KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed to be University)
(Established Under Section 3 of UGC Act 1956)
Coimbatore – 641 021.
(For the candidates admitted from 2018 onwards)

DEPARTMENT OF CHEMISTRY

SUBJECT NAME: MEDICINAL CHEMISTRY **SUBJECT CODE: 18CHP105B**
SEMESTER: I **CLASS: I M. Sc CHEMISTRY**

Course outcome

1. To formulate the chemical synthesis of some drugs.
3. To know the Quantitative structural activity relationship of different class of drugs.
4. Knowledge about the mechanism pathways of different class of medicinal compounds. 5 To understand the chemistry of drugs with respect to their pharmacological activity.
7. Understands the various aspects of Receptors and drug receptor bindings.

Objectives

1. To understand the basics of Medicinal chemistry.
2. To understand the drug targets, drug metabolism and about clinical training.

Methodology

Blackboard teaching, Powerpoint presentation and group discussion.

UNIT I

Drug discovery, design and development: Synthesis of the representative drugs of the following classes: analgesic, antipyretic and anti-inflammatory agents (Aspirin, paracetamol and lbuprofen); antibiotics (Chloramphenicol); antibacterial agents (Sulphonamides), antiviral agents (Acyclovir), Central Nervous System agents (Phenobarbital and Diazepam).

UNIT II

Insilco Drug Design and Computer Assisted New Lead Design: Introduction, historical perspective, drug compounds, preparation and organization for drug seeking, common stages in the drug seeking campaign, sources of hits, leads and candidate drugs, natural products: higher plant and animal products, combinational libraries, lead optimization. Introduction, basic concepts, molecular recognition by receptor and ligand design, active conformation, approaches to discover new functions, approaches to the cases with known and unknown receptor structure and molecular docking study. Introduction to drug metabolism, toxicity and pharmacokinetics, toxicology considerations, problems and drawbacks on drug discovery and development.

UNIT III

Membranes and Receptors: Drug transport mechanism and absorption processes, pharmacodynamic and pharmacokinetic aspects, prodrugs and bioactivation, receptor theories and receptor models, drug receptor interactions drug design, physiochemical principles and basis of drug design, different methods of drug design,

UNIT IV

QSAR: Electronic effects; Hammett equation, Lipophilicity effects; Hansch equation, Steric Effects; Taft Equation; Experimental and theoretical approaches for the determination of physico-chemical parameters, parameter inter-dependence; linearity versus non-linearity; The importance of biological data in the correct form; Molecular docking and dynamics: Rigid docking, flexible docking and manual docking.

UNIT V

Molecular Recognition in Drug-Receptor Binding: Molecular forces and binding energetic, enzyme inhibitors - modes of inhibition and general approaches. Antibacterial drugs - major drug classes and drug resistance, antiviral drugs- major drug classes and drug resistance, anticancer drugs- major cancer drug targets, major drug classes and drug resistance.

SUGGESTED READINGS:

Text Books:

1. Ahluwalia, V. K. (2012). *Green Chemistry-Environmentally Benign Reactions*. New Delhi: Ane Books Pvt Ltd.
2. Ghose, J. (2005). *A Text book of Pharmaceutical Chemistry*. New Delhi: S. Chand Pub Ltd.
3. Ilango, K., & Valentina, P. (2007). *Text Book of Medicinal Chemistry. Vol I*. Chennai: Keerthi Publishers.
4. Ashutosh Kar, (2005). *Medicinal Chemistry* (III Edition). New Delhi: New Age International Publishers.

Reference Books:

1. Stanley E. Manahan, (2006). *Green Chemistry and the Ten Commandments of Sustainability* (II Edition). Columbia, Missouri U.S.A: ChemChar Research. Inc Publishers Columbia.
2. Chatterjea, M. N., & Shinde, R. (2012). *Textbook of Medicinal Biochemistry*. New Delhi: Jaypee Brothers. Medical Publishers (P) Ltd**.**
3. G.L. Patrick, (1995). *Introduction to Medicinal Chemistry* (I Edition). UK: Oxford University Press.
4. Wermuth, C. G. (1992). *Medicinal Chemistry for the 21st Century*. Oxford: Blackwell.

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DEPARTMENT OF CHEMISTRY

SUBJECT NAME: MEDICINAL CHEMISTRY **SUBJECT CODE: 18CHP105-B**

SEMESTER: I **CLASS: I M. Sc CHEMISTRY**

LECTURE PLAN

UNIT-1

Drug discovery, design and development Total no. of hours: 10

S.NO	LECTURE DURATION	TOPICS TO BE COVERED	SUPPORT MATERIALS
1.	**1**	Synthesis of the representative drugs- Introduction	**T1: 6-10, T2: 5-8**
2.	**1**	analgesic, antipyretic and anti-inflammatory agents	**T1: 212-213**
3.	**1**	Aspirin and paracetamol	**T1: 214, 217-218**
4.	**1**	lbuprofen	**T2: 81**
5.	**1**	antibiotics (Chloramphenicol)	**T1: 630**
6.	**1**	antibacterial agents (Sulphonamides)	**T1: 505, 530**
7.	**1**	antiviral agents (Acyclovir)	**T2: 294**
8.	**1**	Central Nervous System agents (Phenobarbital).	**T2: 86**
9.	**1**	Central Nervous System agents (Diazepam).	**T2: 92**
10.	**1**	Discussion of important questions	

Text book:

T1: Ashutosh Kar, (2005). *Medicinal Chemistry* (III Edition). New Delhi: New Age International Publishers.

