suggest a method and possible SM for making the bond, ultimately leading to possible SM for the overall synthesis.



Note: There **must** be a good chemical reaction corresponding to the reverse of the disconnections.

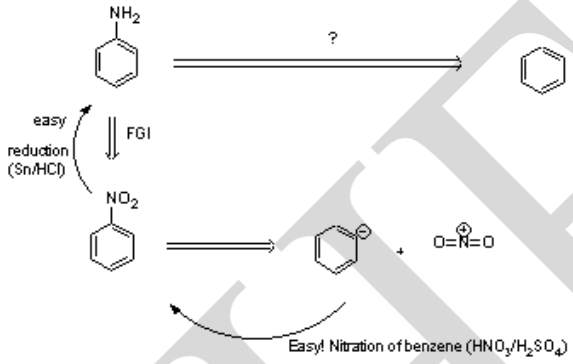
FGI: Functional Group Interconversion:

The operation of writing one functional group for another so that disconnection becomes possible.The reverse of a chemical reaction.Symbol ⇒ with FGI written over it.

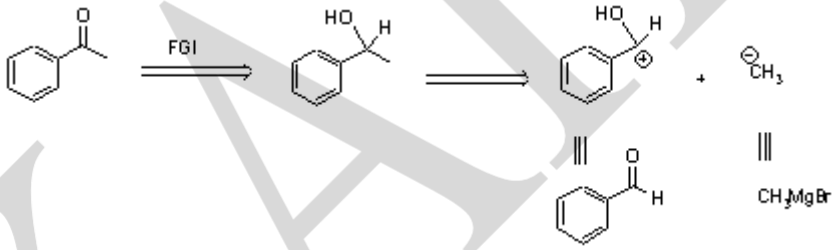
The process of writing one functional group for another to help synthetic planning and to help disconnection.

Note, there **must** be a good reaction in the reverse (forward!) direction.

e.g.

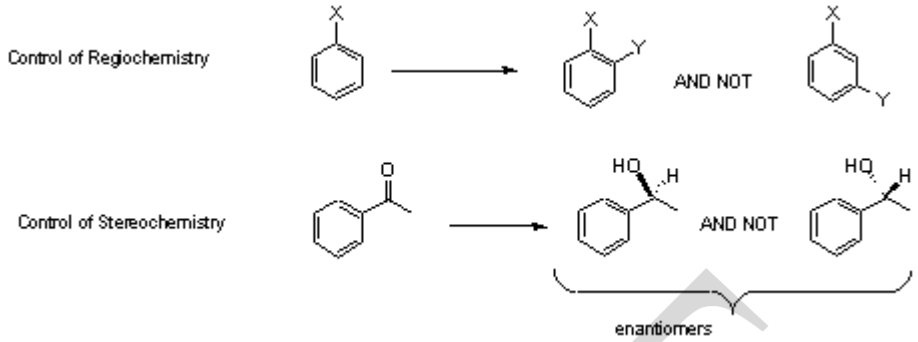


Alternative synthesis of



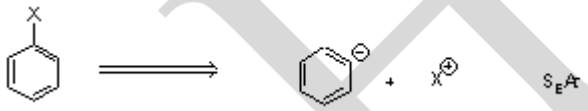
Many ways to make alcohols (e.g. via Grignard reagents) - suggests alternative synthesis to Friedel Crafts.

In planning a synthetic strategy, apart from devising a means of constructing the carbon skeleton with the required functionality as above, there are other subtle factors, which we must address.



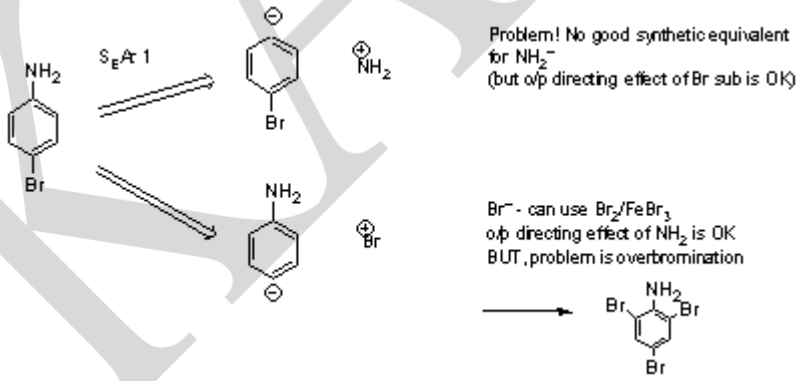
The Synthesis of Substituted Benzene Derivatives

Reactions are usually straightforward (S_EAr) and you will have met most of them before. Synthesis is simplified because the nature of the starting materials is usually clear. Thus, most reactions correspond to the following disconnection:

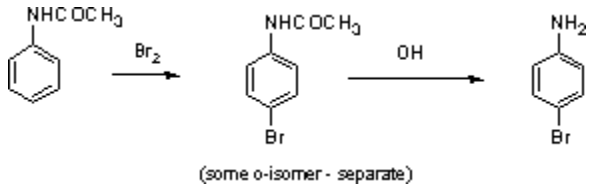


Example 1

1st decision: which bond to disconnect first!

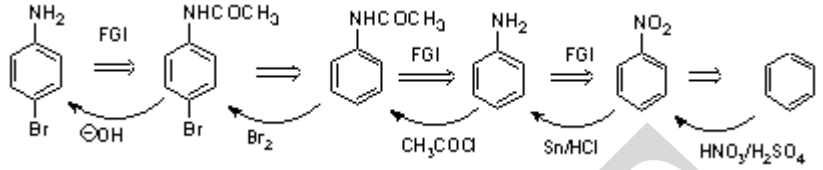


However, we can carry out monobromination on the N-acyl derivative of the amine:

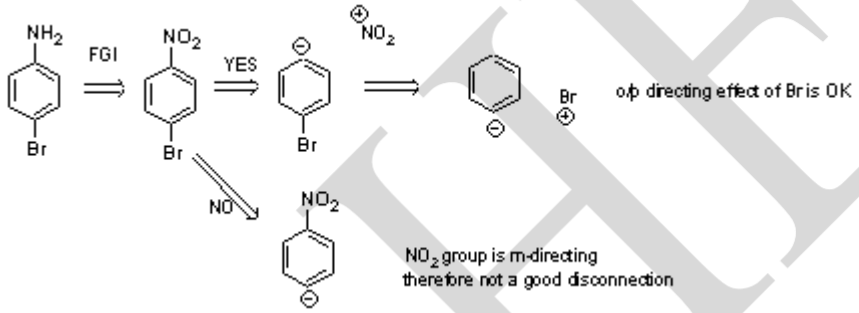


then we can remove the protecting group (HO^-/H_2O) to give the required product.

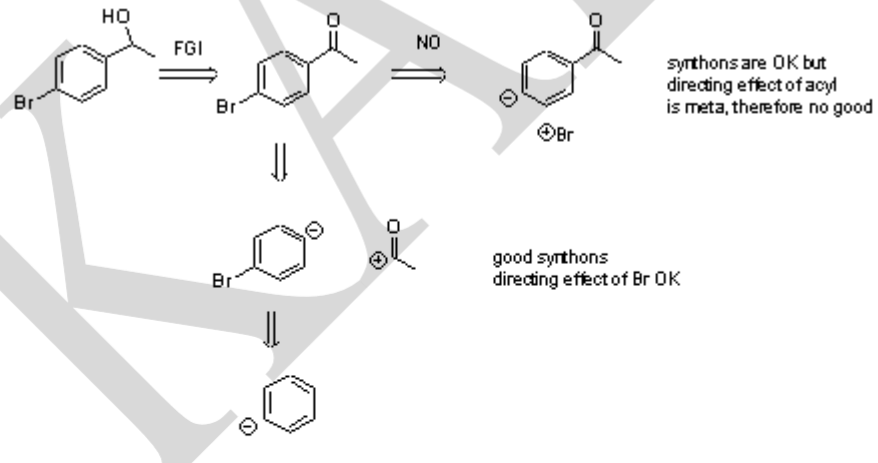
So formally:



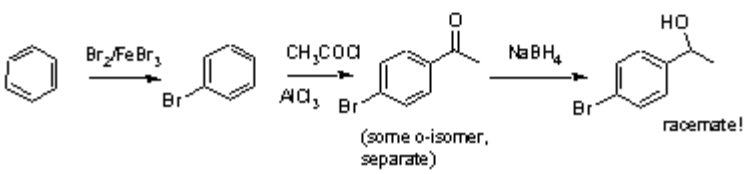
Is there an alternative route? Try a different FGI!



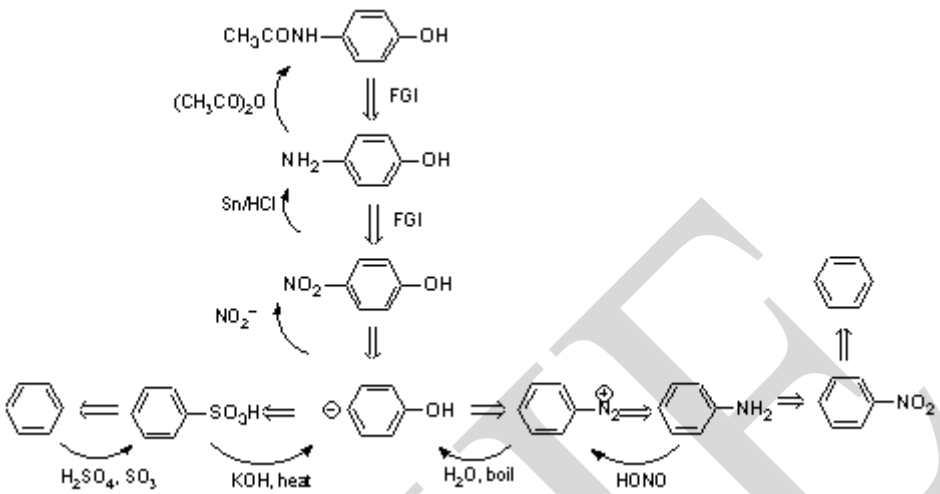
Example 2



Synthesis



Example 3



Guidelines for designing a synthesis

1. Use retrosynthetic analysis to work backwards from TM to the precursors and eventually to RASM.

2. Locate the functional groups in the TM ; for most functional groups there are good DISCONNECTIONS (the **reverse** of real chemical reactions).

3. Examine all possible disconnections and check which are chemically sound (correspond to known reactions, reagents, directing effects etc.)

4. If you can make no progress try FGI: (NO_2/NH_2; CH_3/COOH; C-Br/C-OH; CHO/CH_2OH etc.)

5. Having obtained precursors to TM, repeat the process on these intermediates.

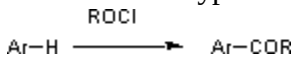
Clearly you will need a good knowledge of your basic chemistry and an appreciation of reaction mechanisms, directing effects etc.

With Aromatic systems the SM, are usually fairly obvious. Usually benzene or a benzene derivative such as toluene, phenol etc. The bond to be disconnected is almost always the bond joining the aromatic ring to the rest of the molecule.

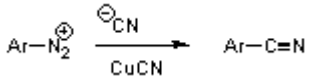
Also FGI's often correspond to some simple types of reaction e.g. reduction (NO_2 to NH_2), oxidation (CH_3 to COOH), diazonium chemistry (NH_2 ⟶ N_2^+ ⟶ Ar-X).

In aromatic chemistry CCBFR revolve around:

1. Friedel Crafts type reactions



2. Displacements on aromatic diazonium salts

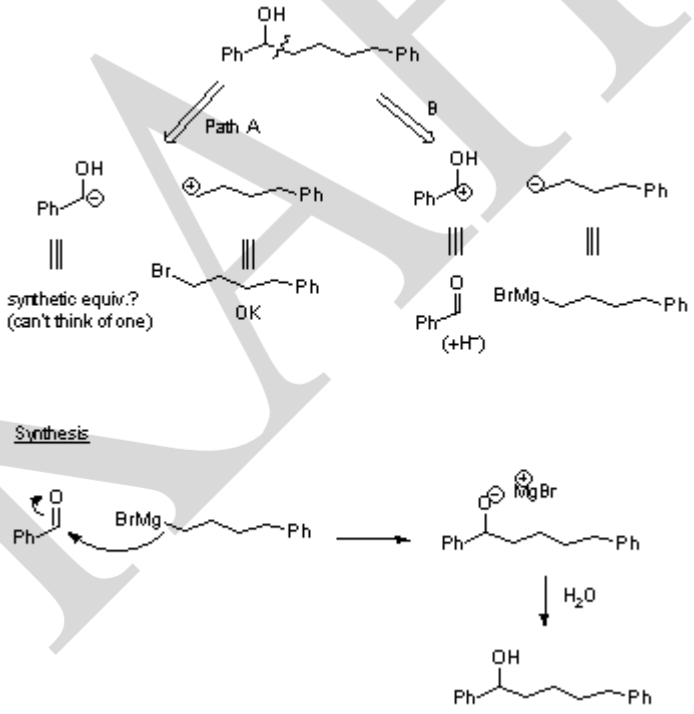


3. Not forgetting Grignard reagents + carbonyls)

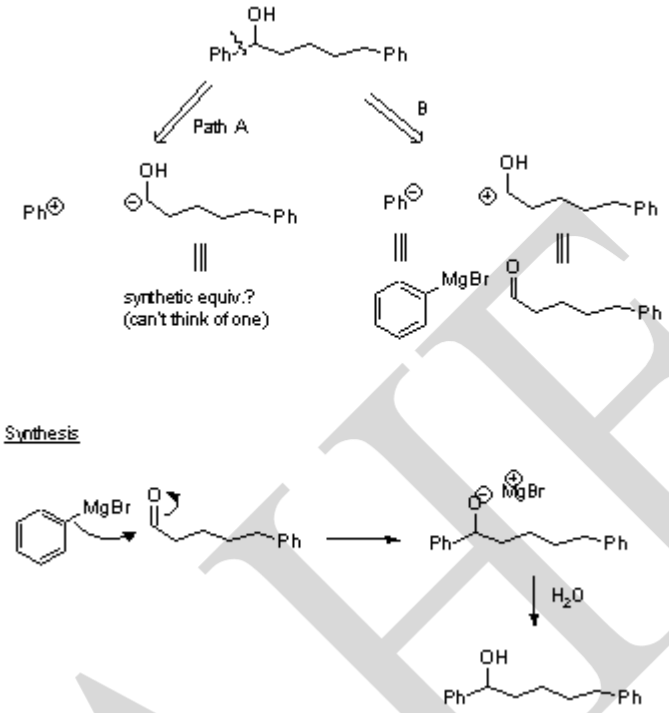
With aliphatic acyclic and cyclic systems the process is not always as straightforward.It need to consider a greater array of CCBFR's and FGI's.

Retrosynthesis In An Aliphatic Molecule A Guide To Alternative Disconnections.

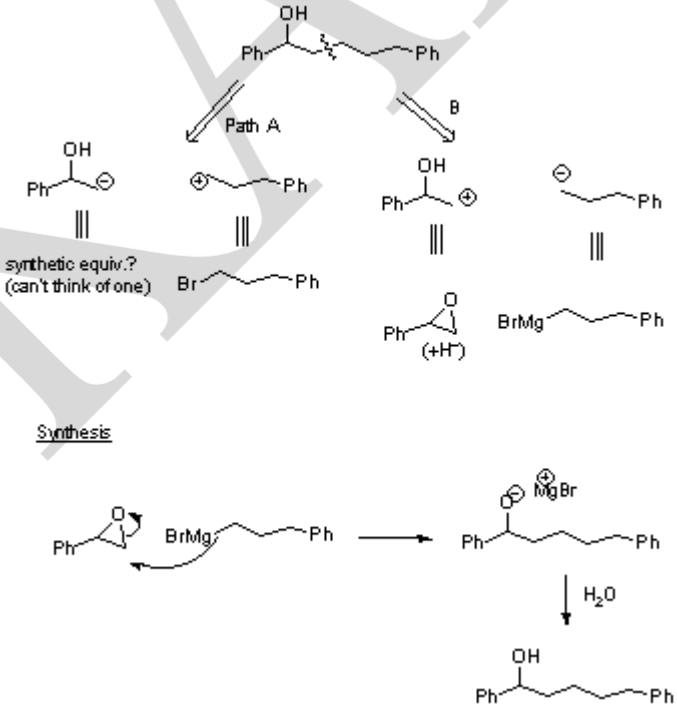
Retrosynthetic analysis 1



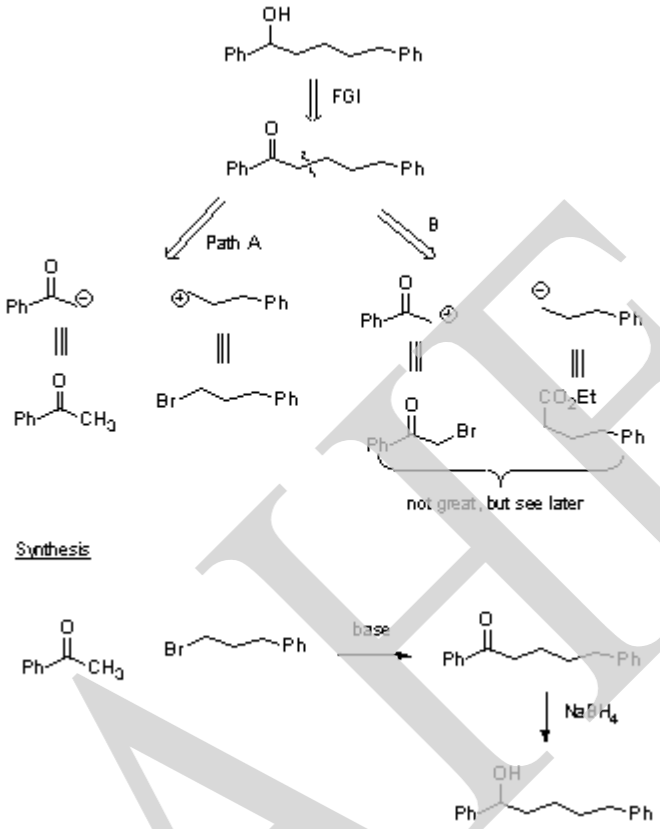
Retrosynthetic analysis 2



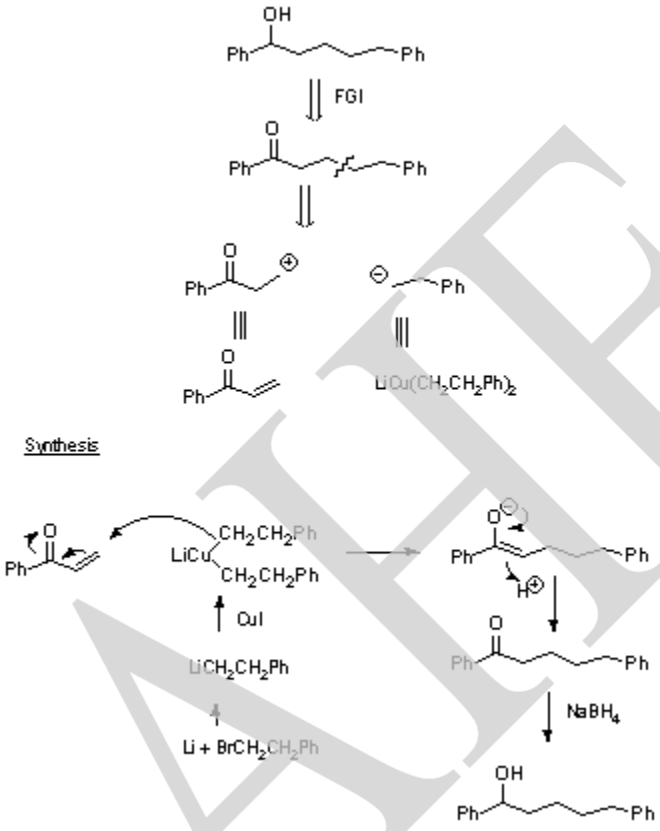
Retrosynthetic analysis 3



Retrosynthetic analysis 4



Retrosynthetic analysis 5



POSSIBLE QUESTIONS

PART A (1 mark Questions)

Online Examination

PART B (2 mark Questions)

1. What is meant by drugs?
2. State retrosynthesis.
3. What is meant by synthons?
4. Mention any two sources of drugs.
5. What are prodrugs?

PART C (6 Marks Questions)

1. Write notes on drug development.
2. What are the challenges to develop a useful drug? Explain.
3. Write note on functional group interconversion.
4. Illustrate retrosynthesis with a suitable example.
5. Explain briefly Geneome analysis.
6. Explain the steps involved in the drug discovery process.
7. How drug discovery process has been classified?
8. Write note on functional group interconversion.