T2: Parimoo, P, 2009. Text Book of Medicinal Chemistry. CBS Publishers & Distributers, New Delhi.

UNIT-2

Insilco Drug Design and Computer Assisted New Lead Design Total no. of hours: 10

S.NO	LECTURE DURATION	TOPIC TO BE COVERED	SUPPORT MATERIALS
1.	**1**	Introduction, historical perspective, drug compounds, preparation and organization for drug seeking,	**T1: 1-2**
2.	**1**	common stages in the drug seeking campaign, sources of hits, leads and candidate drugs, natural products:	
3.	**1**	Higher plant and animal products, combinational libraries, lead optimization.	
4.	**1**	Introduction, basic concepts, molecular recognition by receptor	**T2: 18-24**
5.	**1**	ligand design, active conformation, approaches to discover new functions,	
6.	**1**	approaches to the cases with known and unknown receptor structure and molecular docking study	
7.	**1**	Introduction to drug metabolism	**T2: 30**
8.	**1**	toxicity and pharmacokinetics, toxicology considerations	**T2: 29**
9.	**1**	Problems and drawbacks on drug discovery and development.	
10.	**1**	Discussion of important questions	

Text book:

T1: Ashutosh Kar, (2005). *Medicinal Chemistry* (III Edition). New Delhi: New Age International Publishers.

T2: Parimoo, P, 2009. Text Book of Medicinal Chemistry. CBS Publishers & Distributers, New Delhi.

UNIT -3

Membranes and Receptors Total no. of hours: 10

S.NO	LECTURE DURATION	TOPIC TO BE COVERED	SUPPORT MATERIALS
1	**1**	Drug transport mechanism and absorption processes	
2	**1**	pharmacodynamic	
3	**1**	pharmacokinetic aspects	
4	**1**	prodrugs and bioactivation	
5	**1**	receptor theories and receptor models	
6	**1**	drug receptor interactions drug design	
7	**1**	physiochemical principles	
8	**1**	basis of drug design	
9	**1**	different methods of drug design	
10	**1**	Discussion of important questions	

UNIT -4

QSAR Total no. of hours: 09

S.NO	LECTURE DURATION	TOPIC TO BE COVERED	SUPPORT MATERIALS
1	**1**	Electronic effects; Hammett equation	
2	**1**	Lipophilicity effects; Hansch equation	
3	**1**	Steric Effects; Taft Equation	
4	**1**	Experimental and theoretical approaches for the determination of physico-chemical parameters	
5	**1**	parameter inter-dependence; linearity versus non-linearity	
6	**1**	The importance of biological data in the correct form	
7	**1**	Molecular docking and dynamics	
8	**1**	Rigid docking, flexible docking	
9	**1**	Manual docking.	
10	**1**	Discussion of important questions	

UNIT -5

Molecular Recognition in Drug-Receptor Binding Total no. of hours: 09

S.NO	LECTURE DURATION	TOPIC TO BE COVERED	SUPPORT MATERIALS
1	**1**	Molecular forces and binding energetic	
2	**1**	enzyme inhibitors - modes of inhibition	
3	**1**	General approaches. Antibacterial drugs	
4	**1**	major drug classes and drug resistance	
5	**1**	antiviral drugs- major drug classes	
6	**1**	drug resistance- anticancer drugs	
7	**1**	major cancer drug targets	
8	**1**	major drug classes and drug resistance	
9	**1**	Recapitulation and discussion of Previous year question	

UNIT-1

SYLLABUS

Drug discovery, design and development: Synthesis of the representative drugs of the following classes: analgesic, antipyretic and anti-inflammatory agents (Aspirin, paracetamol and lbuprofen); antibiotics (Chloramphenicol); antibacterial agents (Sulphonamides), antiviral agents (Acyclovir), Central Nervous System agents (Phenobarbital and Diazepam).

INTRODUCTION

Antipyretic analgesics or febrifuges are remedial agents that lower the temperature of the body in pyrexia i.e.,in situations when the body temperatures has been raised above normal. In therapeutic doses they do not have any affect on normal body temperature. They exert their action on the heat regulating centre in the hypothalamus. These antipyretic agents also have mild analgesic activity. Amongst the most common group of compounds used as antipyretic analgesics are salicyclates, aniline and aminophenol analogues, pyrazolones and quinoline derivatives. Though these heterogenous groups of compounds are analgesics, they have no addictive properties. Their analgesic use is limited to mild aches and pains like headache and backache.

Alternatively, amtipyretic is the terminology quite frequently applied to drugs which essentially help to reduce fever to normal body temperature (i.e., 98.4 degree F or 37 degree C). It is, however, worthwhile to mention here that the drug substances belonging to this particular category usually

possess the abilty to alleviate the sensation of pain threshold ranging from mild to severe status. These antipyretic agents are also found to be significantly effective in reducing fever to normal levels in humans. The drugs that are most commonly included here are, namely, acetanilide, phenacetin (acetophentidin), and paracetamol acetaminophen (known in US), para_acetaminophenol. Interestingly, the aforesaid three drug entities are interrelated to one another metabolically, as illustrated below.

It is worthwhile to mention here that both acetanilide and phenacetin have has been withdrawn completely from being used because of its numerous toxic and undesirable effects, such as skin, manifestations, jaundice, cardiac irregularities, and a relatively high incidence of metthemoglobinemia* and quite seldomnly acute blood dyscrasisas, for instance, hemolytic anemia. Phenacetin has also been dropped as a drug since 1982 in US by7 virtue of the fact that it earned a bad reputation for causing nephrotoxicity due to its high_dose long_term abuse in several parts of the globe. It was also reported to cause kidney and liver cancer.