KARPAGAM ACADEMY OF HIGHER EDUCATION

Class: II B.Sc Chemistry **Course Name: Pharmaceutical Chemistry**
Course Code: 18CHU304A **Unit: I** **Batch-2018-2021**

S. no	Question	Option A	Option B	Option C	Option D	Answer
1.	HIV is a	Human immuno deficiency virus	Human influenza virus	Hepatitis virus	Hepatitis B virus	Human immuno deficiency virus
2.	Chloroquine is used in the treatment of	Dengue	Chicken box	Malariae	Plague	Malariae
3.	Chloromycetin is used as a treatment of	Typhoid	Malaria	Diphtheria	Cholera	Typhoid
4.	Leprosy is a chronic infectious disease caused by	Mycobacterium leprae	Mycobacterium tuberculosis	Staphylococcus aurues	Escherichia coli	Mycobacterium leprae
5.	Dapsone is used in the treatment of	Leprosy	Epilepsy	Allergies	Piles	Leprosy
6.	Phenobarbital is used in the treatment of	Epilepsy	Leprosy	Piles	Allergies	Epilepsy
7.	Antibiotic streptomycin is employed for the treatment of	Tuberculosis	Polio	Rickets	Brainfever	Tuberculosis
8.	Chloramphenicol is also known as	Tetracyclin	Chloromycetin	penicillin	Streptomyces venezulae	Streptomyces venezulae
9.	The elements present in chloramphenicol are	C,H	C,H,N,O	C,H,O,N,Cl	C,H,N,Cl	C,H,O,N,Cl
10	Aspirin is	Methyl salicylate	Sodium salicylate	Acetyl salicylic acid	P- amino phenol derivatives	Acetyl salicylic acid
11	Which one differs from the others	Methidine	Morphine	Cocaine	Paracetamol	Paracetamol
12	Salicylates are the	Narcotic	Non- narcotic	Isoquinolene	Phenanthrene	Non -narcotic
13	Aspirin is synthesized from	O-hydroxy benzoic acid	m-hydroxy benzoic acid	p-hydroxy benzoic acid	d-hydroxy benzoic acid	o-hydroxy benzoic acid
14	Paracetamol is mainly prepared from	p-amino benzene	p-amino phenol	p-nitro benzene	o-amino phenol	p-amino phenol
15	4-hydroxy actanilide is known as	Salicin	Paracetamol	Aspirin	Phenacetin	Paracetamol
16	Which is not a true of paracetamol	It is a relief of pain	It is a relief of fever	It is more potent than phenacetin	It is five membere ring	It is five member ring
17	Which is not a true of antibiotics	Obtained from	Obtained from	Obtained from	Obtained from	Obtained from

		fungi	bacteria	virus	actinomy celes	virus
18	Chloramphenicol has a	Four stereoisomers	Two stereoisomers	Six stereoisomers	Eight stereoisomers	Four stereoisomers
19	Which is not a true of chloramphenicol	Inhibits the growth of staphylococcus	Inhibit the growth of streptococcus	Inhibits the growth of bacillus	Inhibit the growth of mycobacterium tuberculosis	Inhibit the growth of mycobacterium tuberculosis
20	Which is the major site of absorption of most drugs	Kidney	Stomach	Small intestine	Liver	Liver
21	Which is not a true of streptomycin	It is used in the treatment of tuberculosis	It is an aldehyde	It is a base	It is a macrocyclic compound	It is an aldehyde
22	The element present in chloramphenicol	C,H	C,H,N,O	C,H,O,N,Cl	C,H,N,Cl	C,H,O,N,Cl
23	Chloramphenicol is used as an	Antipyretics	Antibiotics	Analgesics	Anasthetics	Antibiotics
24	Antibiotic streptomycin is employed for the treatment of	Tuberculosis	Polio	Rickets	Brain fever	Tuberculosis
25	Which is not true of Ibuprofen?	It is strong antiinflammatory	Used as an analgesics	Used as an antipyretics	Used as an antiseptic agents	Used as an antiseptic agents
26	Streptomycin is a	Strong base	Weak base	Strong acid	Weak acid	Strong base
27	Ibuprofen is prepare from	Isobutyl alcohol	Isobutyl benzene	Isopropyl benzene	Isobutane	Isobutyl benzene
28	Which is NOT true of sulpha drugs?	they are sulphanilamides	they are effective chemotherapeutic agents	they are antibiotics	they are useful in the cure of bacterial infections	they are antibiotics
29	Aspirin is	methyl salicylate	sodium salicylate	acetyl salicylic acid	a p-aminophenol derivative	Acetyl salicylic acid
30	Narcotics analgesics should:	Relieve severe pain	Induce loss of sensation	Reduce anxiety and exert a calming effect	Induce a stupor or somnolent state	Relieve severe pain
31	Non-narcotic analgesics are mainly effective against pain associated with:	Inflammation or tissue damage	Trauma	Myocardial infarction	Surgery	Inflammation or tissue damage
32	Non-narcotic agents cause:	Respiratory depression	Antipyretic effect	Euphoria	Physical dependence	Antipyretic effect

33	Select the non-narcotic drug, which is a paraaminophenol derivative:	Analgin	Aspirin	Baclophen	Paracetamol	Paracetamol
34	Which of the following non-narcotic agents is salicylic acid derivative?	Phenylbutazone	Ketamine	Aspirin	Tramadol	Aspirin
35	Which one of the following non-narcotic agents inhibits mainly cyclooxygenase (COX) in CNS?	Paracetamol	Ketorolac	Acetylsalicylic acid	Ibuprofen	Ibuprofen
36	Most of non-narcotic analgetics have:	Anti-inflammatory effect	Analgesic effect	Antipyretic effect	All of the above	All of the above
37	Indicate the non-narcotic analgesic, which lacks an anti-inflammatory effect:	Naloxone	Paracetamol	Metamizole	Aspirin	Aspirin
38	Correct statements concerning aspirin include all of the following EXCEPT:	It inhibits mainly peripheral COX	It does not have an anti-inflammatory effect	It inhibits platelet aggregation	It stimulates respiration by a direct action on the respiratory center	It does not have an anti-inflammatory effect
39	Sulfonamides are effective against:	Bacteria and Chlamidia	Actinomyces	Protozoa	All of the above	All of the above
40	Mechanism of Trimethoprim' action is:	Inhibition of cyclooxygenase	Inhibition of dihydropteroate reductase	Inhibition of dihydropteroate synthase	Inhibition of DNA gyrase	Inhibition of dihydropteroate reductase
41	All of the following antiviral drugs are the analogs of nucleosides, EXCEPT:	Acyclovir	Zidovudine	Saquinavir	Didanozine	Saquinavir
42	Tick the drug, inhibiting viral DNA synthesis:	Interferon	Saquinavir	Amantadine	Acyclovir	Acyclovir
43	All of the following antiviral drugs are antiretroviral agents, EXCEPT:	Acyclovir	Zidovudine	Zalcitabine	Didanozine	Acyclovir
44	All of the following antiviral drugs are anti-influenza agents, EXCEPT:	Acyclovir	Amantadine	Interferons	Rimantadine	Acyclovir
45	Sulpha drugs are used as	antibacterial	anti viral agents	antibiotics	antipyretics	antibacterial

		agents				agents
46	which one is the main constituent of pain reliever of iodix	acetyl salicylic acid	methyl salicylate	phenacetin	Paracetamol	methyl salicylate
47	The drug used to lower body temperature are called	antipyretics	antiseptics	analgesics	disinfectants	antipyretics
48	One of the following is a example for antipyretics	quinine	Paracetamol	tetracycline	lysergic acid	Paracetamol
49	Which is NOT true of sulpha drugs?	they are sulphanilamides	they are effective chemotherapeutic agents	they are antibiotics	they are useful in the cure of bacterial infections	they are antibiotics
50	Aspirin is	methyl salicylate	sodium salicylate	acetyl salicylic acid	p-amino phenol derivatives	acetyl salicylic acid
51	Sulpha drugs can be classified as	antibiotics	analgesics	antidiabetics	vermicides	analgesics
52	ibuprofen is prepare from	isobutyl alcohol	primary alcohol	secondary alcohol	tertiary alcoho	isobutyl alcohol
53	4-hydroxy actanilide is	salicin	Aspirin	paracetamol	iodix	paracetamol
54	Sulphamethoxazole is	analgesic agent	antiviral agent	antibacterial agents	antipyretics	antibacterial agents
55	Ibuprofen is	anti inflammatory agents	anti viral agents	anti diabetics	antipyretics	anti inflammatory agents
56	Acylovir is	antiviral agents	anti diabetic agenta	anti inflammatory agents	anti cancer agents	antiviral agents
57	Sulphacetamide is	antiviral agents	antibacterial agents	antidiabetic agent	anticancer agents	antibacterial agents
58	Identify the category of drug which acts to relieve pain :	Analgesic	Antibiotic	Anticoagulant	Antidiuretic	Analgesic
59	paracetamol is prepared from	p-nitrophenol	o-nitrophenol	m-nitophenol	p-nitrobenzene	p-nitrophenol
60	Aspirin is prepared from	o-salicylic acid	m-salicylic acid	p-salicylic acid	phthalic acid	o-salicylic acid

UNIT II
Syllabus

Synthesis of the representative drugs

Synthesis of the representative drugs of the following classes: analgesic agents, antipyretic agents, anti-inflammatory agents (Aspirin, paracetamol, lbuprofen); antibiotics (Chloramphenicol);antibacterial and antifungal agents (Sulphonamides; Sulphanethoxazol, Sulphacetamide,Trimethoprim); antiviral agents (Acyclovir),

Analgesics (pain relievers)

Analgesics are medications designed to relieve the symptoms of pain. There are a number of different groups of analgesics:

- Simple analgesics
- Non steroidal anti inflammatory drugs (NSAIDS)
- Opioids (opium or morphine –like activity)

There are many different drugs in each group as well as frequent additions, but examples of the most commonly used are:

Simple analgesics such as:

- Paracetamol (e.g. Brand names - Panadol, Panamax, Herron)
- Aspirin (e.g. Brand names - Aspro clear, Aspro, Dispirin)

Non steroidal anti-inflammatory drugs such as:

- Ibuprofen (e.g. brand name -Nurofen)
- Diclofenac Sodium (e.g. brand name – Voltaren)
- Naproxen Sodium (e.g. brand name – Naprogesic)

Weaker opioids such as:

- Combinations including codeine phosphate (e.g. brand names - Panadeine, Panadeine forte, Mersyndol, MersyndolDaystrength, Nurofen plus)
- Tramadol hydrochloride (e.g. brand names – Tramal, Tramhexal)

- Dextropropoxyphe hydrochloride & paracetamol (e.g. brand name – Paradex, Di-gesic)

Stronger opioids such as:

- Morphine sulphate (e.g. brand names – Kapanol, MS Contin, MS Mono)
- Oxycodone (e.g. brand name- Oxycontin)
- Pethidine hydrochloride

Some problems with analgesic use

- Paracetamol – in recommended daily doses, even used long term, it is relatively harmless. In large doses it is harmful to the liver and kidneys and in rare cases can cause heart failure. It also has the potential to damage auditory nerves.

- Aspirin – is not recommended for children, pregnant women, asthmatics or those susceptible to stomach ulcers. In large doses it can be harmful to the kidneys.
- NSAIDS – in people already at risk, large doses can increase the risk of life-threatening heart or circulation problems, including heart attack or stroke. Prolonged use increases this risk. With prolonged use, there is potential for serious harm to the gastrointestinal system, including ulcers, bleeding or perforation. These conditions can be fatal and gastrointestinal effects can occur without warning at any time while taking NSAIDS. Older adults may have an even greater risk of these serious gastrointestinal side effects. Prolonged use can also affect the kidneys.

What are Nonsteroidal anti-inflammatory agents

- Nonsteroidal anti-inflammatory agents (usually abbreviated to NSAIDs) are a group of medicines that have anti-inflammatory (reduce inflammation), analgesic (relieve pain) and antipyretic (lower temperature) effects.

- Although different NSAIDs have different structures, they all work by blocking cyclo-oxygenase (COX) enzymes.

There are two main types of COX enzymes: COX-1 and COX-2. Both types produce produce prostaglandins; however, the main function of COX-1 enzymes is to produce baseline levels of prostaglandins that activate platelets and protect the lining of the gastrointestinal tract, whereas COX-2 enzymes are responsible for releasing prostaglandins after infection or injury. Prostaglandins have a number of different effects, one of which is to regulate inflammation.

- Most NSAIDs inhibit both enzymes, although a few are available that mainly inhibit COX-2. The pain-relieving and anti-inflammatory effects of NSAIDs are mainly due to inhibition of COX-2, and their unwanted side effects are largely due to inhibition of COX-1.
- Some common examples of NSAIDs are aspirin, ibuprofen, and naproxen.

Anti-inflammatory or **antiinflammatory** refers to the property of a substance or treatment that reduces inflammation or swelling. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system to block pain signaling to the brain.

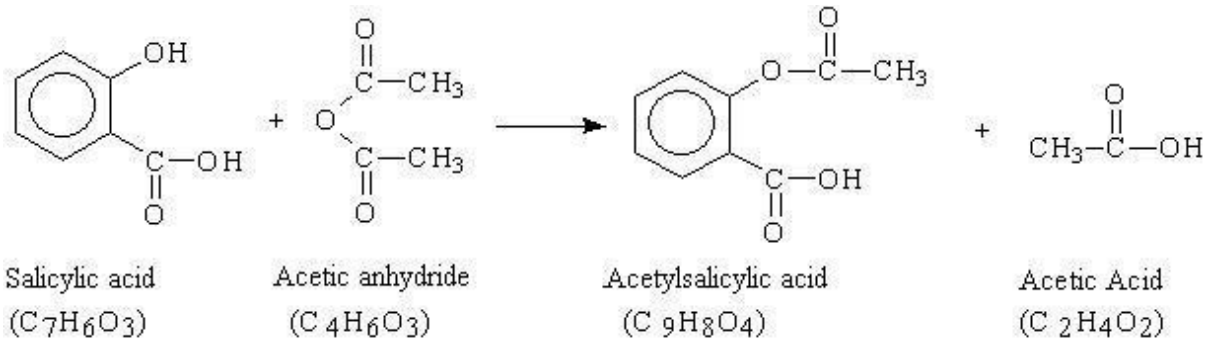
Antipyretics are substances that reduce fever. Antipyretics cause the hypothalamus to override a prostaglandin-induced increase in temperature. The body then works to lower the temperature, which results in a reduction in fever.

Aspirin

Aspirin is the common name for the compound acetylsalicylic acid, widely used as a fever reducer and as a pain killer. Salicylic acid, whose name comes from Salix, the willow family of plants, was derived from willow bark extracts. In folk medicine, willow bark teas were used as headache remedies and other tonics. Nowadays, salicylic acid is administered in the form of aspirin which is less irritating to the stomach than salicylic acid.

Synthesis

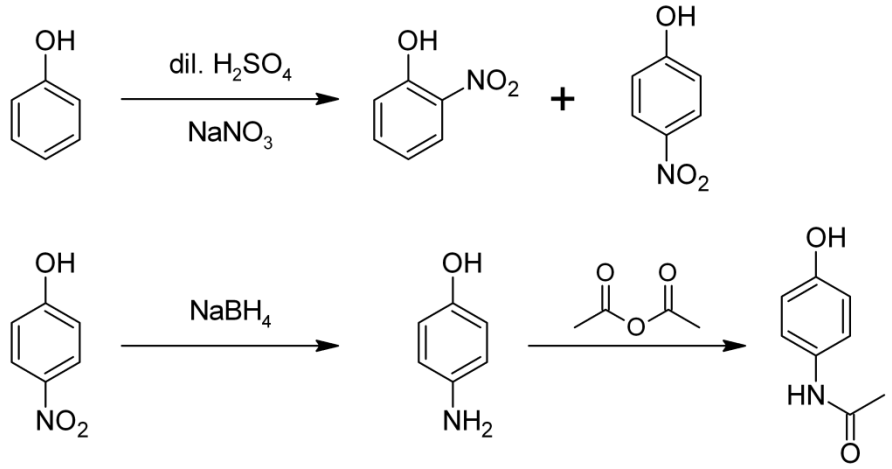
To **synthesize** the common pain killer **aspirin** via an esterification reaction between Salicylic Acid and Acetic Anhydride in the presence of concentrated sulfuric acid acting as a catalyst. If salicylic acid is reacted with an excess of acetic anhydride, a small amount of a strong acid is used as a catalyst which speeds up the reaction. Phosphoric acid will be used as the catalyst. The excess acetic acid will be quenched with the addition of water. The aspirin product is not very soluble in water so the aspirin product will precipitate when water is added. The synthesis reaction of aspirin is shown below:



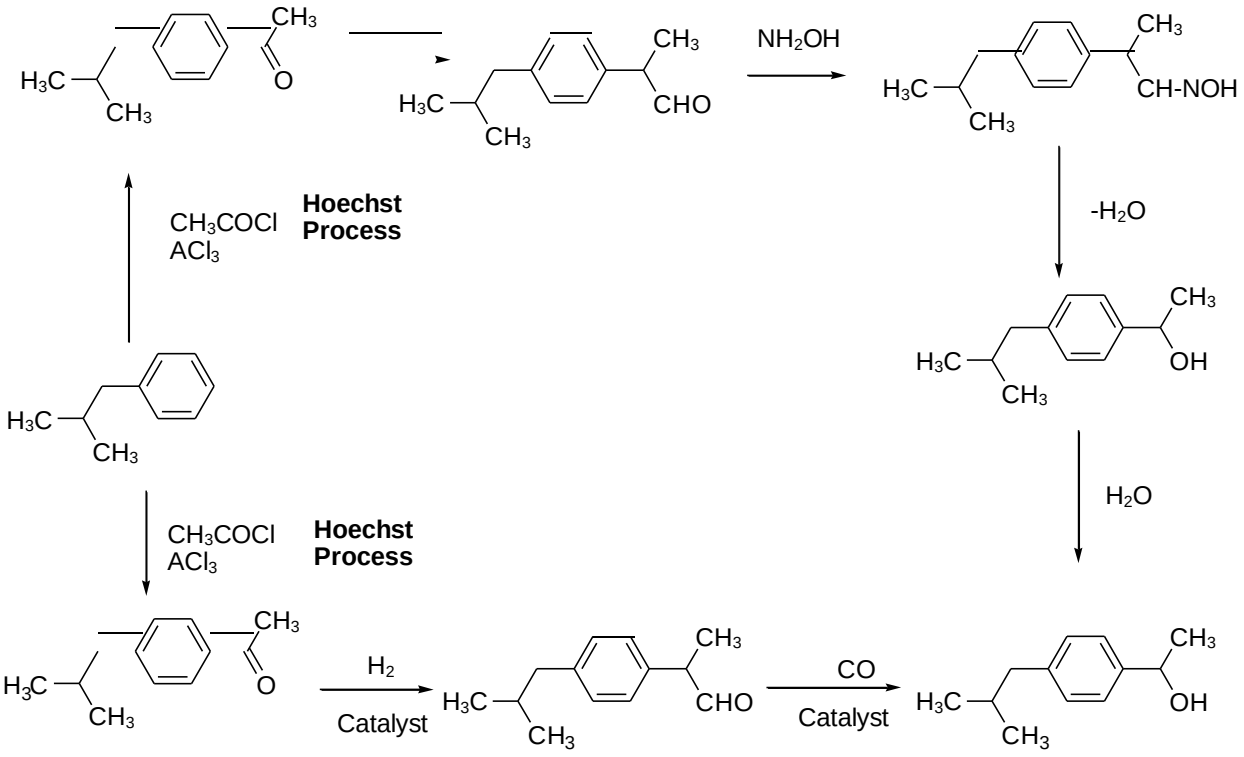
Salicylic acid ($C_7H_6O_3$) + Acetic anhydride ($C_4H_6O_3$) → Acetylsalicylic acid ($C_9H_8O_4$) + Acetic Acid ($C_2H_4O_2$)

Paracetamol

It is made by reacting 4-aminophenol with acetic anhydride. When the reaction is complete the**paracetamol** is then isolated and purified.



Synthesis of Ibuprofen



Antibiotic

1. A chemical substance produced by one microorganism that kills or inhibits the growth of other microbes,
2. The term now applies to both naturally produced substances and those synthesized in the laboratory.
3. Most are produced by either fungi (e.g., penicillin, cephalosporins), Bacillus species (e.g., polymyxin, bacitracin), or Streptomyces species (streptomycin, tetracycline, erythromycin, kanamycin, neomycin, nystatin). Broad-spectrum antibiotics are those that act on both gram-positive and gram-negative bacteria.

Any chemical (natural or synthetic) that is used in medicine is called Chemotherapeutic agent. Ideally, it should attack microorganisms selectively and not harm human cells.

Characteristics of an antibiotic

The ideal antimicrobial agent should be

a. nontoxic to the host (selective toxicity),
b. non-allergenic,
c. soluble in body fluids,
d. able to be maintained at therapeutic levels,
e. have a low probability of eliciting resistance, long shelf life,
f. and low cost.

Types and examples of antibiotics

a. **Natural drug**-one made by microorganisms.

b. **Synthetic drugs** that is made in the laboratory.

c. **Semisynthetic drug**-one synthesized partly in the laboratory and partly by microorganisms.

Spectrum of activity

Antibiotics may either be broad or narrow spectrum. Each antimicrobial drug has a range of microorganisms that it affects. This range is the spectrum of activity of the antimicrobial drug. The spectrum can be narrow (affecting a small number of microorganisms) or broad (affecting a large range of microorganisms).

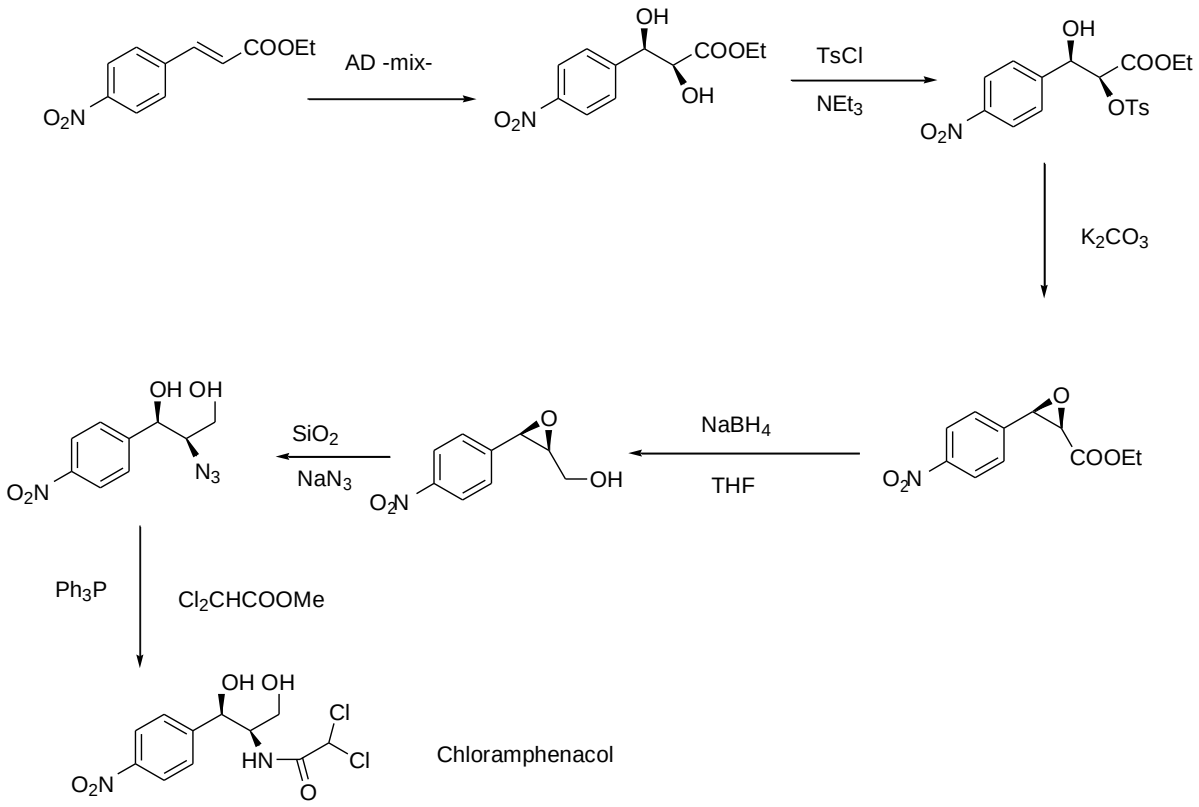
Example

Penicillin has a narrow spectrum of activity and affects only gram-positive, and a few of the gram-negative, bacteria.

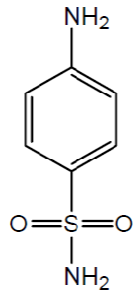
Tetracycline has a broad spectrum of activity and affects gram-negative and gram-positive bacteria, and rickettsias.

Chloramphenicol

Chloramphenicol is a bacteriostatic by inhibiting protein **synthesis**. It prevents protein chain elongation by inhibiting the peptidyltransferase activity of the bacterial ribosome. It specifically binds to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit, preventing peptide bond formation.

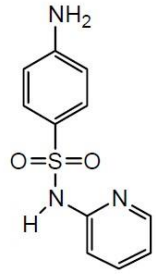


Sulfonamides can be prepared in the laboratory in many ways. The classic approach entails the reaction of sulfonyl chlorides with an amine. A base such as pyridine is typically added to absorb the HCl that is generated. A readily available sulfonyl chloride source is tosyl chloride.

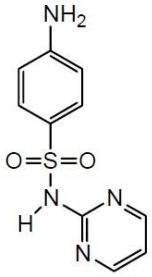


Sulfanilamide

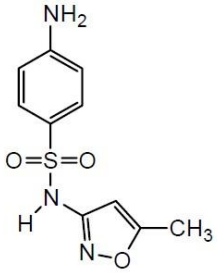
Sulfanilamide itself, a potent antibiotic, never gained widespreaduse due to its greater human toxicity versus its various derivatives



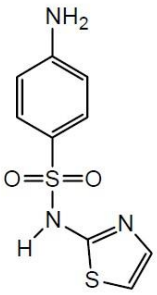
Sulfapyridine



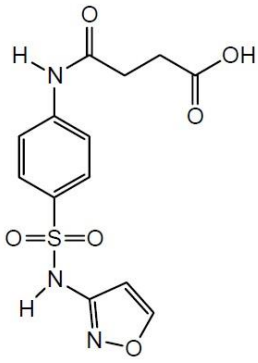
Sulfadiazine



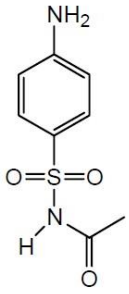
Sulfamethoxazole



Sulfathiazole



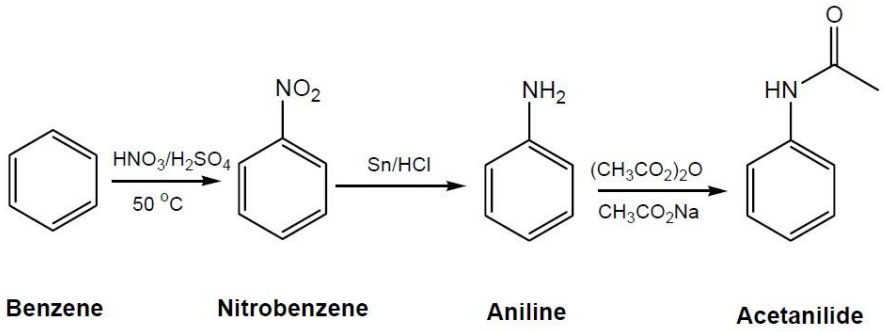
Succinylsulfathiazole



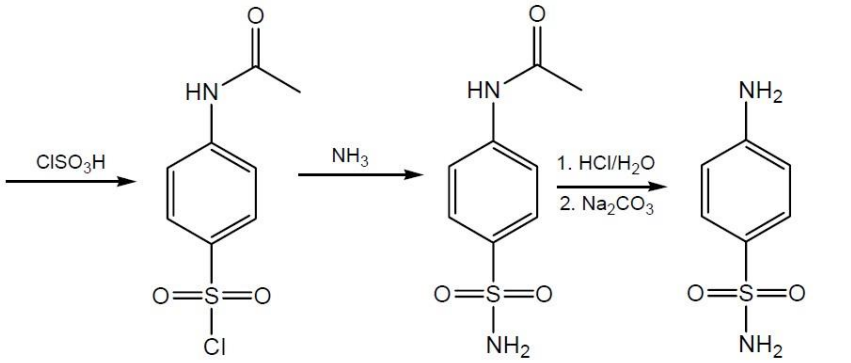
Sulfacetamide

Examples for sulpha drugs

The total synthesis of sulfanilamide from benzene can be carried out in six steps using reactions that are very familiar to intermediate level organic chemists.



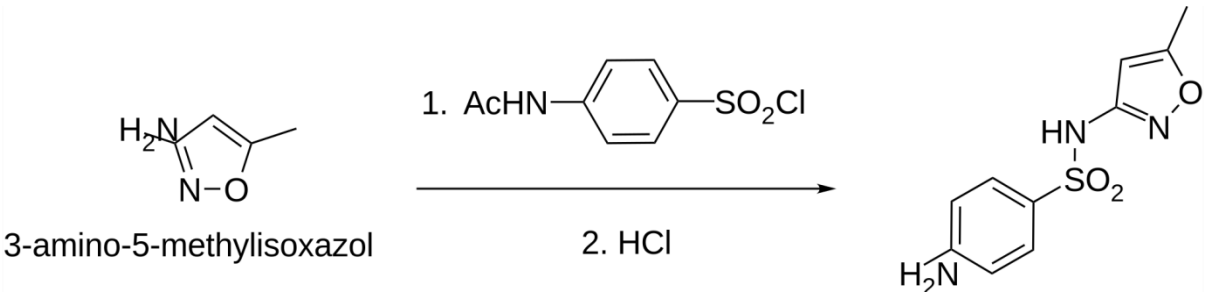
Benzene **Nitrobenzene** **Aniline** **Acetanilide**



4-Acetamidobenzene-sulfanyl chloride **4-Acetamidobenzene-sulfonamide** **Sulfanilamide**

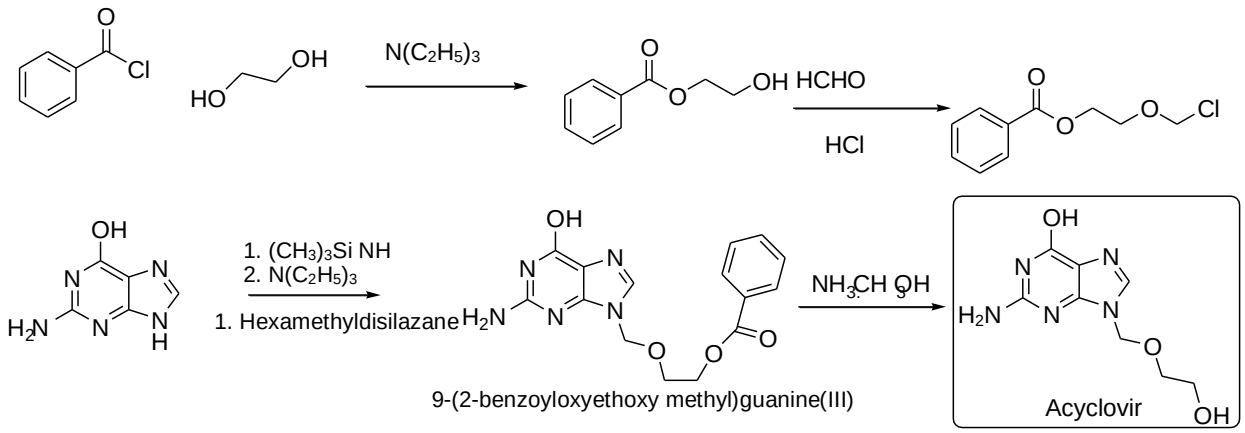
Sulphanethoxazol

Inhibition of dihydrofolic acid **synthesis** decreases the **synthesis** of bacterial nucleotides and DNA.**Sulfamethoxazole** is normally given in combination with Trimethoprim, a dihydrofolatereductase inhibitor, which inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid.



3-amino-5-methylisoxazol

Acyclovir


N(C2H5)3
OH HCHO
HCl
1. (CH3)3Si NH
2. N(C2H5)3
1. Hexamethyldisilazane
NH3CH3OH
9-(2-benzoyloxyethoxy methyl)guanine(III)
Acyclovir

Possible Questions

PART A (1 Mark Questions)

Online Examination

PART B (2 Marks Questions)

1. What are analgesics?
2. What are the medicinal uses of paracetamol?
3. Draw the structure of chloramphenicol
4. What are antipyretics?
5. Give the preparation of acetyl salicylic acid.

PART C (6 Marks Questions)

1. Give the preparation, properties and uses of aspirin.
2. Explain the preparation of chloramphenicol.
3. What are antipyretics? Describe the synthesis of paracetamol.
4. Give the preparation of ibuprofen by two possible synthetic routes.
5. Give the following preparation
   (i) Sulphacetamide (ii) Sulphamethoxazole
6. Outline the synthesis of chloromycetin.
7. Give the synthesis of (i) Acetlyl salicylic acid and (ii) Acetanilide
8. What are antiviral drugs? Give the synthesis of acyclovir.
9. What are antibacterial and anti-inflammatory drugs? Discuss the synthesis and uses of sulphonamides.
10. Give an account of the synthesis and uses of trimethoprim.

KARPAGAM ACADEMY OF HIGHER EDUCATION

Class: II B.Sc Chemistry **Course Name: Pharmaceutical Chemistry**
Course Code: 18CHU304A **Unit: I** **Batch-2018-2021**

S.No	Question	Option A	Option B	Option C	Option D	Answer
1	In the classification of CNS drugs, stimulants are	Tend to *speed up* the activity of a person's central nervous system	Tend to *slow down* the activity of the CNS	alter a user's sensory perceptions by distorting the messages carried in the CNS	Are antidepressants and mood stabilisers	Tend to *speed up* the activity of a person's central nervous system
2	In the classification of CNS drugs, Depressants are	Tend to *speed up* the activity of a person's central nervous system	Tend to *slow down* the activity of the CNS	alter a user's sensory perceptions by distorting the messages carried in the CNS	Are antidepressants and mood stabilisers	Tend to *slow down* the activity of the CNS
3	In the classification of CNS drugs, Hallucinogens are	Tend to *speed up* the activity of a person's central nervous system	Tend to *slow down* the activity of the CNS	alter a user's sensory perceptions by distorting the messages carried in the CNS	Are antidepressants and mood stabilisers	alter a user's sensory perceptions by distorting the messages carried in the CNS
4	Example for CNS drug-stimulants	Cocaine	Benzodiazepines	Psilocybin	Cannabis	Cocaine
5	Example for CNS drug-stimulants	Pseudoephidrine	Benzodiazepines	Psilocybin	Cannabis	Pseudoephidrine
6	Example for CNS drug-stimulants	Nicotine	Benzodiazepines	Psilocybin	Cannabis	Nicotine
7	Example for CNS drug-stimulants	Caffeine	Benzodiazepines	Psilocybin	Cannabis	Caffeine
8	Example for CNS drug-Depressants	Caffeine	tranquillisers	Psilocybin	Cannabis	tranquillisers
9	Example for CNS drug-Depressants	Caffeine	Benzodiazepines	Psilocybin	Cannabis	Benzodiazepines

10	Example for CNS drug- Hallucinogens	Caffeine	Benzodiazepines	Psilocybin	Cannabis	Psilocybin
11	Example for CNS drug- Hallucinogens	Caffeine	Benzodiazepines	Mescaline	Cannabis	Mescaline
12	Example for CNS drug- Depressants	Caffeine	Valium	Psilocybin	Cannabis	Valium
13	Example for CNS drug- Depressants	Caffeine	heroin	Psilocybin	Cannabis	heroin
14	Example for CNS drug- Depressants	Caffeine	morphine	Psilocybin	Cannabis	morphine
15	Cocaine is a	CNS drug- stimulants	CNS drug- Depressants	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- stimulants
16	Pseudoephidrine is a	CNS drug- stimulants	CNS drug- Depressants	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- stimulants
17	Nicotine is a	CNS drug- stimulants	CNS drug- Depressants	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- stimulants
18	Caffeine is a	CNS drug- stimulants	CNS drug- Depressants	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- stimulants
19	Tranquillisers are	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
20	Heroin is a	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
21	Morphine is a	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
22	Valium is a	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
23	Benzodiazepines are	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
24	Psilocybin is a	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Hallucinogens

25	Mescaline is a	CNS drug- stimulants	CNS drug-Depressant	CNS drug-Hallucinogens	Psycho-active drug	CNS drug-Hallucinogens
26	For short-term treatment of sleeplessness, the drug used is	paracetamol	lbuprofen	Trimethoprim	Phenobarbital	Phenobarbital
27	Diazepam is typically synthesized from	2-amino-5-chlorobenzophenone	2-amino-5-chlorobenzaldehyde	5-amino-2-chlorobenzophenone	5-amino-2-chlorobenzaldehyde	2-amino-5-chlorobenzophenone
28	Cardiovascular agents are drugs, which are used to treat	the heart or the circulatory system	Tend to *speed up* the activity of a person's central nervous system	Tend to *slow down* the activity of the CNS	alter a user's sensory perceptions by distorting the messages carried in the CNS	the heart or the circulatory system
29	Anti-hypertensive drugs are used to	lower the blood pressure	Increase the blood pressure	Reduce the cholesterol level in the blood	Reduce the urea in urine	lower the blood pressure
30	Anti-anginal drugs are	used for treating myocardial infarction	treating congestive cardiac failure	lower the blood pressure	used for treating bradecardia and tachecardia	used for treating myocardial infarction
31	Anti-CCF(congestive cardiac failure) drugs are used to	used for treating myocardial infarction	treating congestive cardiac failure	lower the blood pressure	used for treating bradecardia and tachecardia	treating congestive cardiac failure
32	Drugs which are used to control the blood pressure are called	Anti-hypertensive drugs	Anti-anginal drugs	Anti-CCF	Anti-arrythmatic drugs	Anti-hypertensive drugs
33	Anti-arrythmatic drugs are used to	used for treating myocardial infarction	treating congestive cardiac failure	lower the blood pressure	used for treating bradecardia and tachecardia	used for treating bradecardia and tachecardia
34	Drugs used for treating myocardial infarction are called	Anti-hypertensive drugs	Anti-anginal drugs	Anti-CCF	Anti-arrythmatic drugs	Anti-anginal drugs
35	Drugs used for treating bradecardia and tachecardia are called	Anti-hypertensive drugs	Anti-anginal drugs	Anti-CCF	Anti-arrythmatic drugs	Anti-arrythmatic drugs
36	Drugs used for treating congestive cardiac	Anti-hypertensive drugs	Anti-anginal drugs	Anti-CCF	Anti-arrythmatic drugs	Anti-CCF

	failure					
37	Glyceryl trinitrate (GTN) is otherwise called	Nitro glycerine	Anti-arrythmatic drugs	TNT	Picric acid	Nitro glycerine
38	Glycerol with nitric acid and sulphuric acid gives	Nitro glycerine	Anti-arrythmatic drugs	TNT	Picric acid	Nitro glycerine
39	diaminodiphenyl sulfone (DDS), is otherwise called as	Dapsone	Nitroclycerine	Picric acid	Steroidal drug	Dapsone
40	Dapsone is used in the treatment of	Leprosy	Viral fever	Bacterial infection	AIDS	Leprosy
41	AZT is used to cure	Leprosy	Viral fever	Bacterial infection	AIDS	AIDS
42	Azidothymidine is used to cure	Leprosy	Viral fever	Bacterial infection	AIDS	AIDS
43	AIDS and HIV are cured by	Azidothymidine	Dapsone	Glyceryl trinitrate	Diazepam	Azidothymidine
44	2-amino-5-chlorobenzophenone reacts with glycine hydrochloride and dimethyl sulphate to form	Diazepam	Azidothymidine	Dapsone	Glyceryl trinitrate	Diazepam
45	In the preparation of Diazepam the prefinal product is methylated with	Dimethyl sulphate	Methyl iodide	Dimethyl amine	Dimethyl alcohol	Dimethyl sulphate
46	Antihyperlipidemics means	drugs are used to decrease high lipids levels of fats and cholesterols	drugs are used to increase high lipids levels of fats and cholesterols	drugs are used to decrease blood pressure	Drugs are used to increase the blood pressure	drugs are used to decrease high lipids levels of fats and cholesterols
47	Drugs used to decrease high lipids levels of fats and cholesterols are called as	Antihyperlipidemics	Anti-anginal drugs	Anti-hypertensive drugs	Anti bacterial	Antihyperlipidemics
48	Antihyperlipidemics	Steroidal in nature	Alkaloidal in nature	Terpenoidal in nature	Flavanoidal in nature	Steroidal in nature

	Are of					
49	The nitrating agent used to nitrate glycerine to prepare GTN	Nitric acid	Sulphuric acid	A mixture of nitric acid and sulphuric acid	Acetic acid and nitric acid	A mixture of nitric acid and sulphuric acid
50	zidovudine, drug used	to delay development of AIDS	to develop AIDS	To decrease blood pressure	To cure tropical diseases	to delay development of AIDS
51	Benzyl cyanide is used to prepare	zidovudine	Phenobarbital	Valium	morphine	Phenobarbital
52	Benzyl cyanide is converted into ethyl phenyl acetate by using	Ethanol/HCl	Acetic acid/methanol	Ethanol/NaOH	NaOH/ methanol	Ethanol/HCl
53	Urea is used in one of the intermediate steps in the preparation of	zidovudine	Phenobarbital	Valium	morphine	Phenobarbital
54	Anticoagulants are	Cardiovascular drugs	CNS drugs	antibiotics	Antiviral agents	Cardiovascular drugs
55	Example for a volatile substance	Valium	heroin	morphine	petrol	petrol
56	*Relaxants are otherwise called as*	CNS drug- stimulants	CNS drug-Depressants	CNS drug-Hallucinogens	Psycho-active drug	CNS drug-Depressants
57	Pseudoephidrine is used in the treatment of	Cold and flu	diabetes	cancer	Alzmeir disease	Cold and flu
58	The drug used to treat fear and tension	Phenol barbital	heroin	morphine	Paracetemol	Phenol barbital
59	Which is called as narcotics	Phenol barbital	diazepam	morphine	Paracetemol	morphine
60	One among the following is a narcotic drug	Phenol barbital	diazepam	heroin	Paracetemol	heroin

UNIT III
Syllabus

Central Nervous System and Cardiovascular Drugs
Synthesis of therepresentative drugs of the following classes: Central Nervous System agents (Phenobarbital, Diazepam),Cardiovascular (Glyceryltrinitrate), antilaprosy (Dapsone), HIV-AIDS related drugs (AZT- Zidovudine).