Paracetamol (acetaminophen) enjoys still the world_wide recognition as the only aniline_based analgetic_antipyretic for its abundant utility in controlling fever in most non_inflammatory conditions very much akin to aspirin. It has also been demonstrated adequately that both paracetamol and aspirin are equianalgetic at a dose of 650 mg.

Analgesics may be defined as agents that relieve pain by elevating the pain threshold without disturbing conciousness or altering other sensory_modalities. Besides, pain may also be defined

in psychological perspective as a particular type of sensory experience distinguished by nerve tissue from sensations, such as touch, heat, pressure and cold. In the latest context pain essentially involves a major chunk of psychological factor which exclusively rests on perception. Therefore, more realistically pain may be defined introspectively in an exclusive manner.

Broadly speaking, the most probable and logical explanation for the mechanism by which certain analgesics specifically enhances the pain threshold has been caused solely due to the presence of the opiate receptors strategically located in selected parts of the CNS overtly and covertly associated with the pain regulation. It has been established that the opiate receptors are located in the following critical zones, namely,

(a) Medial thalamus which processes chronic, deep and burning pain thtat is usually suppressed by **narcotic analgesics only**,
(b) Brainstem vagus nuclei which triggers the cough centres, and

(c)Layers I and II in the spinal cord at the specific zone where the different nerves which solely hold the pain perception first synapse.

Importantly, endorphins** mostly logistically lower the instensity of pain by modulating particularly the pain threshold the critical material point at which one may commence to perceive a stimulus as painful sensation.

CLASSIFICATION

Antipyretic analagesics may be classified on the basis of their chemical structures.

Aniline and p_Aminophenol Analogues

In 1886. Cohn and Hepp first identified the powerful antipyretic activities residing in both aniline and acetanilid. The basic origin of this particular class of compounds from aniline has probably suggested these to be known as coal tar analgesics. However, the aminophenols (o,m,p) are reported to be relatively less toxic than aniline. The para_isomer is claimed to be the least toxic of the three isomers of aminophenols and it also possesses a significant antipyretic action. A few examples belonging to this category of antipyretics are described below.

Paracetanol INN, BAN, Acetaminophen USAN,

It may be prepared by the reduction of p_nitrophenol and the resulting p_aminophenol is acetylated by a mixture of acetic anhydride and glacial acetic acid. The crude product can be purified by recrystallization from a water, ethanol mixture (1 is to 1) or from other appropriate solvents.

It is a metabolite of acetanilide and phenacetin employued as an anti pyretic and analgesic. It may be used effectively in a broad spectrum of arthritic and rheumatic conditions linked with musculoskeletal pain, headache, neuralgias, myalgias, and dysmennorhea. It is particularly useful in aspirin_sensitive patients.

Dose Usual oral, adult, 500 mg to 1 g 3 or 4 times per day.

Aspirin BAN,USAN,

Salicyclic acid acetate , Benzoic acid, 2_(acetyloxy)_,Acetylsalicyclic acid , o_Acetylsalicyclic acid , B.P., U.S.P., Eur P., Int.P.,Ind. P.,

Emipirin ® (Burroughs Wellcome), A.S.A. ® (Lilly), Bufferin ® (Bristol_Myers)

Synthesis

Acetylation of salicyclic acid with acetic anhydride yields aspirin. The crude product may be recrystallized from benzene,mixture of acetic acid and water (1 1) or various other non_aqueous solvents.

It is used as an antipyretic anti_inflammatory and an analgesic in a variety of conditions ranging from headache, discomfort and fever associated with the common cold, and muscular pains and aches. Aspirin is regarded as the drug of choice in the reduction of fever because of its high degree of effectiveness and wide safety margin. As aspirin inhibits platelet function, it has been employed prophylactically to minimise the incidence of myocardial infarction and trasnsient ischemic attacks.

Dose Usual adult oral 300 to 650 mg every 3 or 4 hours, or 650 mg to 1,3 g as the sustained release tablet every 8 hours, Rectal 200 mg to 1.3 g 3 or 4 times a day.

CHLORAMPHENICOL

Chloramphenicol (chloromycetin) is a levorotatory broadspectrum antibiotic originally produced from several streptomycetes, namely S. venezualae, S. omiyamensis and S. phacochromogenes var chloromyceticus. It has been reported to be the drug of choice for the treatment of typhus and

typhoid fever.

However, chloramphenicol is of paramount interest owing to the following three reasons

(a) It is a naturally occurring aromatic nitro compound of which there is only one previously recorded example of hiptagin, obtain from the root bark of Hiptage madablota Gaertn is noteworthy.

(b) It is capable of exerting its effect against viral diseases as well as those due to bacterial invasion and opens up the whole field of the chemotherapy of virus and rickettsial infections in man including typhus, undulant fever, Salmonella septicaemia, whooping cough, gastroenteritis, lymphogranuloma inguinale, typhoid and paratyphoid. So far, chloramphenicol_fast strains have not been isolated.

(c) It is amenable to synthesis on an industrial scale.

Structure of Chloramphenicol

The structure of chloramphenicol has been established on the basis of the following vital chemical evidences. They are,

(I) The molecular formula of chloramphenicol is C11H12O5N2Cl2.

(II) Its absorption spectrum is similar to that of nitrobenzene.

(III) The presence of a nitro group was revealed by the reduction of chloramphenicol with tin (Sn) and hydrochloric acid, followed by diazotization and then coupling to yield an orange precipitate with beta_naphthol (Rebstock et al.1949).

(IV) When reduced catalytically (with palladium, Pd) it gives a product which has an

aborption spectrum very similar to that of para_toluidine and the resulting solution gives a positive test for ionic chlorine.

(V) Hydrolysis of chloramphenicol with either acid or alkali produces dichloroacetic acid together with an optically active base C9H12O4N2. Thus ,

VI) The resulting base was shown to contain a primary amino group, and on being treated with methyl dichloroacetate, the base regenerated chloramphenicol (Rebstock et al. 1949).

VII) Chloramphenicol is converted into a diacetyl derivative on treatment with acetic anhydride in pyridine, whereas the base obtained from chloramphenicol yields a triacetyl derivative on similar treatment thereby suggesting that chloramphenicol probably contains two_OH groups.

VIII) When the chloramphenicol base is treated with periodic acid (HIO4) two molecules of the latter are consumed with the formation of one molecule each of ammonia, formaldehyde and para_nitrobenzaldehyde respectively.

However, these products may be accounted for provided the base is assumed to be 2_amino_1_nitrophenyl propane_1, 3_diol (Rebstock et al. 1949). Thus,

Hence, chloramphenicol may be written as.

Synthesis of Chloramphenicol

Chloramphenicol has been successfully synthesized by different methods and the present global demand of this drug is adequately met exclusively by chemical synthesis. The synthesis put forward by Long et al. (1949) is discussed below.

Thus there are two possible of enantiomorphs.

It has been observed that the biological activity resides almost exclusively in the **D_Threo_isomer** whereas the L_Threo, and D_ and L_Erythro isomers are virtually inactive.

A large number of structural analogues of chloramphenicol have been prepared on the basis of the following themes, removal of the chlorine atom, transference of chlorine atom to the aromatic nucleus, transference of the nitro ,moiety to the ortho_ or meta_position, esterification of the hydroxyl function (s), replacement of the phenyl ring with furyl, naphthyl and xenyl rings respectively, addition of alkyl or alkoxy substituents to the aryl ring and lastly replacement of the inherent nitro group by a halogen atom. It is however, pertinent to mention here that none of these structurally modiefied analogues showed an activity approaching to that of chloramphenicol towards Shigella paradysenteriae.

S.No	Question	Option 1	Option 2	Option 3	Option 4	Answer
	UNIT-I					
1	Analgesics	Relieve pain	Reduce elevated body temperatures	To treat inflammation & mild pain	To treat Bacterial infection	Relieve pain
2	Antipyretics	Relieve pain	Reduce elevated body temperatures	To treat inflammation & mild pain	To treat Bacterial infection	Reduce elevated body temperatures
3	Anti-inflammatory drugs	Relieve pain	Reduce elevated body temperatures	To treat inflammation & mild pain	To treat Bacterial infection	To treat inflammation & mild pain
4	Antibacterial agents	Relieve pain	Reduce elevated body temperatures	To treat inflammation & mild pain	To treat Bacterial infection	To treat Bacterial infection
5	Antiviral agents	To treat viral infection	Reduce elevated body temperatures	To treat inflammation & mild pain	To treat Bacterial infection	To treat viral infection
6	Pain releiver	Analgesics	Antipyretics	Anti-inflammatory drugs	Antibacterial agents	Analgesics
7	Reduce elevated body temperatures	Analgesics	Antipyretics	Anti-inflammatory drugs	Antibacterial agents	Antipyretics
8	To treat inflammation & mild pain	Analgesics	Antipyretics	Anti-inflammatory drugs	Antibacterial agents	Anti-inflammatory drugs

9	To treat Bacterial infection	Analgesics	Antipyretics	Anti-inflammatory drugs	Antibacterial agents	Antibacterial agents
10	To treat viral infections	Analgesics	Antipyretics	Anti-inflammatory drugs	Anti viral agents	Anti viral agents
11	Example for analgesics	Aspirin	Chloramphenicol	Sulphonamides	Diazepam	Aspirin
12	One among the following is an antipyretic	paracetamol	Chloramphenicol	Sulphonamides	Diazepam	paracetamol
13	Example for an antibacterial agent	paracetamol	Chloramphenicol	Sulphonamides	Diazepam	Sulphonamides
14	One among the following is an antiviral	paracetamol	Chloramphenicol	Sulphonamides	Acyclovir	Acyclovir
15	Example for an anti-inflammatory drug	paracetamol	Chloramphenicol	ibuprofen	Acyclovir	ibuprofen
16	Example for an antibiotic	paracetamol	Chloramphenicol	ibuprofen	Acyclovir	Chloramphenicol
17	Aspirin is prepared from	Salicyclic acid	aniline	Phenyl salicylate	Amino benzaldehyde	Salicyclic acid
18	Aspirin is	Acetyl salicylic acid	salicylaldehyde	Phenyl salicylate	Amino benzaldehyde	Acetyl salicylic acid
19	Acylation of salicyclic acid gives	Aspirin	Chloramphenicol	Sulphonamides	Diazepam	Aspirin
20	Paracetamol is otherwise called as	Aspirin	Acetaminophen	Sulphonamides	Diazepam	Acetaminophen
21	Paracetamol is prepared from	p-nitro phenol	Salicyclic acid	phenacetin	Phenyl salicylate	p-nitro phenol
22	Paracetamol is prepared from	p-amino phenol	Salicyclic acid	phenacetin	Phenyl salicylate	p-amino phenol