Central nervous system drugs

Central nervous system agents are drugs that affect the central nervous system i.e. the brain and the spinal cord, and produce a response that could be used to alleviate or treat a particular medical condition.

Central nervous system agents can be used as analgesics, anesthetics, anti-emetics, anti-convulsants, and have many more therapeutic uses.

Classifying drugs by their effect on CNS

Stimulants

Tend to *speed up* the activity of a person's central nervous system (CNS) including the brain. These drugs often result in the user feeling more alert and more energetic.

e.g.

Amphetamines

- Cocaine
- Pseudoephidrine (found in medications such as Sudafed, Codral Cold and Flu)
- Nicotine
- Caffeine

Depressants *(also known as relaxants)*

Tend to *slow down* the activity of the CNS, which often results in the user feeling less pain, more relaxed and sleepy.These symptoms may be noticeable when a drug is taken in large amounts.It is important to note that the term 'depressant' is used to describe the effect on the CNS, not

mood.CNS depressants are more likely to result in euphoria than depression, especially in moderate use.

e.g.

- Alcohol
- Major tranquillisers
- Benzodiazepines (e.g. Valium, Temazepam) Opioids (heroin, morphine)
- Volatile substances (can also be classified as 'other' (glue, petrol, and paint).

Hallucinogens

Have the ability to alter a user's sensory perceptions by distorting the messages carried in the CNS. A common example is LSD (trips).Hallucinogens alter one's perceptions and states of consciousness.

e.g.

- LSD
- Psilocybin (magic mushrooms)
- Mescaline (peyote cactus)

Others

Includes psycho-active drugs that do not fit neatly into one of the other categories, but which are clearly psycho-active, such as antidepressants (e.g. Zoloft) and mood stabilisers (e.g. Lithium).

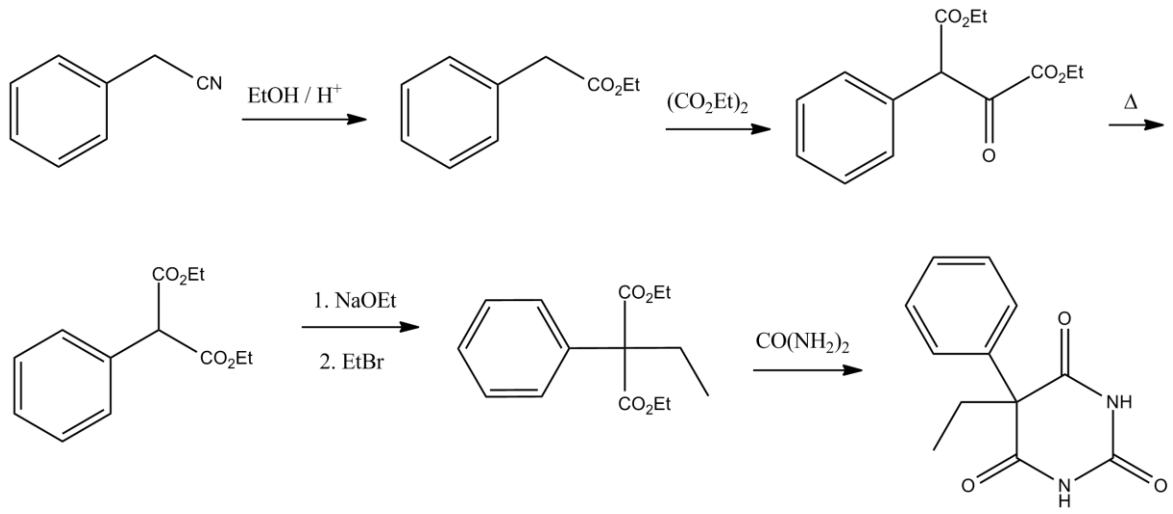
e.g.

- MDMA (ecstasy)*
- Cannabis*
- Volatile substances (petrol, glue, paint)

Phenobarbital

The short-term treatment of sleeplessness, the relief of anxiety, tension, and fear, and the treatment of certain types of seizures, especially in emergency situations. Phenobarbital is a barbiturate. It works by depressing the central nervous system. This aids you in relaxing and going to sleep.

Synthesis of Phenobarbital



Diazepam

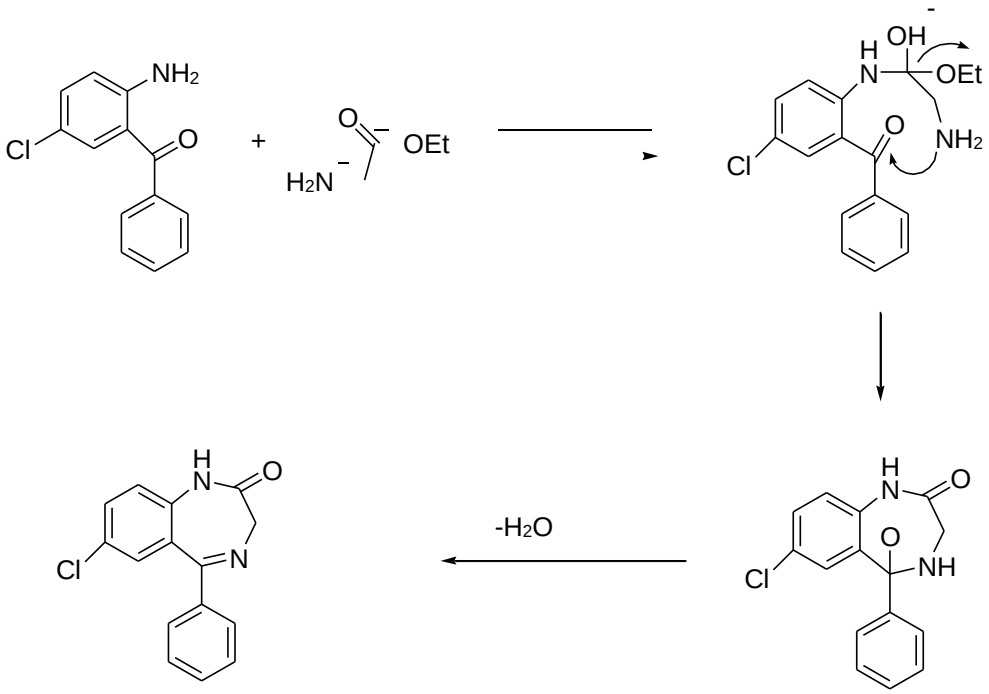
Treating anxiety disorders or for the short-term relief of the symptoms of anxiety. It is also used to treat seizures, certain types of muscle spasms, and symptoms of alcohol withdrawal (eg, agitation, tremor, hallucinations). Diazepam is also used before surgery or other medical procedures to help reduce anxiety and tension. It may also be used for other conditions as determined by your doctor.

Diazepam is a benzodiazepine. It works by increasing the action of a certain chemical (gamma-aminobutyric acid [GABA]) in the brain and nervous system. This helps to reduce anxiety. It also helps to reduce seizure activity in the brain and to reduce muscle spasms.

Diazepam, marketed as Valium, is a benzodiazepine drug. Benzodiazepines are a class of central nervous system depressants, which work by increasing the activity of the GABA(gamma-amino butyric acid) neurotransmitter. GABA inhibits nerve transmission in thebrain, which leads to depression of the central nervous system

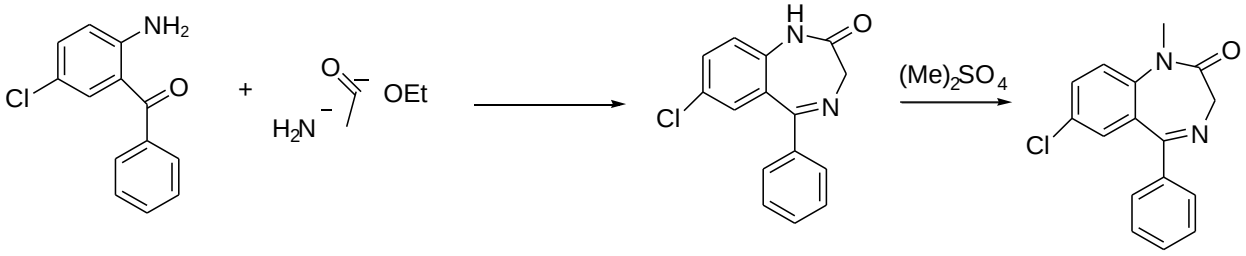
Diazepam is typically synthesized from 2-amino-5-chlorobenzophenone by first combining it with glycine hydrochloride and then methylating the amide nitrogen with dimethyl sulfate. Here

is the mechanism for the first step, which is the creation of 7-chloro-1,3-dihydro-5-phenly-2H-1,4-benzodiazepin-2-one from 2-amino-5-chlorobenzophenone and glycine hydrochloride.



Diazepam is used to treat anxiety, alcohol withdrawal, and seizures. It is also used to relieve muscle spasms and to provide sedation before medical procedures.

This medication works by calming the brain and nerves. Diazepam belongs to a class of drugs known as benzodiazepines.



Cardiovascular drugs

Cardiovascular drugs are those drugs that are used to treat various pathological conditions of cardiovascular system. These drug comprise a huge arsenal of drugs that fight an extended area

of diseases in medical science i.e **heart diseases**. Chemically these drugs are more or less alike some are synthetic and some semi synthetic versions of their natural crude sources.

Cardiovascular drugs can be broadly categorized as

1) anti-anginals,

2) anti-arrhythmics,

3) anti-hypertensives,

4) anticoagulants,

5) anti-hyperlipidemic agents,

6) hypo-glycemic agents, and

7) anti-thyroid drugs and thyroid hormones.

Basis of classification

- **site of action**
- **mechanism of action**
- **chemical nature of drug**
- **nature of disease**

Here for general classification of cardiovascular drugs we take **nature of disease** as the basis of classification. In other words drugs are classified on the basis of **cardiovascular diseases** that they treat.

Classification of cardiovascular drugs

Cardiovascular drugs are classified into the following five classes.

1. **Antihypertensive drugs**
2. **anti-anginal drugs**
3. **anti-congestive cardiac failure (CCF) drugs**
4. **anti-arrhythmic drugs**
5. **anti-hyperlipidemic drugs**

Anti-hypertensive drugs

These are drugs used to lower B.P in hypertension.Hypertension is a very common disorder, particularly past middle age. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity.drugs included in this category are

- beta blocker
- alpha blockers
- diuretics
- ace-inhibitors
- calcium channel blocker
- angiotensin ii receptor blocker
- renin angiotensin aldosterone system blockers

(they will further be explained in their respective post)

Anti-anginal drugs

These drugs are used for treating angina pectoris and myocardial infarction.

- Nitrates(particularly organic nitrates)
- beta Blockers
- Calcium channel blockers
- Potassium channel opener
- sodium channel blockers

and some others.

Anti-CCF(congestive cardiac failure)

These drugs are used for treating congestive cardiac failure.they include..

- rennin angiotensin aldosterone system blockers
- beta blockers
- Diuretics
- direct acting vasodilators
- inotropic drugs
- aldosterone antagonist

Anti-arrythmatic drugs

They are used for treating arrythmias like bradecardia and tachecardia.they are alpha blockers. These drugs are classified as classes.

- **class I antiarrythmics**

  Predominantly sodium channel blockers
- **class II antiarrythmics**

  Class II antiarrythmics are beta blockers i.e**propranolol,metoprolol,esmolol**
- **class III antiarrythmics**

  They are potassium channel blockers and block the outflow of k ions during repolarization of cardiac cells.**amidarone** and **dronadarone** are examples.
- **class IV antiarrythmics**

  Class 4 antiarrythmic includes calcium(Ca2+) channel blockers other than dipine class(only diltiazem and verapamil).
- **other antiarrythmics**

digoxin and adenosine are classified as other anriarrythmics.

Antihyperlipidemics

These drugs are used to decrease high lipids levels of fats and cholesterols.chemically most of these drugs are **steroids** in nature.

They are further classified as..

- cholesterolemic
- triglyceridemic

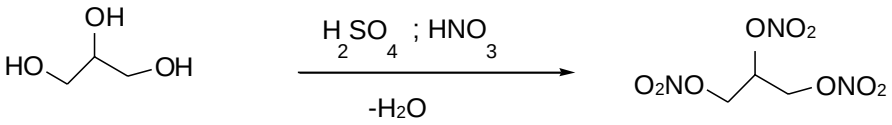
these drugs include "HMG-coAreductase" inhibitors i.e **provastatin** and**fluvastatin**.

Glyceryltrinitrate

Nitroglycerin, also known as **glyceryltrinitrate** (**GTN**) is a medication used for heart failure, high blood pressure, and to treat and prevent chest pain from not enough blood flow to the heart or due to cocaine. This includes chest pain from a heart attack. It is taken by mouth, under the tongue, applied to the skin, and by injection into a vein.

Synthesis

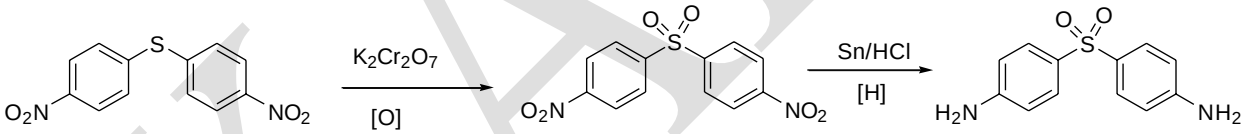
Nitration glycerine with nitric acid and sulfuric acid



Dapsone

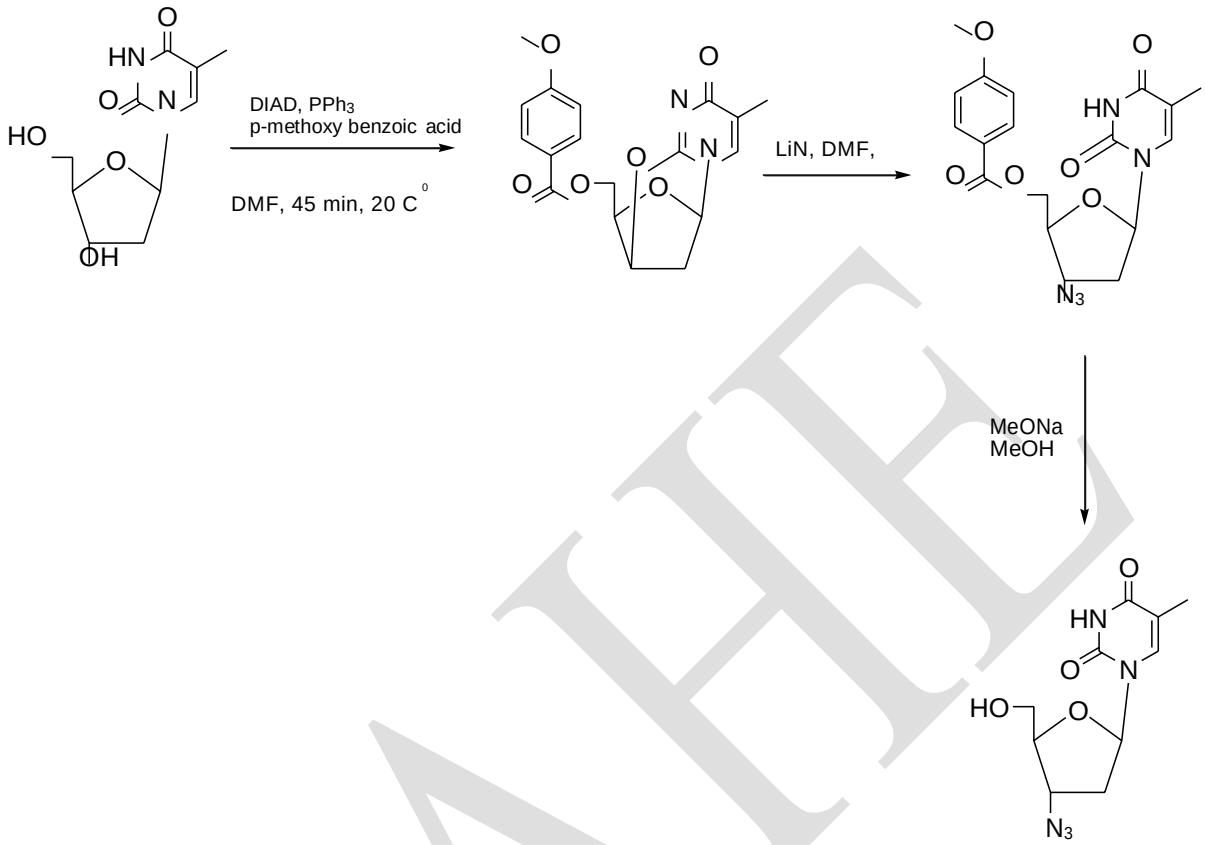
Dapsone, also known as **diaminodiphenylsulfone** (**DDS**), is an antibiotic commonly used in combination with rifampicin and clofazimine for the treatment of leprosy. It is a second-line medication for the treatment and prevention of pneumocystis pneumonia and for the prevention of toxoplasmosis in those who have poor immune function. Additionally, it has been used for acne, dermatitis herpetiformis, and various other skin conditions.

A sulfone active against a wide range of bacteria but mainly employed for its actions against **Mycobacterium leprae**. Its mechanism of action is probably similar to that of the **sulfonamides** which involves inhibition of folic acid synthesis in susceptible organisms. It is also used with **pyrimethamine** in the treatment of malaria.



AZT synthesis

AZT**,** in full azidothymidine, also called zidovudine, drug used to delay development of AIDS (acquired immunodeficiency syndrome) in patients infected with HIV (human immunodeficiency virus). AZT belongs to a group of drugs known as nucleoside reverse transcriptase inhibitors (NRTIs). In 1987 AZT became the first of these drugs to be approved by the U.S. Food and Drug Administration for the purpose of prolonging the lives of AIDS patients.



Zidovudine (**3'-azido-3'-deoxythymidine**, **azidothymidine**, or simply **AZT**) is an analog of thymidine in which the 3' hydroxyl group is replaced by an azido group. For this reason, AZT is considered a chain terminator of DNA synthesis. It was synthesized in 1964 by Jerome Horwitz.AZT belongs to a class of chemical compounds known as *nucleoside analog reverse transcriptase inhibitors*, commonly called *NRTI's*. It is sold under the names **Retrovir.**

AZT is only active against HIV when the virus is replicating into proviral DNA (viral DNA synthesized prior to integration into host DNA). This is because the active compound of AZT, known as zidovudine 5-triphosphate, has a high affinity (attraction) for an enzyme called reverse transcriptase, which is used by retroviruses such as HIV to replicate viral single-stranded RNA (ribonucleic acid) into proviral double-stranded DNA (deoxyribonucleic acid).

Zidovudine 5-triphosphate is similar in structure to thymidine triphosphate, which is normally produced by cells and is one of several nucleoside compounds(structural units of nucleic acids) needed to synthesize DNA. However, zidovudine 5-triphosphate has a greater affinity for reverse transcriptase than thymidine triphosphate, and it contains a nitrogen group (an azide; N_3) in place of the usual nucleoside hydroxyl group (−OH). As a result, reverse transcriptase incorporates zidovudine 5-triphosphate into growing strands of HIV proviral DNA, and DNA synthesis and replication are terminated, since subsequent nucleosides cannot bind to the nitrogen group of zidovudine 5-triphosphate.

Possible Questions

PART A (1 Mark Questions)

Online Examination

PART B (2 Marks Questions)

1. What is phenobarbital?
2. State cardio vascular drugs.
3. What is meant by virus?
4. Draw the structure of glyceryl trinitrate.
5. Give three examples of antileprosy drugs

PART C (8 Marks Questions)

1. Describe the preparation of phenobarbital.
2. What are central nervous system agents? Illustrate the preparation of diazepam.
3. Give the synthesis and therapeutic uses of glyceryltrinitrate.
4. What are antilaprosy drugs? Describe the dapsone preparation.
5. Provide the synthetic plan of phenobarbital and give the preparation.
6. What is AIDS? Describe the preparation of azidothymidine.
7. Give the following preparation of
   (i) Zudovidine (ii) Nitroglycerine
8. How will you get phenobarbital from phenyl acetic acid? Explain.
9. Illustrate the preparation of diazepam.
10. What are cardiovascular agents? Describe the suitable preparation.

KARPAGAM ACADEMY OF HIGHER EDUCATION

Class: II B.Sc Chemistry **Course Name: Pharmaceutical Chemistry**
Course Code: 18CHU304A **Unit: I** **Batch-2018-2021**

S. No	Question	Option A	Option B	Option C	Option D	Answer
1.	Alcohol:	Increases body temperature	Decreases body heat loss	Increases body heat loss	Does not affect body temperature	Increases body heat loss
2.	Effect of moderate consumption of alcohol on plasma lipoproteins is:	Raising serum levels of high-density lipoproteins	Increasing serum concentration of low-density lipoproteins	Decreasing the concentration of high-density lipoproteins	Raising serum levels of very low-density lipoproteins	Raising serum levels of high-density lipoproteins
3.	Which of the following metabolic alterations may be associated with chronic alcohol abuse?	Hyperglycemia	Increased serum concentration of phosphate	Severe loss of potassium and magnesium	Decreased serum concentration of sodium	Severe loss of potassium and magnesium
4.	Which of the following drugs is most commonly used for causing a noxious reaction to alcohol by blocking its metabolism?	Naltrexone	Disulfiram	Diazepam	Morphine	Disulfiram
5.	Which of the following agents is an inhibitor of aldehyde dehydrogenase?	Fomepizole	Ethanol	Disulfiram	Naltrexone	Disulfiram
6.	Indicate the drug, which alters brain responses to alcohol:	Naltrexone	Disulfiram	Amphetamine	Chlorpromazine	Naltrexone
7.	If starch containing substrates are used for ethanol production, yeast strain can't be used directly because	it doesn't contain amylases to hydrolyze starch	starch is not a suitable substrate for the production of ethanol	it is converted to pentose sugar	none of the above	it doesn't contain amylases to hydrolyze starch
8.	Which of the following is used to check vortex and to improve aeration efficiency in a fermentor?	Impeller	Baffles	Sparger	All of these	Baffles
9.	What are different substrates used for ethanol production?	Starch containing substrate	Juices from sugarcane or molasses or sugar beet	Waste product from wood or processed wood	All of the above	All of the above
10.	Which of the following is used for	Impeller	Baffles	Sparger	All of these	Sparger

	aeration in a fermentor?					
11.	Ethanol is produced by	continuous fermentation	batch fermentation	continuous and batch fermentation	none of these	continuous and batch fermentation
12.	Yeast is used in the production of	ethyl alcohol	cheese	curd	acetic acid	ethyl alcohol
13.	*S cerevisiae* start producing ethanol with in	10 h	12 h	15 h	24 h	12 h
14.	Which of the following microorganisms is not used in the ethanol production?	*Saccharomyces cerevisiae*	*Zygomonas mobilis*	*Saccharomyces uvarum*	*Staphyllococcus aureus*	Staphyllococcus aureus
15.	After the fermentation is over, ethanol is recovered by	centrifugation	distillation	filtration	cell disintegration	distillation
16.	Which of the following organism is not used in any of the traditional industrial fermentation?	*E. coli*	*Yeast*	*Bacillus*	*Pseudomonas*	*E. coli*
17.	What are the fermentation conditions for the ethanol production?	pH 6; temperature 35℃	pH 5; temperature 35℃	pH 6; temperature 30℃	pH 5; temperature 30℃	pH 5; temperature 35℃
18.	Which of the following is not used for agitation in a fermentor?	Impeller	Baffles	Sparger	Stirrer	Stirrer
19.	High ethanol concentration	promotes yeast growth	inhibits yeast growth	promotes bacterial growth	inhibits bacterial growth	inhibits yeast growt
20.	Enzyme aconitase converts citric acid into	Iso-citric acid	trans citric acid	cis citric acid	meso citric acid	Iso-citric acid
21.	Citric acid heated at 150 C to gives	Aconitic acid	Acetic acid	benzoic acid	oxalic acid	Aconitic acid
22.	Vinegar consists of	formic acid	Acetic acid	oxalic acid	citric acid	citric acid
23.	Vinegar is typically produced in fed batch reactors because	a fed batch reactor can be used to maintain low acetic acid concentrations	a fed batch reactor can be used to maintain low ethanol concentrations	acetic acid bacteria tend to ferment at high ethanol concentrations	acetic acid bacteria tend to ferment at low ethanol concentrations	a fed batch reactor can be used to maintain low ethanol concentrations
24.	For the recovery of citric acid after fermentation, $Ca(OH)_2$ is added to the slurry to	precipitate calcium carbonate	precipitate calcium citrate	precipitate calcium phosphate	precipitate calcium sulphate	precipitate calcium citrate
25.	Which of the following microorganism is used for the	*Lactobacillus bulgaricus*	*Saccharomyces cerevisiae*	*Aspergillus niger*	*Streptococcus lactis*	*Aspergillus niger*

	production of citric acid?					
26.	Sugar content of the fermentation medium for citric acid is maintained at	10-15%	15-20%	20-25 %	25-30 %	20-25 %
27.	Spirit vinegar is produced from	fruit juices	malted grain	ethanol	ale	ethanol
28.	What is the pH of the medium when sucrose is used as substrate for the production of citric acid?	3	4	5	6	3
29.	What is the pH of the medium when molasses is used as substrate for the production of citric acid?	3	4	5	6	5
30.	Which of the following nitrogen sources is added in the fermentation medium of citric acid production?	Ammonium salt	acetone	sodium salt	Peptone	Ammonium salt
31.	Alegar is a type of vinegar produced from	fruit juices	malted grain	ethanol	ale	ale
32.	During recovery step of citric acid, calcium citrate formed is treated with which of the following acid to precipitate calcium?	HCl	HNO_3	H_2SO_4	BaSO4	H_2SO_4
33.	Vinegar production consists of	aerobic fermentation	anaerobic fermentation	aerobic fermentation followed by anaerobic fermentation	anaerobic fermentation followed by aerobic fermentation	anaerobic fermentation followed by aerobic fermentation
34.	Cider vinegar is produced from	fruit juices	malted grain	ethanol	ale	fruit juices
35.	Malt vinegar is produced from	fruit juices	malted grain	ethanol	ale	malted grain
36.	In nature high concentrations of citric acid remain present in,	Vegetables	Citrus fruits	Grains	carbohydrates	Citrus fruits
37.	The strain of fungi used for large scale production of citric acid is	Penicillium chrysogenum	Saccharomyces cerevisae	Aspergillus niger	penicillium citrinum	Aspergillus niger
38.	In 1880; Citric acid was first synthesized from	Glycerol	Glucose	Fructose	Acetone	Glycerol
39.	Which is the method of choice for citric acid purification?	Precipitation	Filtration	Centrifugation	distillation	Filtration

40.	When energy-depleted elements associated with a proton are accepted by an organic molecule, the process is called	fermentation	anaerobic	aerobic	catabolism	fermentation
41.	An example of anaerobic would be	production of sulfates from H2S	production of methane by methanogens	glycolysis by purple bacteria	utilization of methane by methanogens	production of methane by methanogens
42.	The end product of glycolysis is	NADH	acetyl-CoA	lactate	pyruvate	pyruvate
43.	The final output of the Krebs cycle includes all of the following except	NADP	$FADH_2$	ATP	CO_2	NADP
44.	The usefulness of fermentation as a means of deriving energy is limited because	it cannot generate enough ATP	it produces too much NH_2	the end products are toxic to the producer	it uses more energy than it produces	the end products are toxic to the producer
45.	Which of the following is not a product of fermentation?	pyruvate	glucose	acetyl-CoA	CO_2	acetyl-CoA
46.	Hans Krebs discovered	glycolysis	fermentation	the oxidation of pyruvate	the citric acid cycle	the citric acid cycle
47.	In aerobic cellular respiration, which generates more ATP, substrate-level phosphorylation or chemiosmosis?	substrate-level phosphorylation	chemiosmosis	both generate the same amount of ATP	neither generates any ATP	chemiosmosis
48.	What role does O_2 play in aerobic respiration?	it plays no rol	it combines with acetyl-CoA at the start of the Krebs cycle	it combines with H_2O to help drive the formation of ATP	it is the final electron acceptor at the end of the electron transport chain	it is the final electron acceptor at the end of the electron transport chain
49.	During aerobic respiration, $FADH_2$ is produced in	glycolysis	the oxidation of pyruvate	the Krebs cycle	fermentation	the Krebs cycle
50.	Glucose breakdown is	coupled with ATP breakdown	combined with carbon dioxide to form oxygen plus water	an oxidation-reduction reaction	the removal of electrons from O2 that are eventually received by substrates	an oxidation-reduction reaction
51.	Which pathway for aerobic cellular respiration is located in the	glycolysis	Krebs cycle	electron transport system	transition reaction	glycolysis

	cytoplasm of the cell?					
52.	During aerobic cellular respiration, which molecule originates from the digestive system?	oxygen	carbon dioxide	ATP	glucose	glucose
53.	Which of the following pathways does NOT occur in aerobic cellular respiration?	glycolysis	Krebs cycle	electron transport system	Calvin cycle	Calvin cycle
54.	Which coenzyme is used in cellular respiration?	NAD^+	NADP	alcohol dehydrogenase	cytochrome oxidase	NAD^+
55.	Pyruvate is the end product of the _____reactions.	Krebs cycle	alvin cycle	electron transport system	glycolysis	glycolysis
56.	Which of the following pathways will use coenzyme A during aerobic cellular respiration?	glycolysis	transition reaction	Krebs cycle	electron transport system	transition reaction
57.	Which pathway will result in the production of four carbon dioxide molecules, two ATP molecules, $NADH_2$ and $FADH_2$?	glycolysis	transition reaction	Krebs cycle	Calvin cycle	Krebs cycle
58.	Which of the following molecules is NOT formed as a result of the Krebs cycle during aerobic cellular respiration?	carbon dioxide	ATP	water	NADH	water
59.	Which molecule is the final acceptor of electrons at the end of the electron transport system in aerobic cellular respiration?	oxygen	carbon dioxide	lactate	citrate	oxygen
60.	Based on chemiosmosis, hydrogen ions accumulate in the_____of the mitochondrion to create a large electrochemical gradient for aerobic cellular respirati	intermembrane space	intramembrane spac	cristae	cristae	intermembrane space
61.	Ethanol is	primary alcohol	secondary alcohol	tertiary alcohol	neopentyl alcohol	primary alcohol

UNIT IV
Syllabus

Fermentation
Aerobic and anaerobic fermentation. Production of ethyl alcohol and citric acid.

Fermentation

Fermentation is a metabolic process that consumes sugar in the absence of oxygen. The products are organic acids, gases, or alcohol. It occurs in yeast and bacteria, and also in oxygen-starved muscle cells, as in the case of lactic acid fermentation.

Fermentation simply means the production of alcohol: grains and fruits are fermented to produce beer and wine. If a food soured, one might say it was fermented. Here are some definitions of fermentation. They range to informal, general usage to more scientific definitions.

1. Preservation methods for food using microorganisms (general use).
2. Any process that produces alcoholic beverages or acidic dairy products (general use).
3. Any large-scale microbial process occurring with or without air (common definition used in industry).
4. Any energy-releasing metabolic process that takes place only under anaerobic conditions (becoming more scientific).
5. Any metabolic process that releases energy from a sugar or other organic molecule, does not require oxygen or an electron transport system, and uses an organic molecule as the final electron acceptor (most scientific).

Sugars are the most common substrate of fermentation, and typical examples of fermentation products are ethanol, actic acid, citric acid, carbondioxide and hydrogen gas. However, more exotic compounds can be produced by fermentation, such asbutyric acid and acetone.

Aerobic Fermentation

The term "Aerobic fermentation" is misnamed because fermentation is an anaerobic process. Simply, this is a process of burning simple sugars to energy in cells; more scientifically, it can be called **aerobic respiration**.

It can be defined as the process of producing cellular energy in the presence of oxygen. It roughly produces 36 ATP molecules by breaking down foods in the mitochondria. It includes three steps namely glycolysis, citric acid cycle, and electron transport system. It consumes Carbohydrates, Fats, and Proteins; the final products of this process are carbon dioxide and water.

Simplified reaction

$C_6H_{12}O_6$ (s) + 6 O_2 (g) → 6 CO_2 (g) + 6 H_2O (l) + heat; $\Delta G = -2880$ kJ per mol of $C_6H_{12}O_6$

(-) indicates that reaction can occur spontaneously

1. Glycolysis

It is a metabolic pathway that occurs in the cytosol of cells in living organisms. This can function either in the presence or absence of oxygen. It produces pyruvate in the presence of oxygen. Two ATP molecules are produced as the net energy form.

The overall reaction can be expressed as follows:

Glucose + 2 NAD^+ + 2 P_i + 2 ADP → 2 pyruvate + 2 NADH + 2 ATP + 2 H^+ + 2 H_2O + heat

Pyruvate is oxidized to acetyl-CoA and CO_2 by the pyruvate dehydrogenase complex (PDC). It's located in mitochondria of eukaryotic and cytosol of prokaryotes.

2. Citric Acid Cycle

Citric Acid Cycle is also called Krebs cycle and occurs in the mitochondrial matrix. This is a 8 step process involving different types of enzymes and co-enzymes. The net gain from one glucose molecule is 6 NADH, 2 $FADH_2$, and 2 GTP.

Anaerobic Fermentation

Anaerobic fermentation is a process that causes the breakdown of organic compounds. This process reduces nitrogen to organic acids and ammonia. Carbon from organic compounds is released mainly as methane gas (CH_4). A small portion of carbon may be respired as CO_2. The decomposition technique occurred here is used in composting. The decomposition occurs as four stages namely: hydrolysis, acidogenesis, acetogenesis, and methanogenesis.

1. Hydrolysis

$C_6H_{10}O_4 + 2H_2O \rightarrow C_6H_{12}O_6 + 2H_2$

2. Acidogenesis

$C_6H_{12}O_6 \leftrightarrow 2CH_3CH_2OH + 2CO_2$

$C_6H_{12}O_6 + 2H_2 \leftrightarrow 2CH_3CH_2COOH + 2H_2O$

$C_6H_{12}O_6 \rightarrow 3CH_3COOH$

3. Acetogenesis

$CH_3CH_2COO^- + 3H_2O \leftrightarrow CH_3COO^- + H^+ + HCO_3^- + 3H_2$

$C_6H_{12}O_6 + 2H_2O \leftrightarrow 2CH_3COOH + 2CO_2 + 4H_2$

$CH_3CH_2OH + 2H_2O \leftrightarrow CH_3COO^- + 2H_2 + H^+$

4. Methanogenesis

$CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O$

$2C_2H_5OH + CO_2 \rightarrow CH_4 + 2CH_3COOH$

$CH_3COOH \rightarrow CH_4 + CO_2$

What is the difference between Aerobic and Anaerobic Fermentation?

Characteristics of Aerobic and Anaerobic Fermentation

1. Oxygen Usage:

Aerobic fermentation: Aerobic fermentation uses oxygen.
Anaerobic fermentation: Anaerobic fermentation does not use oxygen.

2. ATP Yield:

Aerobic fermentation: Aerobic fermentation yields 38 ATP molecules
Anaerobic fermentation: Anaerobic fermentation does not produce ATP molecules.

3. Occurrence:

Aerobic fermentation: Aerobic fermentation occur inside living organisms.
Anaerobic fermentation: Anaerobic fermentation occurs outside living organisms.

4. Microorganism's Involvement:

Aerobic fermentation: No microorganisms are involved
Anaerobic fermentation: Microorganisms are involved

5. Temperature:

Aerobic fermentation: An ambient temperature is not required for the process.
Anaerobic fermentation: Ambient temperature is required for the process.

6. Technique:

Aerobic fermentation: Aerobic fermentation is an energy production method.
Anaerobic fermentation: Anaerobic fermentation is a decomposition method.

7. Stages:

Aerobic fermentation: Stages include Glycolysis, Krebs cycle, and electron transport system
Anaerobic fermentation: Anaerobic fermentation has no glycolysis or other stages.

8. CH_4 Production:

Aerobic fermentation: Aerobic fermentation does not produce CH_4 .
Anaerobic fermentation: Anaerobic fermentation produces CH_4.

Key Difference – Aerobic vs Anaerobic Fermentation

The term Aerobic fermentation is a misnomer since fermentation is anaerobic, i.e., it does not require Oxygen. Thus, aerobic fermentation does not actually refer to a fermentation process; this process refers to the process of cellular respiration. The key difference between aerobic and anaerobic fermentation is that aerobic fermentation uses oxygen whereas anaerobic fermentation does not use oxygen.

Some examples of anaerobic **respiration include alcohol** fermentation**, lactic acid fermentation and in decomposition of organic matter.**

Aerobic fermentation **is a metabolic process by which cells metabolize sugars via fermentation in the presence of oxygen and occurs through the repression of normal respiratory metabolism.**

Preparation of ethanol by fermentation

Background:

Many chemical compounds are prepared by the action of microorganisms (bacteria or yeast most commonly) acting on appropriate starting materials. One of the oldest of such processes is the preparation of ethyl alcohol (ethanol) from carbohydrates (sugars) by fermentation.
The microorganism is yeast which will convert glucose to ethanol by fermentation according the following chemical reaction:

$$C_6H_{12}O_6 \rightarrow 2\ C_2H_5OH + 2\ CO_2$$

As the alcohol concentration increases, the yeast suffers inhibition and ultimately death. The maximum concentration of alcohol in water that most yeast can tolerate is about 12%, which explains why wine, a product prepared by natural fermentation, has an alcoholic content of about 12%. The yeast literally kills itself by converting the sugars found in grapes into ethyl alcohol.

The product of fermentation is a mixture of yeast, alcohol, and water, from which the alcohol can be purified by a technique known as distillation. When a mixture of ethyl alcohol and water is heated, the lower boiling point (that of ethyl alcohol) will be reached first and that substance will begin to be vaporize while the other substance will remain behind in the liquid state. At this point the vapours contain a very high percentage of alcohol molecules and can be condensed and collected to achieve a product of high alcohol content. Ethyl alcohol undergoes many reactions, some of which can be used to indicate the presence of the alcohol.

One such reaction is called the iodoform reaction in which iodine in a basic environment oxidises ethanol to form iodoform, which is a yellow solid that has historically been used as an antiseptic.

That reaction is: $C_2H_5OH + 4\ I_2 + 6\ OH^- \rightarrow CHI_3\ (s) + HCOO^- + 5\ I^- + 5\ H_2O$

The chemical equations below summarize the fermentation of sucrose ($C_{12}H_{22}O_{11}$) into ethanol (C_2H_5OH). Alcoholic fermentation converts one mole of glucose into two moles of ethanol and two moles of carbon dioxide, producing two moles of ATP in the process.