23	Acylation of p-amino phenol gives	paracetamol	Chloramphenicol	ibuprofen	Acyclovir	paracetamol
24	Paracetamol is used as an	Analgesic and antipyretic	Anti-inflammatory drugs	Antibacterial agents	Antiviral agent	Analgesic and antipyretic
25	p-amino phenol on treatment with acetic anhydride and acetic acid gives	paracetamol	Chloramphenicol	ibuprofen	Acyclovir	paracetamol
26	Ibuprofen is prepared from	Isobutyl benzene	p-nitro phenol	Salicyclic acid	phenacetin	Isobutyl benzene
27	Ibuprofen is used to treat	Rheumatoid arthritis	Elevated body temperature	Blood pressure	diabeties	Rheumatoid arthritis
28	An example of a sulfonamide antibacterial agent	sulfadiazine	ofloxacin	nitrofurazone	methenamine	sulfadiazine
29	An example of a quinolone antibacterial agent	sulfadiazine	ofloxacin	nitrofurazone	methenamine	ofloxacin
30	An example of anitrofuran antibacterial agent	sulfadiazine	ofloxacin	nitrofurazone	methenamine	nitrofurazone
31	An example of methanamine antibacterial agent	sulfadiazine	ofloxacin	nitrofurazone	methenamine	methenamine
32	The term sulphonamide is usually employed as a generic name for the derivatives of	p-amino benzene sulphonamides	p-nitro benzene sulphonamides	p-hydroxy benzene sulphonamides	p-chloro benzene sulphonamides	p-amino benzene sulphonamides
33	Sulphonamides are	bacteriostatic	bacterocide	viriocide	virostatic	bacteriostatic
34	The compound which essential for the synthesis of DNA and RNA	Folic acid	Benzoic acid	Salicyclic acid	salol	Folic acid
35	The compound which essential for the synthesis of folic acid	P-amino benzoic acid	P-nitro benzoic acid	P-hydoxy benzoic acid	P-chloro benzoic acid	P-amino benzoic acid

36	Sulphonamide for general infection	sulphanilamide	Sulphaisoxazole	Phthalyl sulphathiazole	sulphaacetamide	sulphanilamide
37	Sulphonamide for urinary tract infection	sulphanilamide	Sulphaisoxazole	Phthalyl sulphathiazole	sulphaacetamide	Sulphaisoxazole
38	Sulphonamide for intestinal tract infection	sulphanilamide	Sulphaisoxazole	Phthalyl sulphathiazole	sulphaacetamide	Phthalyl sulphathiazole
39	Sulphonamide for local infection	sulphanilamide	Sulphaisoxazole	Phthalyl sulphathiazole	sulphaacetamide	sulphaacetamide
40	Sulphanilamide is a	Sulphonamide for general infection	Sulphonamide for urinary tract infection	Sulphonamide for intestinal tract infection	Sulphonamide for local infection	Sulphonamide for general infection
41	Sulphaisoxazole is a	Sulphonamide for general infection	Sulphonamide for urinary tract infection	Sulphonamide for intestinal tract infection	Sulphonamide for local infection	Sulphonamide for urinary tract infection
42	Phthalyl sulphathiazole is a	Sulphonamide for general infection	Sulphonamide for urinary tract infection	Sulphonamide for intestinal tract infection	Sulphonamide for local infection	Sulphonamide for intestinal tract infection
43	sulphaacetamide is a	Sulphonamide for general infection	Sulphonamide for urinary tract infection	Sulphonamide for intestinal tract infection	Sulphonamide for local infection	ulphonamide for local infection
44	Poorly adsorbed sulphonamides are	Called locally acting sulphonamides	Systemic sulphonamides	Topically used	Used in dermatitis	Called locally acting sulphonamides
45	Rapidly adsorbed sulphonamides are	Called locally acting sulphonamides	Systemic sulphonamides	Topically used	Used in dermatitis	Systemic sulphonamides

46	Topically used sulphonamides are	Called locally acting sulphonamides	Systemic sulphonamides	Applied in burns	Used in dermatitis	Applied in burns
47	locally acting sulphonamides	Poorly adsorbed sulphonamides	Rapidly adsorbed sulphonamides	Topically used sulphonamides	Used in dermatitis	Poorly adsorbed sulphonamides
48	Applied in burns	Poorly adsorbed sulphonamides	Rapidly adsorbed sulphonamides	Topically used sulphonamides	Used in dermatitis	Topically used sulphonamides
49	Systemic sulphonamides	Poorly adsorbed sulphonamides	Rapidly adsorbed sulphonamides	Topically used sulphonamides	Used in dermatitis	Rapidly adsorbed sulphonamides
50	Antibiotic is a chemical compound that inhibits the growth of	bacteria	virus	Cancer cells	Acetylcholine esterase	bacteria
51	Antibiotic is a chemical compound that inhibits the growth of	Fungi	virus	Cancer cells	Acetylcholine esterase	Fungi
52	Antibiotic is a chemical compound that inhibits the growth of	Protozoans	virus	Cancer cells	Acetylcholine esterase	Protozoans
53	Chloramphenicol belongs to	Lactam antibiotics	tetracyclines	Macrolide antibiotics	Miscellaneous group	Miscellaneous group
54	Chloramphenicol is a	Antifungal antibiotic	Anticancer ntibiotic	Antityphoid antibiotic	Antidihhareoal antibiotic	Antityphoid antibiotic
55	The number of asymmetric carbons present in Chloramphenicol is	one	two	three	Four	two
56	Chloramphenicol on hydrolysis gives	Dichloro acetic acid	Monochloric acid	Trichloric acetic cid	Acetic acid	Dichloro acetic acid