The overall chemical formula for alcoholic fermentation is:

$$C_6H_{12}O_6 \rightarrow 2\ C_2H_5OH + 2\ CO_2$$

Sucrose is a dimer of glucose and fructose molecules. In the first step of alcoholic fermentation, the enzyme invertase cleaves the glycosidic linkage between the glucose and fructose molecules.

$$C_{12}H_{22}O_{11} + H_2O + \text{invertase} \rightarrow 2\ C_6H_{12}O_6$$

Next, each glucose molecule is broken down into two pyruvate molecules in a process known as glycolysis. Glycolysis is summarized by the equation:

$$C_6H_{12}O_6 + 2\ ADP + 2\ P_i + 2\ NAD^+ \rightarrow 2\ CH_3COCOO^- + 2\ ATP + 2\ NADH + 2\ H_2O + 2\ H^+$$

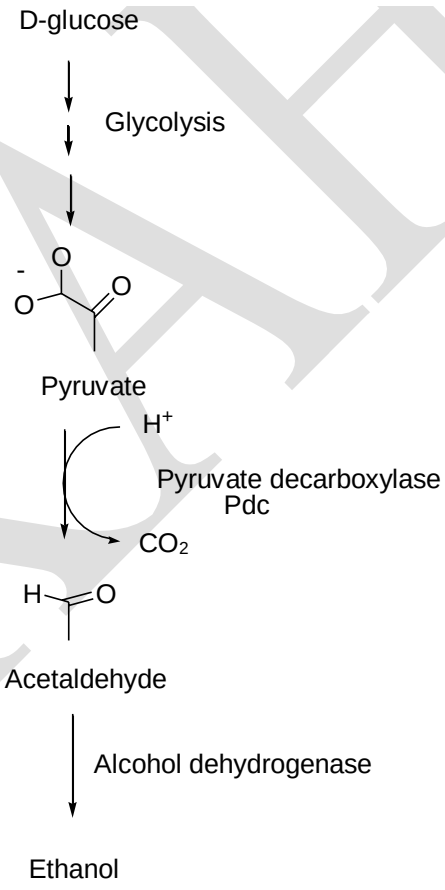
The chemical formula of pyruvate is CH_3COCOO^-. P_i stands for the inorganic phosphate. Finally, pyruvate is converted to ethanol and CO_2 in two steps, regenerating oxidized NAD+ needed for glycolysis:

1. $CH_3COCOO^- + H^+ \rightarrow CH_3CHO + CO_2$

   catalyzed by **pyruvate decarboxylase**

2. $CH_3CHO + NADH + H^+ \rightarrow C_2H_5OH + NAD^+$

   This reaction is catalyzed by **alcohol dehydrogenase** (ADH1 in baker's yeast)



A scheme of transformation of glucose to alcohol by alcoholic fermentation.

Citric acid

Applications of citric acid

Citric acid is mainly used in food industry because of its pleasant acid taste and its high solubility in water. The pharmaceutical and cosmetic industries retain 10% of its utilization and the remainder is used for various other purposes. The Table below presents main applications of citric acid.

Table: Applications of Citric acid

Industry	Applications
Beverages	Provides tartness and complements fruits and berries flavours. Increase the effectiveness of antimicrobial preservatives. Used in pH adjustment to provide uniform acidity.
Jellies, Jams	Provide tartness, pH adjustment
Candy	Provide tartness, Minimizes sucrose inversion. Produces dark color in hard candies. Acts as acidulant.
Frozen fruit	Lowers pH to inactivate oxidative enzymes. Protects ascorbic acid by inactivating trace metals.
Dairy products	As emulsifier in ice creams and processed cheese; acidifying agent in many cheese products and as an antioxidant
Pharmaceuticals	As effervescent in powders and tablets in combination with bicarbonates. Provides rapid dissolution of active ingredients. Acidulant in mild astringent formulation, anticoagulant
Cosmetics and toiletries	pH adjustment, antioxidant as a metallic-ion chelator, buffering agent.
Industrial applications	Sequestrant of metal ions, buffer agent
Metal cleaning	Removes metal oxides from surface of the ferrous and non ferrous metals for preperational and operational cleaning or iron and copper oxides
Others	In electroplating, copper plating,metal cleaning, leather tanning, printing inks, bottle washing compounds, floor cement, textiles, waste treatment.

Citric acid is a commercially important product that has been obtained by submerged fermentation of glucose or sucrose by *Aspergillusniger*. Yields of citric acid varied considerably and were found to depend significantly on the strain of *Aspergillusniger* used and the following factors: the type of raw material fermented, the initial moisture content of the substrate, the amount of methyl alcohol present, and the fermentation time and temperature. Under favourable conditions, yields from more than 50 to nearly 90% were obtained on the basis of the amount of carbohydrate consumed.

Possible Questions

PART A (1 Marks Questions)

Online Examination

PART B (2 Marks Questions)

1. State aerobic fermentation.
2. What is anaerobic fermentation?
3. Define cellular inspiration.
4. What is meant by fermentation?
5. What is benedict reagent? Draw the structure.

PART C (6 Marks Questions)

1. Write notes on aerobic fermentation.
2. Briefly explain about anaerobic fermentation.
3. Describe the fermentation mechanism.
4. Explain the production of ethyl alcohol from molasses.
5. Describe the production of ethyl alcohol from starch.
6. How will you prepare ethyl alcohol from the following
   (i) Indirection hydration of ethylene
   (ii) Direction hydration of ethylene
   (iii) From acetylene
7. Give the fermentation production of citric acid from glucose.
8. Writes note on synthetic preparation of citric acid.
9. How will you citric acid from molasses.
10. What is fermentation? How will you prepared citric acid from starch?

KARPAGAM ACADEMY OF HIGHER EDUCATION

Class: II B.Sc Chemistry **Course Name: Pharmaceutical Chemistry**
Course Code: 18CHU304A **Unit: I** **Batch-2018-2021**

S. No.	Question	Option A	Option B	Option C	Option D	Answer
1.	Which vitamins helps to convert ferric ion in to ferrous ion	Vitamin D	Vitamin E	Vitamin C	Vitamin K	Vitamin C
2.	Penicillin was discovered by	Alxender Fleming	Lueis Pasteur	Ehrlich	S. Waksmann	Alxender Fleming
3.	Which one is differ from other three?	Penicillin	Streptomycin	Gentamycin	Neomycin	Penicillin
4.	Functional group present In the antibiotic penicillin-G is	Lactum	Lactone	Acetal	Nitro	Lactum
5.	Chloramphenicol is also known as	Tetracycline	Chloromycetin	Penicillin	Streptomyces venezulae	Streptomyces venezulae
6.	The atoms present in the penicillin	C,H,O	C,H,O,S	C,H,N,O,S,R	C,H,N,O,R	C,H,N,O,S,R
7.	Optically active penicillin is	Mono carboxylic	Dicarboxylic	Tri carboxylic	Tetra carboxylic	Mono carboxylic
8.	Deficiency of vitamin B causes	Beriberi	Scurvy	Night blindness	Sterility	Beriberi
9.	Which vitamin is used in the treatment of anaemia is	D	B_{12}	C	A	B_{12}
10.	Which of the vitamin decomposed when boiling?	Vitamin K	Vitamin E	Vitamin C	Vitamin A	Vitamin C
11.	Deficiency of vitamin C causes a disease known as	Rickets	Blindness	Anemia	Scurvy	Scurvy
12.	Which is water soluble vitamin	Vitamin A	Vitamin B	Vitamin E	Vitamin K	Vitamin B
13.	Ascorbic acid is also known as	Vitamin A	Vitamin K	Vitamin C	Vitamin H	Vitamin C
14.	Ascorbic acid has a	One assymmetric carbon	Two assymmetric carbon	Three assymmetric carbon	Four assymmetric carbon	One assymmetric carbon
15.	Ascorbic acid is soluble in	Benzene	Chloroform	Water	Fatty acids	Water
16.	Vitamin B_{12} also known as	Thiamine	Pyridoxine	Riboflavin	Cyanogobalamine	Cyanogobalamine
17.	Vitamin B12 deficiency causes	Degradation of spinal cord	Causes sterility	Bleeding	Deformity	Degradation of spinal cord

18.	The deficiency of vitamin B_{12} causes	Cheilosis	Sterility	Anemia	Blindness	Cheilosis
19.	Cheilosis formed by deficiency of	Retinol	Thiamine	Riboflavin	Pyridoxine	Riboflavin
20.	Which is not true about streptomycin?	it is used in the treatment of tuberculosis	it is an aldehyde	it is a base	it is a macrocyclic compound	it is a macrocyclic compound
21.	Vitamin B2 is called as	ascorbic acid	pyridoxine	riboflavin	retinol	riboflavin
22.	On a per weight basis which foodstuffs generate most energy?	Proteins	Carbohydrates	Fats	Fibre	Fats
23.	Why do water soluble vitamins have to be taken in the diet more frequently than fat soluble vitamins?	They are metabolised faster than the fat soluble vitamins	There are no extensive stores as any excess taken in the diet is excreted	Only small amounts are present in foodstuffs	They are destroyed by gastrointestinal flora	There are no extensive stores as any excess taken in the diet is excreted
24.	Which vitamin deficiency manifests itself as impaired wound healing, gastrointestinal bleeding and sore and bleeding oral tissues?	Vitamin A	Folate	Vitamin C	Vitamin D	Vitamin C
25.	Vitamins are classified	organic and inorganic.	fat-soluble and water soluble.	essential and nonessential.	elements and compounds.	fat-soluble and water soluble.
26.	All of the following diseases may lead to poor absorption of vitamins A, E, and K except:	Crohn's disease.	cystic fibrosis.	celiac disease.	scurvy.	scurvy.
27.	Which of the following water-soluble vitamins does not pose a particularly high risk of toxicity?	vitamin B-6	thiamin	niacin	vitamin C	thiamin
28.	Sources of vitamin C does not includes	UV from sun	beef liver	citrus fruits	leafy green vegetables	UV from Sun
29.	Vitamin C is also known as	acetic acid	citric acid	absorbic acid	ascorbic acid	ascorbic acid
30.	Vitamin C is required for the production and maintenance of:	Collagen	Hormone	Ascorbic Acid	Red Blood Cells	Collagen
31.	Vitamin C deficiency is called:	Scurvy	Cold	Cancer	Rickets	Scurvy
32.	Which of the following is a function of Vitamin B-12?	Influences the cells that build bone tissue	Is essential to the formation of bone	Helps maintain acid-base balance	Maintains the sheaths that surround and	Maintains the sheaths that surround and

					protect nerve fibers	protect nerve fibers
33.	Vitamin B-12 deficiency caused by lack of intrinsic factor is called:	Pernicious anemia	Poor circulation of the red blood cells	Beri Beri		Pernicious anemia
34.	A common function of Thiamin, Riboflavin and Niacin is that	They all are used in synthesis of blood clotting proteins	They all work as a part of a coenzyme used in energy metabolism	They all help to strengthen blood vessel walls	They are used to stabilize cell membranes	They all work as a part of a coenzyme used in energy metabolism
35.	The vitamin Folate works together with_____to produce new red blood cells.	Vitamin D	Vitamin A	Vitamin B-12	Vitamin C	Vitamin B-12
36.	Which of the following is a function of Vitamin B-12?	Red blood cell formation	Myelin sheath that protects nerve biers	Vision	Both A and B	Both A and B
37.	Vitamin C helps maintenance and repair of collagen which	Forms the base for all connective tissue in the body	Aids in digestive processes	Promotes good eyesight	Prevents PMS symptoms	Forms the base for all connective tissue in the body
38.	Ascorbic acid acts as an	reducing agent	oxidizing agent	oxidizing and reducing agent both	none of the above	reducing agent
39.	A deficiency of thiamin produces the disease known as	beri-beri	scurvy	cataract	anemia	beri-beri
40.	Vitamin B12 (Cobalamin) is only synthesized by	fishes	micro-organisms	plants	animals	micro-organisms
41.	The absence of ascorbic acid in the human diet gives rise to	rickets	pernicious anemia	cataract	beri-beri	pernicious anemia
42.	Cephalosporin antibiotics are used in treatment of	lung cancer	bronchitis	urinary tract infection	intestine infection	bronchitis
43.	Drugs that are synthesized in laboratories and are not available naturally are called	nucleases drugs	synthetic drugs	addictive drugs	coli bacterium drugs	synthetic drugs
44.	Which of the following is NOT a	Ampicillin	Methicillin	Penicillin	Sulfonamide	Penicillin

	semisynthetic chemotherapeutic agent?					
45.	Which antibiotic has a beta-lactam ring?	Cephalosporin	Penicillin	Tetracycline	Chloramphenicol	Penicillin
46.	Which of the following is used only in life-threatening situations when no other drug is adequate?	Cephalosporin	Penicillin	Chloramphenicol	Streptomycin	Chloramphenicol
47.	The most selective antibiotics are those that interfere with the synthesis of	bacterial DNA	bacterial RNA.	bacterial cell walls.	bacterial plasma membrane.	bacterial cell walls.
48.	The larger the_____, the better the chemotherapeutic agent	therapeutic index	toxic dose	therapeutic dose	selective toxicity	therapeutic index
49.	Most antibiotics are isolated from	viruses.	fungi.	aquatic microorganisms.	soil microorganisms	soil microorganisms
50.	Misuse of antibiotic streptomycin can cause	dumb	deafness	mental retardness	memory loss	deafness
51.	Chemotherapeutic chemical substances which are used to treat infectious diseases are	antibseptics	antibiotics	antifungal	anti inflammatory	antibiotics
52.	Which of the following scientists discovered streptomycin, an antimicrobial treatment for tuberculosis?	Paul Ehrlich	Sahachiro Hata	Gerhard Domagk	Selman Waksman	Selman Waksman
53.	The minimal inhibitory concentration (MIC) is	The lowest concentration of a drug that inhibits infection	The lowest concentration of a drug that kills the host	The lowest concentration of a drug that prevents growth of a particular pathogen	The lowest concentration of a drug that kills the pathogen	The lowest concentration of a drug that prevents growth of a particular pathogen
54.	The most selective antibiotics are those that	Inhibit cell wall synthesis	Inhibit protein synthesis	Act as metabolic antagonists	Inhibit nucleic acid synthesis	Inhibit cell wall synthesis
55.	The most important feature of the penicillin molecule is the	Amino sugars	Lactone groups	Beta-lactam ring	Multi-ring structures	Beta-lactam ring
56.	In addition to penicillins, which group of antibiotics also exhibits a beta-lactam ring structure?	Trimethoprim	Sulfonamides	Cephalosporins	Chloramphenicol	Cephalosporins

57.	Which antibiotic is fairly toxic to humans and, as a result, is used only in life-threatening situations when no other drug is adequate?	Penicillin	Sulfonamides	Chloramphenicol	Quinolones	Chloramphenicol
58.	Which of the following groups of antibiotic drugs functions as a metabolic antagonist?	Penicillins	Sulfonamides	Aminoglycosides	Quinolones	Sulfonamides
59.	Sulfonamides work by	Inhibiting folic acid synthesis	Inhibiting cell wall synthesis	Inhibiting nucleic acid synthesis	Lysing plasma membranes	Inhibiting folic acid synthesis
60.	The first drug to be developed to combat HIV infection was	Acyclovir	Azidothymidine (AZT)	Amantadine	Tamiflu	Azidothymidine (AZT)

UNIT V
Syllabus

Production of antibiotics and vitamins
Production of (i) Antibiotics; Penicillin, Cephalosporin, Chloromycetin and Streptomycin, (iii) Lysine,Glutamic acid, Vitamin B2, Vitamin B12 and Vitamin C.

Antibiotics:

Antibiotics are powerful medicines that fight bacterial infections. Used properly, antibiotics can save lives. They either kill bacteria or keep them from reproducing. Your body's natural defenses can usually take it from there.Antibiotics do not fight infections caused by viruses, such as

- Colds
- Flu
- Most coughs and bronchitis
- Sore throats, unless caused by bacteria

If a virus is making you sick, taking antibiotics may do more harm than good. Using antibiotics when you don't need them, or not using them properly, can add to antibiotic resistance. This happens when bacteria change and become able to resist the effects of an antibiotic.

What are antibiotics?

Antibiotics are strong medicines used to treat infections, including life-threatening contagious diseases. But antibiotics can cause more harm than good when they aren‟t used the right way. You can protect yourself and your family by knowing when you should use antibiotics and when you should not.

Do antibiotics work against all infections?

No. Antibiotics only work against infections caused by bacteria, fungi and certain parasites. They don‟t work against any infections caused by viruses. Viruses cause colds, the flu and most coughs and sore throats.

What is "antibiotic resistance?"

"Antibiotic resistance" and "bacterial resistance" are two ways of describing the same thing. Usually, antibiotics kill bacteria or stop them from growing. However, some bacteria have become resistant to some types of antibiotics. This means that the antibiotics no longer work against them. Bacteria become resistant more quickly when antibiotics are used too often or are not used correctly (such as not taking a full course of antibiotics as prescribed by your doctor).

Bacteria that are resistant to one antibiotic can sometimes be treated with other antibiotics. These other medicines may have to be given intravenously (through a vein) in a hospital. A few kinds of bacteria are resistant to all antibiotics and are now untreatable.

Most antibiotics fall into their individual antibiotic classes. An antibiotic class is a grouping of different drugs that have similar chemical and pharmacologic properties. Their chemical structures may look comparable, and drugs within the same class may kill the same or related bacteria.

1. Penicillins

Another name for this class is the beta-lactam antibiotics, referring to their structural formula. The penicillin class contains five groups of antibiotics: aminopenicillins, antipseudomonalpenicillins, beta-lactamase inhibitors, natural penicillins, and the penicillinase resistant penicillins. Common antibiotics in the penicillin class include:

- penicillin V potassium
- amoxicillin
- amoxicillin/clavulanate (Augmentin)

2. Tetracyclines

Tetracyclines are broad-spectrum against many bacteria and treat conditions such as acne, urinary tract infections (UTIs), intestinal tract infections, eye infections, sexually transmitted diseases, periodontitis (gum disease), and other bacterial infections. The tetracycline class contains well-known drugs such as:

- doxycycline

- tetracycline
- minocycline

3. Cephalosporins

There are **five generations of cephalosporins**, with increasing expanded coverage to include gram-negative infections. Cephalosporins treat many infections, including strep throat, ear infections, urinary tract infections, skin infections, and meningitis. The fifth generation cephalosporin ceftaroline (Teflaro) is active against methicillin-resistant *Staphylococcus aureus* (MRSA). You‟ve probably heard of common medications in this class, like:

- cefuroxime (Ceftin)
- ceftriaxone (Rocephin)
- Cefdinir (Omnicef)

4. Quinolones

The quinolones, also known as the fluoroquinolones, are a synthetic, bactericidal antibacterial class with a broad-spectrum of activity. The quinolones can be used for difficult-to-treat urinary tract infections when other options are aren‟t effective, hospital-acquired pneumonia, bacterial prostatitis, and even anthrax or plague. Familiar names in the fluoroquinolone class include:

- ciprofloxacin (Cipro)
- levofloxacin (Levaquin)
- moxifloxacin (Avelox)

5. Lincomycins

This class has activity against gram-positive aerobes and anaerobes (bacteria that can live without oxygen), as well as some gram-negative anaerobes. The lincomycin derivatives may be used to treat serious infections like pelvic inflammatory disease, intra-abdominal infections, lower respiratory tract infections, and bone and joint infections. These drugs include:

- clindamycin (Cleocin)
- lincomycin (Lincocin)

6. Macrolides

The macrolides can be used to treat community-acquired pneumonia, pertussis (whooping cough), or for uncomplicated skin infections, among other susceptible infections. Ketolides are a newer generation of antibiotic developed to overcome macrolide bacterial resistance. Frequently prescribed macrolides are:

- azithromycin (Zithromax)
- clarithromycin (Biaxin)
- erythromycin

7. Sulfonamides

Sulfonamides are effective against some gram-positive and many gram-negative bacteria, but resistance is widespread. Common uses for sulfonamides include UTIs, treatment or prevention of pneumocystis pneumonia, or ear infections (otitis media). Familiar names include:

- sulfamethoxazole-trimethoprim (Bactrim, Bactrim DS, Septra)
- sulfasalazine (Azulfidine)
- sulfisoxazole (combined with erythromycin)

8. Glycopeptide Antibiotics

Members of this group may be used for treating methicillin-resistant *staphylococcus aureus* (MRSA) infections, complicated skin infections, C. difficile-associated diarrhea, and enterococcal infections such as endocarditis which are resistant to beta-lactams and other antibiotics. Common drug names include:

- dalbavancin (Dalvance)
- oritavancin (Orbactiv)
- telavancin (Vibativ)
- vancomycin (Vancocin)

9. Aminoglycosides

Aminoglycosides inhibit bacterial synthesis by binding to the 30S ribosome and act rapidly as bactericidal antibiotics (killing the bacteria). These drugs are usually given intravenously (in a vein through a needle). Common examples in this class are:

- gentamicin
- tobramycin
- amikacin

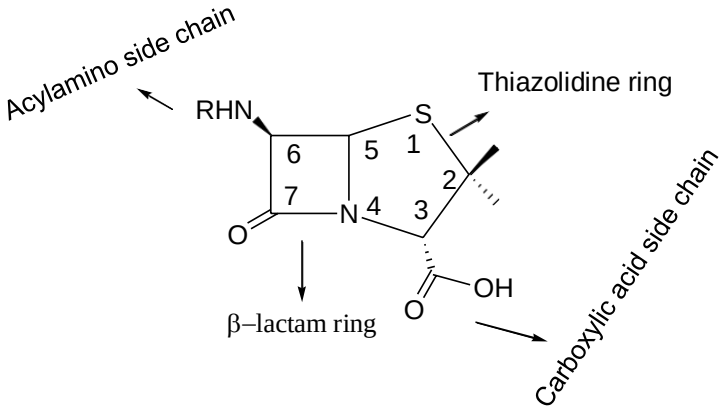
10. Carbapenems

These injectable beta-lactam antibiotics have a wide spectrum of bacteria-killing power and may be used for moderate to life-threatening bacterial infections like stomach infections, pneumonias, kidney infections, multidrug-resistant hospital-acquired infections and many other types of serious bacterial illnesses. Members of this class include:

- imipenem/cilastatin (Primaxin)
- meropenem (Merrem)
- doripenem (Doribax)
- ertapenem (Inanz)

Penicillins

Structure



Commercial Production of Penicillin:

The commercial production of most of the antibiotics follows a similar plan. The major differences relate to the microorganism, media composition, and extraction procedure. For penicillin production, inoculum of a high yielding strain of *P. chrysogenum* is prepared as follows: inoculum is first cultured in flasks in wheat bran nutrient solution for 1 week at 24°C.