57	Chloramphenicol inhibits the	Synthesis of protein	Cell wall synthesis	Synthesis of DNA	Synthesis of enzymes	Synthesis of protein
58	Attachment of virus to the host cell is called	adsorption	penentration	uncoating	translation	adsorption
59	Acyclovir is a	Purine nucleoside	Pyrimidine nucleoside	Thio-semicarbazone	interferons	Purine nucleoside
60	Example for a Purine nucleoside antiviral agent	Acyclovir	Methisazone	Amantadine	Ribavirin	Acyclovir

UNIT-II

SYLLABUS

Introduction, historical perspective, drug compounds, preparation and organization for drug seeking, common stages in the drug seeking campaign, sources of hits, leads and candidate drugs, natural products: higher plant and animal products, combinational libraries, lead optimization. Introduction, basic concepts, molecular recognition by receptor and ligand design, active conformation, approaches to discover new functions, approaches to the cases with known and unknown receptor structure and molecular docking study. Introduction to drug metabolism, toxicity and pharmacokinetics, toxicology considerations, problems and drawbacks on drug discovery and development.

Drug design, sometimes referred to as **rational drug design** or more simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target.[1] The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques.[2]This type of modeling is often referred to as **computer-aided drug design**. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as **structure-based drug design**.

Ligand-based

Ligand-based drug design (or **indirect drug design**) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.[4] In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their

experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs.

Active site identification

Active site identification is the first step in this program. It analyzes the protein to find the binding pocket, derives key interaction sites within the binding pocket, and then prepares the necessary data for Ligand fragment link. The basic inputs for this step are the 3D structure of the protein and a pre-docked ligand in PDB format, as well as their atomic properties. Both ligand and protein atoms need to be classified and their atomic properties should be defined, basically, into four atomic types:

- **hydrophobic atom**: All carbons in hydrocarbon chains or in aromatic groups.
- **H-bond donor**: Oxygen and nitrogen atoms bonded to hydrogen atom(s).
- **H-bond acceptor**: Oxygen and sp2 or sp hybridized nitrogen atoms with lone electron pair(s).
- **Polar atom**: Oxygen and nitrogen atoms that are neither H-bond donor nor H-bond acceptor, sulfur, phosphorus, halogen, metal, and carbon atoms bonded to hetero-atom(s).

The space inside the ligand binding region would be studied with virtual probe atoms of the four types above so the chemical environment of all spots in the ligand binding region can be known. Hence we are clear what kind of chemical fragments can be put into their corresponding spots in the ligand binding region of the receptor.

Rational drug discovery

In contrast to traditional methods of drug discovery, which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value. In order for a biomolecule to be selected as a drug target, two essential pieces of information are required. The first is evidence that modulation of the target will have therapeutic value. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states. The second is that the target is "drugable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

Once a suitable target has been identified, the target is normally cloned and expressed. The expressed target is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.

The search for small molecules that bind to the target is begun by screening libraries of potential drug compounds. This may be done by using the screening assay (a "wet screen"). In addition, if the structure of the target is available, a virtual screen may be performed of candidate drugs. Ideally the candidate drug compounds should be "drug-like", that is they should possess properties that are predicted to lead to oral bioavailability, adequate chemical and metabolic stability, and minimal toxic effects. Several methods are available to estimate drug likeness such as Lipinski's Rule of Five and a range of scoring methods such as Lipophilic efficiency. Several methods for predicting drug metabolism have been proposed in the scientific literature, and a recent example is SPORCalc. Due to the complexity of the drug design process, two terms of interest are still serendipity and bounded rationality. Those challenges are caused by the large chemical space describing potential new drugs without side-effects.

Computer-aided drug design

Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically activemolecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

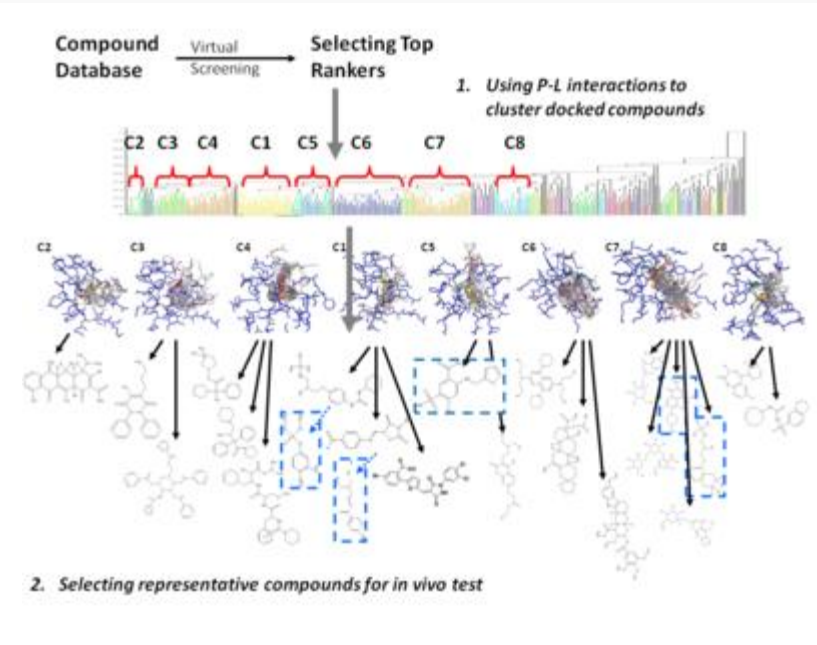
Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-basedscoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural netsor other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.

Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized. The reality however is that present computational methods are imperfect and provide at best only qualitatively accurate estimates of affinity. Therefore in practice it still takes several iterations of design, synthesis, and testing before an optimal molecule is discovered. On the other hand, computational methods have

accelerated discovery by reducing the number of iterations required and in addition have often provided more novel small molecule structures.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or ligand-based design)
2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
3. lead optimization optimization of other pharmaceutical properties while maintaining affinity



Flowchart of a Usual Clustering Analysis for Structure-Based Drug Design

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used to analysis. For structure-based drug design, several post-screening analysis focusing on protein-ligand interaction has been developed for improving enrichment and effectively mining potential candidates:

- Consensus scoring
- Selecting candidates by voting of multiple scoring functions
- May lose the relationship between protein-ligand structural information and scoring criterion

- Geometric analysis
- Comparing protein-ligand interactions by visually inspecting individual structures
- Becoming intractable when the number of complexes to be analyzed increasing
- Cluster analysis[19][20]
- Represent and cluster candidates according to protein-ligand 3D information
- Needs meaningful representation of protein-ligand interactions.

Prodrugs

Prodrugs are pharmacologically inactive derivatives of active drugs. They are designed to maximize the amount of active drug that reaches its site of action, through manipulation of the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug. Prodrugs are converted into the active drug within the body through enzymatic or non-enzymatic reactions.

A **prodrug** is a pharmacological substance that is administered in an inactive (or less than fully active) form, and is subsequently converted to an active pharmacological agent (drug) through normal metabolic processes (bioactivation). A prodrug serves as a type of 'precursor' to the intended drug.

Prodrugs can be used to improve how the intended drug is absorbed, distributed, metabolized and excreted (ADME).[1][2] Prodrugs are often designed to improve oral bioavailability in cases where the intended drug is poorly absorbed through the gastrointestinal tract. A prodrug may also be used to improve how selectively the intended drug interacts with cells or processes that are not its intended target. This reduces the adverse or unintended effects of the intended drug, especially important in treatments like chemotherapy, which can have severe unintended and undesirable side effects.

Prodrugs can be classified into two major types, based on how the body converts the prodrug into the final active drug form. Type I prodrugs are bioactivated intracellularly. Examples of these are anti-viral nucleoside analogs and lipid-lowering statins. Type II prodrugs are bioactivated extracellularly, especially in digestive fluids or in the body's circulation system. Examples of these are antibody-, gene- or virus-directed enzyme prodrugs [ADEP/GDEP/VDEP] used in chemotherapy or immunotherapy.

Table 1: Classification of prodrugs

Type	Bioactivation site	Subtype	Tissue location of bioactivation	Examples
Type I	Intracellular	Type IA	Therapeutic target tissues/cells	Acyclovir, 5-fluorouracil, cyclophosphamide, diethylstilbestrol diphosphate, L-dopa, 6-mercaptopurine, mitomycin C, zidovudine
Type I	Intracellular	Type IB	Metabolic tissues (liver, GI mucosal cell,lung etc.)	Carbamazepine, captopril, carisoprodol, heroin, molsidomine,paliperidone, phenacetin, primidone, psilocybin, sulindac,fursultiamine
Type II	Extracellular	Type IIA	GI fluids	Lisdexamfetamine, loperamide oxide, oxyphenisatin, sulfasalazine
Type II	Extracellular	Type IIB	Systemic circulation and Other Extracellular Fluid Compartments	Acetylsalicylate, bacampicillin, bambuterol, chloramphenicol succinate, dihydropyridine pralidoxime, dipivefrin, fosphenytoin
Type II	Extracellular	Type IIC	Therapeutic Target Tissues/Cells	ADEPTs, GDEPs, VDEPs

Type IA prodrugs include many antimicrobial and chemotherapy agents (e.g., 5-flurouracil). Type IB agents rely on metabolic enzymes, especially in hepatic cells, to bioactivate the prodrugs intracellularly to active drugs. Type II prodrugs are bioactivated extracelluarly, either in the milieu of GI fluids (Type IIA), within the systemic circulation and/or other extracellular fluid compartments (Type IIB), or near therapeutic target tissues/cells (Type IIC), relying on common enzymes such as esterases and phosphatases or target directed enzymes. Importantly, prodrugs can belong to multiple subtypes (i.e., Mixed-Type). A Mixed-Type prodrug is one that is bioactivated at multiple sites, either in parallel or sequential steps.

Soft drugs

Drugs are sometimes divided into "hard drugs " and "soft drugs". Hard drugs are "non-metabolizable drugs" or drugs which are metabolized to biologically active metabolites. The metabolites of hard drugs are frequently toxic oxidation products. Soft drugs are drugs which are characterized by a predictable and controllable in vivo destruction (i.e. metabolism) to non-toxic products after they have achieved their therapeutic role. Similarly "hard compounds" can be defined as compounds which do not degrade in the environment or compounds which do it very slowly. Thus, these compounds will lead to progressive pollution of the environment. An example of a hard compound is the insecticide DDT. "Soft compounds" can be defined as biologically active compounds which are readily degraded to non-toxic and biologically inactive degradation products in the environment. The purpose of this project is to design, synthesise and test soft drugs and soft environmental-friendly compounds.