The culture is then transferred to inoculum tanks, and grown for 1-2 days under aeration; this supports heavy mycelial growth. The inoculum is now added to very large fermentors containing the production medium, which consists of 10 per cent total glucose/molasses, 4-5% corn-steep liquor solids, 0.5-0.8 per cent phenylacetic acid and 0.5% vegetable oil; pH is adjusted to 6.0 and temperature is regulated at 25- 26°C.

Earlier media contained lactose, but it is no longer used. The fermentation is carried out under aerobic conditions, and nutrient supply is maintained by regular feeding (fed-batch culture). The fungus grows in a submerged culture mostly as mycelial balls.

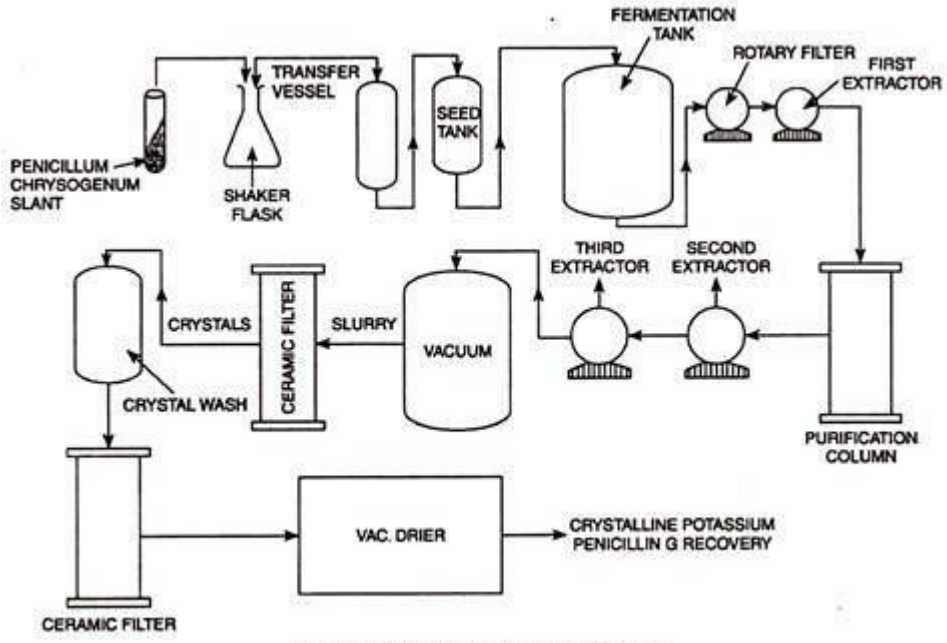


FIG. 40.7. Commercial production of penicillin

The fermentation is carried out for 7 days. Initially, mycelial growth occurs, and carbohydrates are used up. This reduces the carbohydrate level in the medium; this favours penicillin production, which begins from the second day of fermentation. The pH of medium

rises to 8.0 by the 7th day, and penicillin production stops at this stage. Phenylacetic acid is the precursor for the benzene ring side chain of Penicillin G.

The presence of precursor promotes the production of Penicillin G. At the end of fermentation period, the fungal biomass is separated by filtration and used as animal feed supplement. Penicillin G is present in the broth, and is extracted using an organic solvent. Penicillin G is finally purified as potassium salt; it is converted to 6-aminopenicillanic acid (6-APA) cither chemically or biologically.

The side chain of 6-APA is variously modified to obtain a variety of derivatives of penicillin, which are used in medicine. In addition, several other fungal metabolites are used as antibiotics.

Chloramphenicol

Chloramphenicol is an antibiotic useful for the treatment of a number of bacterial infections. This includes as an eye ointment to treat conjunctivitis. By mouth or by injection into a vein it is used to treat meningitis, plague, cholera, and typhoid fever. Its use by mouth or by injection is only recommended when safer antibiotics cannot be used and if used monitoring both blood levels of the medication and blood cell levels every two days is recommended during treatment. Chloramphenicol is a broad-spectrum antibiotic that typically stops bacterial growth by stopping the production of proteins

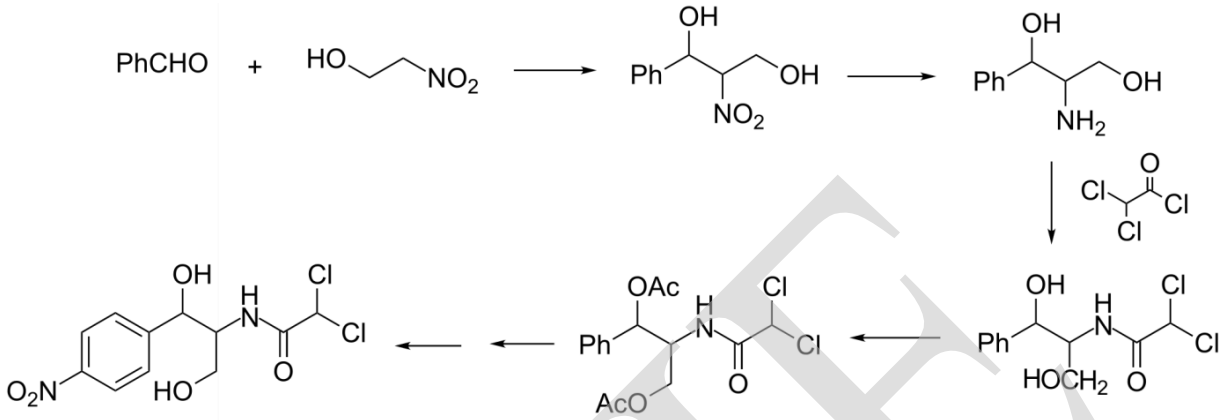
Chloramphenicol was first described as a new antibiotic produced by cultures of an actinomycete isolated from soil by Ehrlich et al. (1947). The soil samples from which the strains were isolated were collected from a mulched field near Caracas, Venezuela (strain ATCC 10712) and from a compost soil on the horticultural farm of the Illinois Agricultural Experiment Station at Urbana (strain ATCC 10595), respectively. It was demonstrated by Ehrlich et al. (1948) that this actinomycete was a new species.

Production and stability in soil

Gottlieb &Siminoff (1952) studied the adsorption, stability, and rate of production of chloramphenicol in soil under different laboratory conditions. Chloramphenicol was poorly adsorbed to soil. When sterilized soil was infested with *S. venezuelae* and was incubated for long periods, the authors were able to show the presence in soil of chloramphenicol formed

by the microorganism following a lag phase of several weeks. The highest concentration measured was 1.12 mg/kg.

Synthesis of chloramphenicol



Vitamin C

The chemical name of ascorbic acid (V**itamin C**) is L-ascorbic acid. The empirical formula is $C_6H_80_6$, and the molecular weight is 176.13. The synthesis of ascorbic acid was achieved by Reichstein in 1933, followed by industrial **production**of ascorbic acid two years later by Roche.

Ascorbic acid (vitamin C) is a water-soluble vitamin. Ascorbic acid (Vitamin C) is freely soluble in water; sparingly soluble in alcohol; insoluble in chloroform, in ether, and in benzene. It occurs as a white or slightly yellow crystal or powder with a slight acidic taste. It is an antiscorbutic product. On exposure to light, it gradually darkens. In the dry state, it is reasonably stable in air, but in solution it rapidly oxidizes.

Production

Vitamin C has been produced commercially by extraction from plants, by chemical synthesis, by fermentation and by mixed fermentation/chemical synthesis methods. Fermentation is a chemical reaction in which a micro-organism or enzyme causes an organic compound to split into simpler substances. The manufacture of vitamin C is now carried out in two ways.

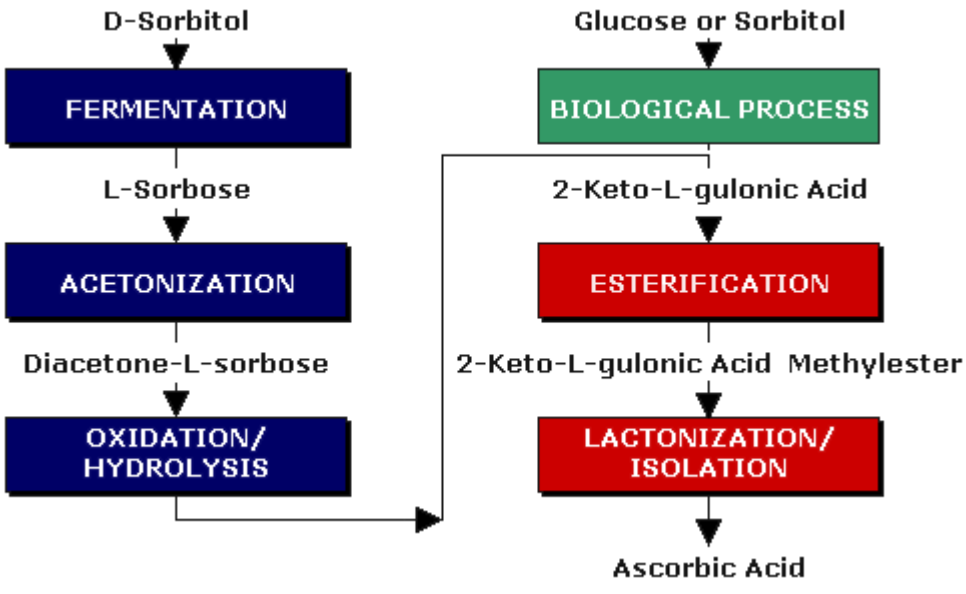
In the first step of both the traditional Reichstein process and the newer two-stage fermentation process, sorbitol is oxidized into sorbose by fermentation. All producers use the same micro-organism for this fermentation. (Sorbitol itself is made by reducing glucose at high temperature.)

Reichstein process

The Reichstein process is a mixed fermentation/chemical synthesis method. In it, sorbose is transformed into di-acetoneketogulonic acid (DAKS) in a two-stage chemical process. The first step involves a reaction with acetone. This produces di-acetone sorbose, which is then oxidized using chlorine and sodium hydroxide to produce DAKS.

In the next step, DAKS is dissolved in a mix of organic solvents and its structure is rearranged to form vitamin C, using an acid catalyst. (This stage of the process is similar in the two-stage fermentation process.)

In the last production step, the crude vitamin C is purified by recrystallization. (This step is identical for both processes.). Many technical and chemical modifications have been made to the Reichstein process to optimize and shorten the various reaction routes. Consequently, each step now has a yield of over 90 per cent. The overall yield of vitamin C from glucose is about 60 per cent.



Vitamin B12

Vitamin B_{12} also called cobalamine is a water soluble vitamin with a key role in the normal functioning of the brain and nervous system and for the formation of blood. It is one of the eight B vitamins. It is normally involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid synthesis and energy production. Vitamin B_{12} is important for the way the body works, and people who don‟t have enough of it may feel tired or have a lack of energy.

Neither plants nor animals are independently capable of constructing vitamin B_{12}. Only bacteria and archaea have the enzymes required for its biosynthesis. Species from the following genera are known to synthesise Vitamin B_{12}.

Acetobacterium, *Aerobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Bacillus*, *Clostridium* , *Corynebacterium*, *Flavobacterium*, *Lactobacillus*, *Micromonospora*, *Mycobacterium*, *Nocar dia*, *Propionibacterium*, *Protaminobacter*, *Proteus*, *Pseudomonas*, *Rhizobium*, *Salmonella*, *Se rratia*, *Streptomyces*, *Streptococcus* and *Xanthomonas*.

Industrial production of B_{12} is achieved through fermentation of selected microorganisms. *Streptomyces griseus*, a bacterium once thought to be a yeast, was the commercial source of vitamin B_{12} for many years. The species *Pseudomonas denitrificans* and *Propionibacteriumfreudenreichii subsp. shermanii* are more commonly used today.Since a number of species of Propionibacterium produce no exotoxins or endotoxins and are **g**enerally **r**ecognized **a**s **s**afe and they are presently the FDA-preferred bacterial fermentation organisms for vitamin B_{12} production

Steps involved in microbial cyanocobalamine production

Formulation of the medium

↓

Sterlization of the medium

↓

Making Starter culture

↓

Anaerobic fermentation

↓

Aerobic fermentation

↓

Recovery of cyanocobalamine

For Media Preperation

Carbon source-as

1. Corn Steep glucose
2. Beet molasses
3. Soyabean Meal

Nitrogen Sources

Ammonium Phosphate,
Ammonium Hydroxide

B_{12} is the most chemically complex of all the vitamins. The structure of B_{12} is based on a corrin ring, which is similar to the porphyrin ring found in heme, chlorophyll, and cytochrome. The central metal ion is cobalt. Four of the six coordination sites are provided by the corrin ring, and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the center of reactivity, is variable, being a cyano group (-CN), a hydroxyl group (-OH), a methyl group ($-CH_3$) or a 5'-deoxyadenosyl group (here the C5' atom of the deoxyribose forms the covalent bond with Co), respectively, to yield the four B_{12} forms mentioned below. Historically, the covalent C-Co bond is one of the first examples of carbon-metal bonds to be discovered in biology. The hydrogenases and, by necessity, enzymes associated with cobalt utilization, involve metal-carbon bonds.

Vitamin B_{12} is a generic descriptor name referring to a collection of cobalt and corrin ring molecules which are defined by their particular vitamin function in the body. All of the substrate cobalt-corrin molecules from which B_{12} is made must be synthesized by bacteria. After this synthesis is complete, the human body has the ability (except in rare cases) to convert any form of B_{12} to an active form, by means of enzymatically removing certain prosthetic chemical groups from the cobalt atom and replacing them with others.

The four forms (vitamers) of B_{12} are all deeply red colored crystals and water solutions, due to the color of the cobalt-corrin complex.

Production

Cyanocobalamine is the industrially produced stable cobalamine form which is not found in nature

Vitamin B12 is entirely produced on a commercial basis by the fermentation. It is usually manufactured by submerged culture process. Such a fermentation process is completed in 3 to 5 days

They use glucose as a carbon source

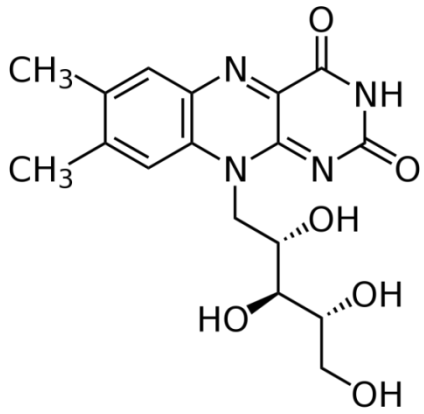
The microorganisms used are

Streptomyces griseus
Streptomyces olivaceus
Bacillus megaterium
Bacillus coagulans
Pseudomonas denitrificans
Propionibacterium freudenreichii
Propionibacterium Shermanii

Vitamin B2

Riboflavin, also known as **vitamin B_2**, is a vitamin found in food and used as a dietary supplement. As a supplement it is used to prevent and treat riboflavin deficiency and prevent migraines

It was discovered in 1920 and firstisolated in egg albumen in 1933. Its chemical structure, which was determined in 1935, has two distinctparts: a ribose sugar unit and a three-ring flavin structure, known as lumichrome. The chemical structureof vitamin B2 is shown below



Vitamin B2 has been produced commercially by chemical synthesis, by fermentation and bymixed fermentation/chemical synthesis methods. Fermentation is the most recent and most cost-effective method.

Fermentation/chemical synthesis process

A number of chemical synthesis production routes have been used commercially. Currently,producers use a mixed fermentation/chemical synthesisprocess. In thisprocess, a four-step reaction sequence is used, starting from glucose. First, ribose is produced fromglucose by fermentation. A reaction with xylidine is next used to convert ribose into a riboside, which isthen hydrogenated to produce ribamine. This intermediate product is next purified by crystallization.

The following stage involves a reaction between ribamine and a phenyl diazonium salt derivedfrom aniline, which produces phenylazoribitylamine. This compound is then crystallized, dried, andconverted into vitamin B2 by cyclocondensation with barbituric acid. An overall product yield of over60 per cent can be obtained.

Several of the chemical stages in this process involve the use of toxic reagents. The wasteproducts therefore require stringent environmental control and may need special forms of effluenttreatment.Chemical synthesis produces approximately 96 per cent pure vitamin B2

Glutamic acid

Amino acids are major biological components commercially used as additives in food, feed supplements, infusion compounds, thera-peutic agents and precursors for peptides synthesis or agriculture based chemicals. The amino acids are the second most important category, after antibiotics, with fermentation products exhibiting the highest growth rates. L-glutamic acid was the first amino acid produced commercially. The substance was discovered and identified in the year 1866 by the German chemist Karl Heinrich Leopold Ritt-hausen. L-glutamic acid was mainly produced by microbial fermentations and the chemical mode of synthesis is not widely preferred due to the formation of racemic mixture

Glutamic acid commercial production by microbial fermentation provides 90% of world"s total demand, and remaining 10% is met through chemical methods. For the actual fermentation the microbial strains are grown in fermentors as large as 500 m^3. The raw materials used include carbohydrate (glucose, molasses, sucrose, etc.), peptone, inorganic salts and biotin.

Biotin concentration in the fermentation medium has a significant influence on the yield of glutamic acid. Fermentation completes within 2-4 days and, at the end of the fermentation, the broth contains glutamic acid in the form of its ammonium salt.

In a typical downstream process, the bacterial cells are separated and the broth is passed through a basic anion exchange resin. Glutamic acid anions get bound to the resin and ammonia is released. This ammonia can be recovered via distillation and reused in the fermentation.

Elution is performed with NaOH to directly form monosodium glutamate (MSG) in the solution and to regenerate the basic anion exchanger. From the elute, MSG may be crystallized directly followed by further conditioning steps like decolourization and serving to yield a food-grade quality of MSG.

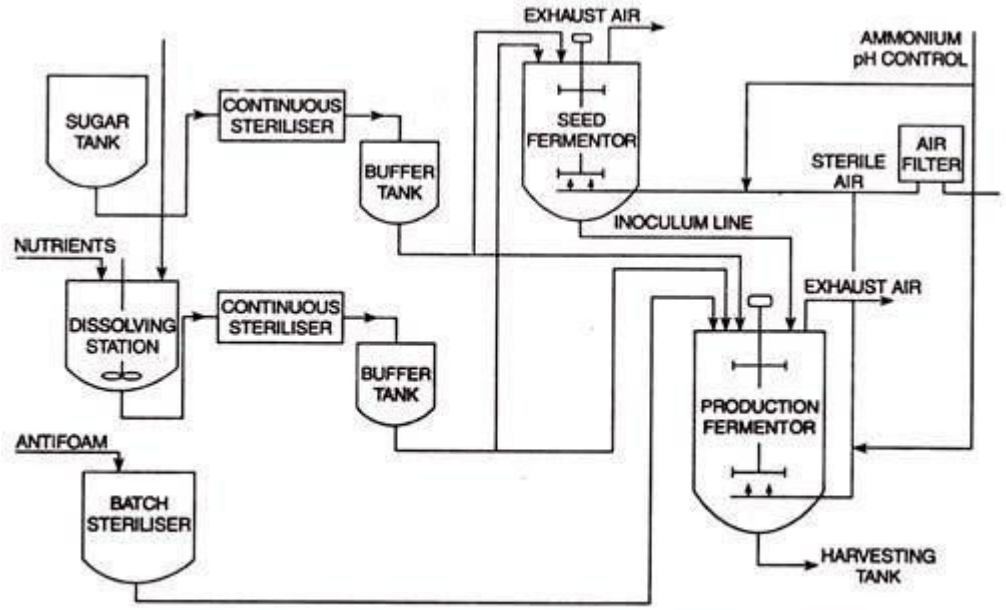
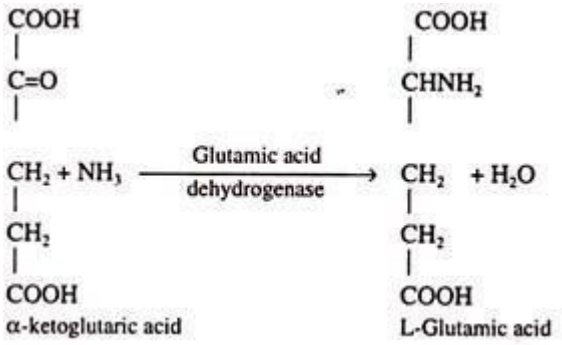


FIG. 40.6. A flow diagram of commercial production method of glutamic acid (glutamate).

α-ketoglutaric acid serves as the precursor of glutamic acid and the conversion of the α-ketoglutaric acid to glutamic acid occurs in presence of enzyme glutamic acid dehydrogenase. It has been found that if penicillin is added in he medium, the glutamic acid production can be increased manifold.



Uses of Glutamic Acid:

As stated earlier, glutamic acid is widely used in the production of monosodium glutamate (MSG) which is commonly known as the „seasoning salt". The world production of glutamic acid is to the tune of 800,000 tonnes/year. Monosodium glutamate is condiment and flavour-enhancing agent, it finds its greatest use as a common ingredient in convenient food-stuffs.

Lysine:

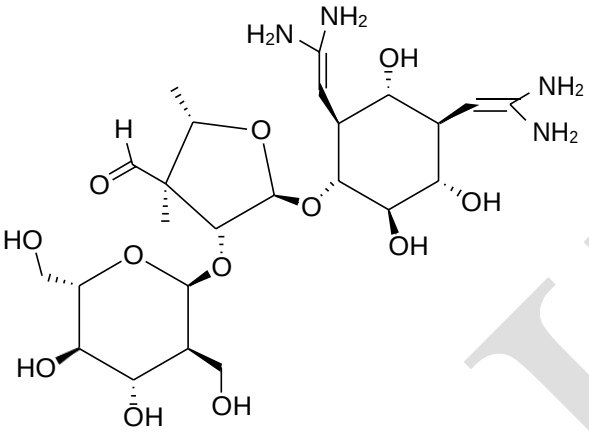
In recent years, a „single state" fermentation process is being used for the commercial production of lysine. This process has replaced the "two-stage" fermentation process of lysine production in which Escherichia coli was used to produce diammopimelic acid (DAP) in the first stage, and Enterobacteraerogenes was used for the formation of lysine from diaminopimelic acid through decarboxylation by an enzyme called diaminopimelic decarboxylase (DAP-decarboxylasc) in the second stage.

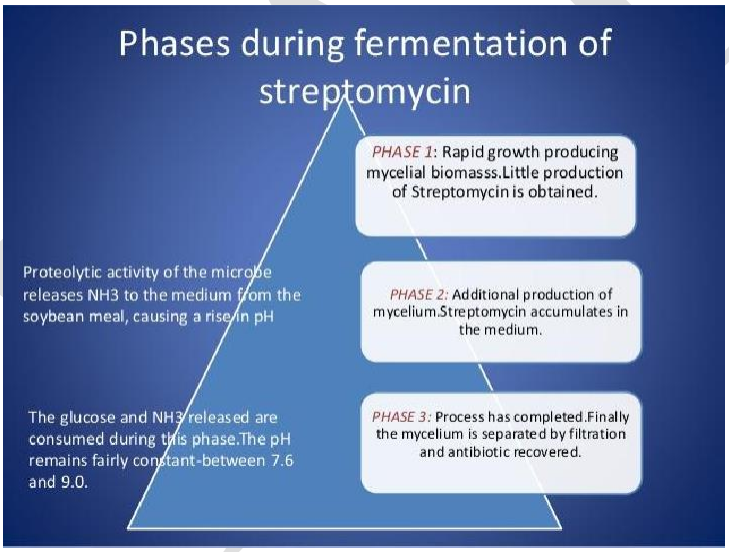
The „single-stage" process of fermentation of lysine involves mutants of Carynebacterium, Brevibacterium, etc. These bacteria are grown in a synthetic medium containing carbohydrate (glucose), an inorganic nitrogen source, small concentration of homoserine or methionine, and small concentration of biotin. The process of fermentation is completed within 48-70 hours and the yield of the amino acid is as high as 30 gm/litre.

Uses

Lysine is a vital amino acid for humans. Since cereal proteins are often deficient in lysine. I is generally used as a supplement for nutritional requirement such as bread and other food stuff for human being.

Streptomycin





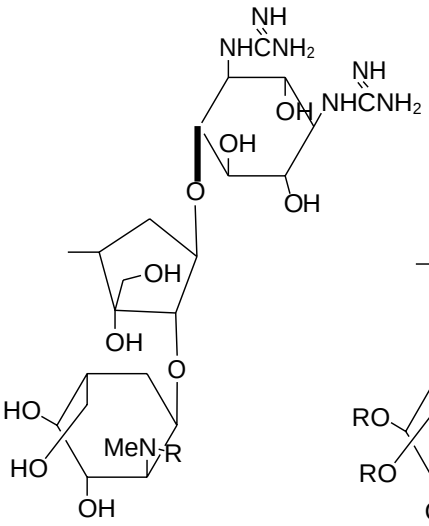
Streptomycin is an antibiotic produced by the soil actinomycete Streptomyces griseus. It acts by inhibiting the initiation and elongation processes during protein synthesis.

Chemical synthesis

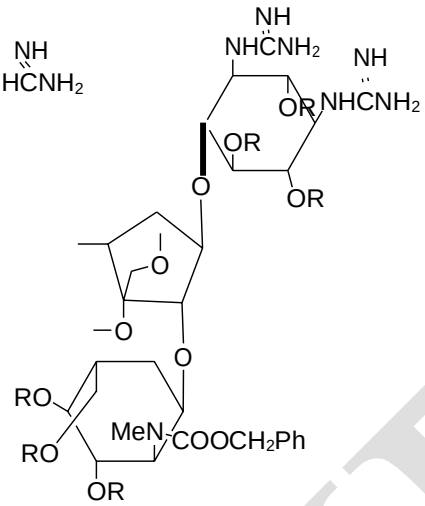
When DSM (**1**) trihydrochloride was treated with equimolecular quantities of benzyl chloroformate and sodium carbonate in aqueous acetone with cooling, benzyloxycarbonylation selectively occurred at the N-methyl group of the L-glucosamine portion, giving 2"-Nbenzyloxycarbonyldihydrostreptomycin (**2**) dihydrochloride. Treatment of **2** with excess 2,2-dimethoxypropane in the presence of a trace amount of p-toluenesulfonic acid gave a mixture of perO-isopropylidenated products. However, on treatment with 20 % acetic acid in methanol at 50°C for 4.5 hours, the mono-isopropylidene derivative (**3**) was obtained.

It should be noted that the isopropylidene group in the dihydrostreptose portion is the most stable. Acetylation of 3 with acetic anhydride in the presence of a catalytic amount of ptoluenesulfonic acid at 50°C for 70 hours gave the hexaacetyl derivative (**4**).Selective hydrolysis of 4 with 75 % aqueous acetic acid at 55°C for 30 hours led to the compound (**5**), which has free primary and tertiary hydroxyl groups in the dihydrostreptose portion.

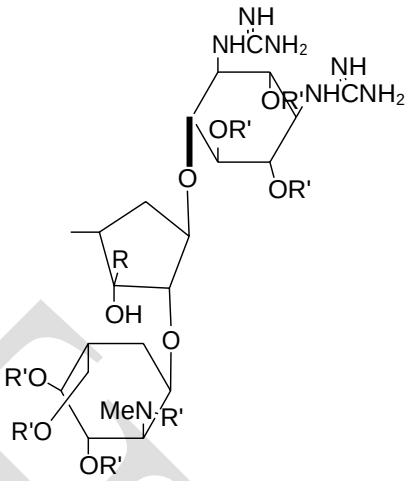
Compound **5** was then converted into the aldehyde derivative (**6**) by PFITZNER-MOFFATT oxidation with dimethyl sulfoxide, dicyclohexylcarbodiimide, trifluoroacetic acid, and pyridine at room temperature for 1.5 hours. The desired compound from the reaction product was difficult to isolate, so the crude product was deacetylated with methanolic ammonia and chromatographed to get the compound **6.** Finally, catalytic hydrogenolysis of the synthetic **6** with palladium black in aqueous solution acidified with acetic acidproduced streptomycin.



1. R = H
2. R = $COOCH_2Ph$

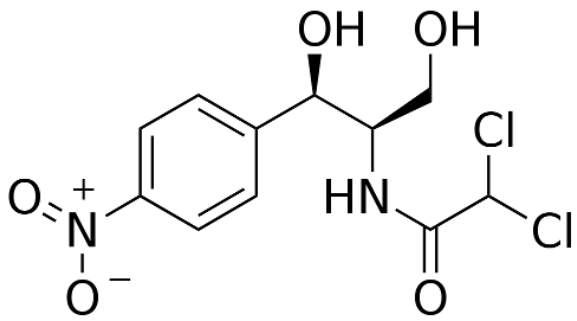


3. R = H
4. R = Ac

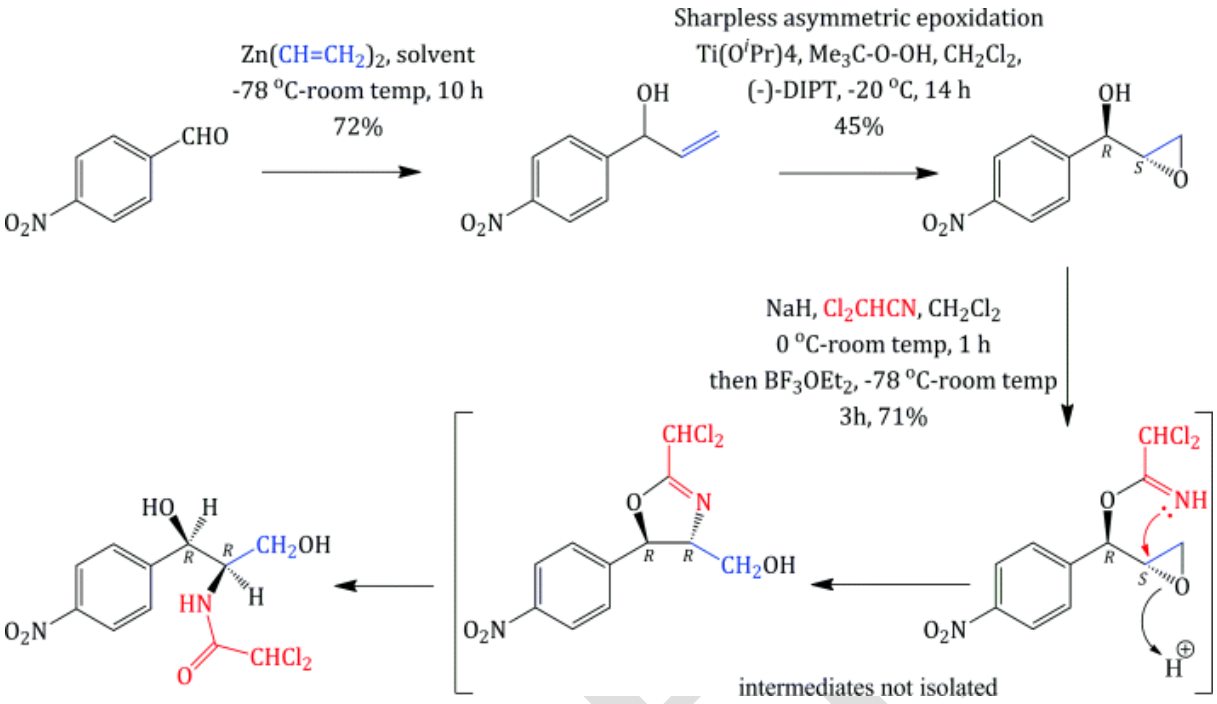


5. R = CH_2OH; R' = Ac
6. R = CHO; R' = H
7. R= H; R' + CHO

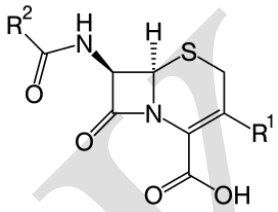
Chloromycetin



Synthesis



Cephalosporins



Cephalosporins are bactericidal and have the same mode of action as other β-lactam antibiotics (such as penicillins), but are less susceptible to β-lactamases. These compounds are closely related in structure, mechanism of action, spectrum of activity and pharmacology to the penicillins. They are produced by fungi and synthetic modification. Contains 6-membered dihydrothiazine ring. Substitutions at position 3 generally affect pharmacology; substitutions at position 7 affect antibacterial activity, but this is not invariably true. Cephalosporins are bactericidal. They inhibit enzymatic reactions necessary for stable bacterial cell walls by binding to PBPs. Bacterial cells must be growing.**Cephalosporins** disrupt the synthesis of the peptidoglycan layer forming the bacterial cell wall.

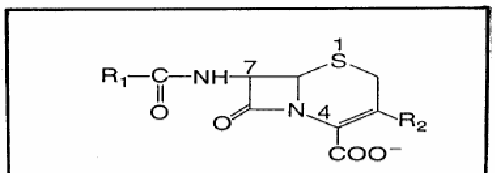
Mechanism of resistance to cephalosporins

A. Failure to reach receptor sites, permeability.

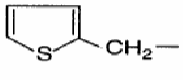
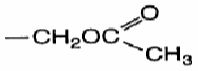
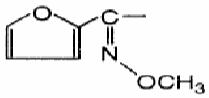
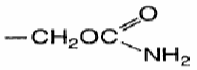
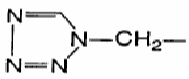
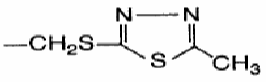
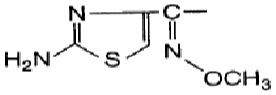
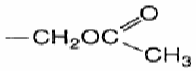
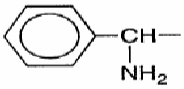
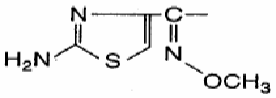
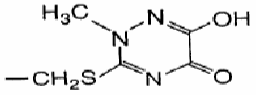
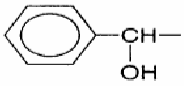
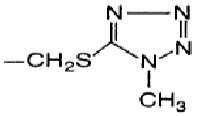
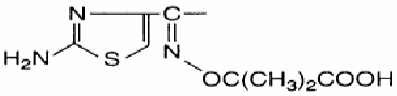
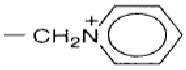
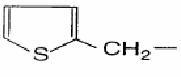
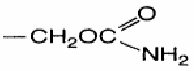
B. Destroyed by β-lactamase. Some gram-negative bacteria produce large amounts of β-lactamase constitutively.

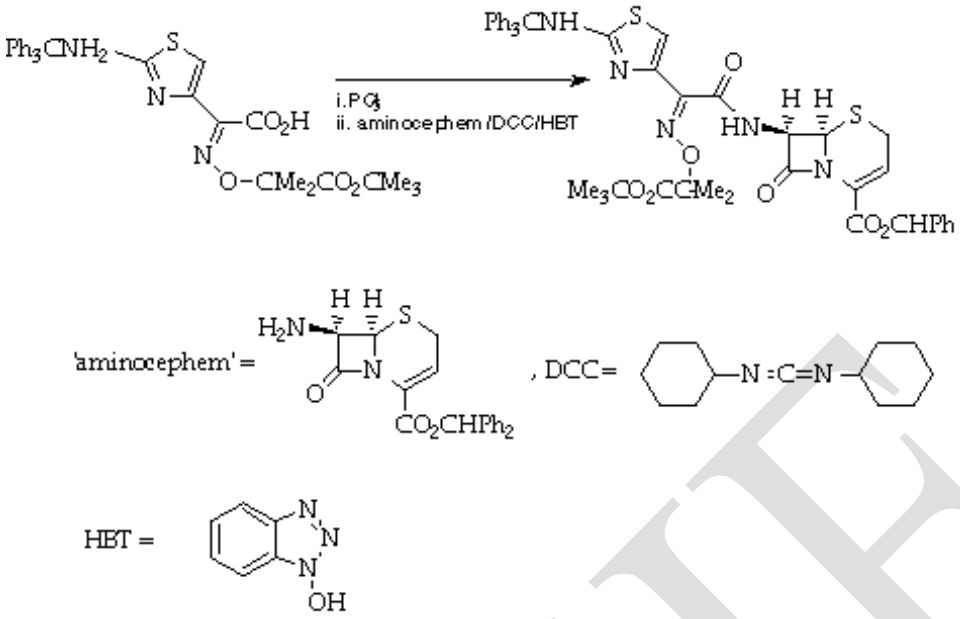
C. Failure to bind to penicillin binding proteins, in gram negative and gram positive organisms.

The cephalosporins have been grouped into "generations" corresponding to their development by the pharmaceutical industry in response to clinical needs. In general, the later generations of cephalosporins have greater gram-negative activity at the expense of gram-positive activity.



Basic structure of a Cephalosporin

Compound	R_1	R_2	Compound	R_1	R_2
Cephalothin			Cefuroxime		
Cefazolin			Cefotaxime		
Cephalexin			Ceftriaxone		
Cefamandole			Ceftazidime		
Cefoxitin					



Production of Cephalosporins

13 therapeutically important semisynthetic cephalosporins are commercially produced.

These have been synthesized by chemical splitting to form 7- aminocephalospioranic acid (7-ACA) with subsequent chemical acylation as well as by modification on the C-3 site.

Complex media with Corn steep liquor, meat meal, sucrose, glucose and ammonium acetate are used in a fed batch system at PH 6-7 and temperature 24-28^{0}C.

Recently chemical synthesis of cephalosporin by ring expansion of pencillin has been developed. Eg. Use of Penicillin V to produce oraspor, an orally active cephalosporin.

L-a- AAA + L-Cys + L Val

↓

LLD Tripeptide

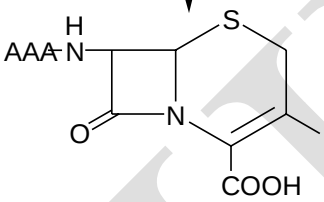
↓

Isopenicillin N

↓

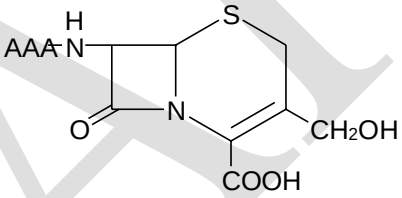
Penicillin N
D-a-AAA-APA

↓ Ring Formation



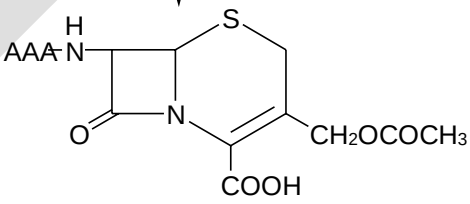
Deacetoxy cephalosporin C

↓



Deacetyl cephalosporin C

↓



Cephalosporin C

POSSIBLE QUESTIONS

PART A (1 Marks Questions)

Online Examination

PART B (2 Marks Questions)

1. What are antibiotics?
2. Draw the structure of penicillin.
3. Why we need vitamins?
4. What are fat soluble vitamins?
5. Write the source of vitamin C.

PART C (6 Marks Questions)

1. Give a detailed account on production of penicillin.
2. Write note on the discovery of cephalosporin.
3. Illustrate the preparation of chloromycetin.
4. Give the synthesis of streptomycin.
5. Explain the preparation of lysine.
6. Discuss the preparation of glutamic acid.
7. Discuss briefly about the production of vitamin B_2.
8. How do you prepare vitamin B_{12}? Explain.
9. Discuss the preparation and uses of vitamin C.
10. Give the source, preparation and uses of ascorbic acid.