Soft drug design represents a new approach aimed to design safer drugs with an increased therapeutic index by integrating metabolism considerations into the drug design process. Soft drugs are new therapeutic agents that undergo predictable metabolism to inactive metabolites after exerting their therapeutic effect.

Some of my drinking buddies have started smoking weed. I was concerned that this was drug abuse, but they said not to worry about it because weed is a soft drug. So what is the difference between soft drugs and hard drugs?

Answer:

The terms "soft drugs" and "hard drugs" are arbitrary terms, with little to no clear criteria or scientific basis.

Typically, the term "hard drug" has been used to categorize drugs that are addictive and injectable, notably, heroin, cocaine, and crystal meth. Marijuanais usually the only drug included within the category of "soft" drugs, although some people include nicotine and alcohol in the soft drug category because of their legal status for use by adults, and their relative social acceptability compared to illegal drugs. The term "soft drug" is sometimes used interchangably with the term gateway drug, a term that is equally inaccurate.

Use of the terms "hard" and "soft" drugs raises more questions than it answers. Is a drug only "hard" when it is injected? Surely heroin, crack and meth are not "soft" drugs when they are smoked. With these drugs, it is the purity, amount, frequency of use, social context, and route of administration that typically determines how harmful it is.

And the implication that marijuana is a soft or relatively harmless drug is being increasingly questioned. There are several different types of marijuana, with hashish and hash oil traditionally being thought of as harder forms of cannabis. However, stronger strains of weedare being genetically engineered and longer-term harms are becoming more apparent.

1. What is meant by an enzyme inhibitor.
2. What are enzyme activators

An **enzyme inhibitor** is a molecule which binds to enzymes and decreases their activity. Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance, many drugs are enzyme inhibitors. They are also used as herbicides and pesticides. Not all molecules that bind to enzymes are inhibitors; *enzyme activators* bind to enzymes and increase their enzymatic activity, while enzyme substrates bind and are converted to products in the normal catalytic cycle of the enzyme.

The binding of an inhibitor can stop a substrate from entering the enzyme'sactive site and/or hinder the enzyme from catalyzing its reaction. Inhibitor binding is either reversible or irreversible. Irreversible inhibitors usually react with the enzyme and change it chemically (e.g. via covalent bond formation). These inhibitors modify key amino acid residues needed for enzymatic activity. In contrast, reversible inhibitors bind non-covalently and different types of inhibition are produced depending on whether these inhibitors bind to theenzyme, the enzyme-substrate complex, or both.

Many drug molecules are enzyme inhibitors, so their discovery and improvement is an active area of research in biochemistry and pharmacology. A medicinal enzyme inhibitor is often judged by its specificity (its lack of binding to other proteins) and its potency (its dissociation constant, which indicates the concentration needed to inhibit the enzyme). A high specificity and potency ensure that a drug will have few side effects and thus low toxicity.

Enzyme inhibitors also occur naturally and are involved in the regulation of metabolism. For example, enzymes in a metabolic pathwaycan be inhibited by downstream products. This type

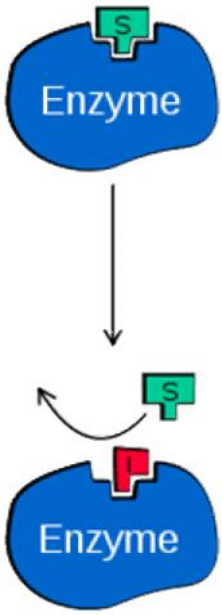
of negative feedback slows the production line when products begin to build up and is an important way to maintain homeostasis in a cell. Other cellular enzyme inhibitors are proteins that specifically bind to and inhibit an enzyme target. This can help control enzymes that may be damaging to a cell, like proteases or nucleases. A well-characterised example of this is the ribonuclease inhibitor, which binds to ribonucleases in one of the tightest known protein–protein interactions.[1]Natural enzyme inhibitors can also be poisons and are used as defences against predators or as ways of killing prey.

3. What is meant by an enzyme inhibitor.
4. What are enzyme activators
5. How the Reversible inhibitors bind to enzymes
6. How many kinds of reversible inhibitors are available
7. What are enzymes. Give examples
8. What is meant by irreversible inhibition
9. What are the different types of irreversible inhibition
10. What is meant by **non-competitive inhibition**
11. What is meant by **competitive inhibition**
12. **Differentiate competitive inhibition and non-competitive inhibition**
    a. What are the primary physicochemical considerations in preparing pharmaceutical solutions
    b. How temperature affects the pharmaceutical solutions
    c. PKa values
    d. How quinine was discovered.
    e. Give an example for accidental discoveries of drugs
    f. What is meant by a clinical trial.
    g. What for a clinical trial may be designed to do

    3. What are the different phases in the clinical trial.

Types of reversible inhibitors

Reversible inhibitors bind to enzymes with non-covalent interactions such as hydrogen bonds, hydrophobic interactions and ionic bonds. Multiple weak bonds between the inhibitor and the active site combine to produce strong and specific binding. In contrast to substratesand irreversible inhibitors, reversible inhibitors generally do not undergo chemical reactions when bound to the enzyme and can be easily removed by dilution or dialysis.



Competitive inhibition: substrate (S) and inhibitor (I) compete for the active site.

There are four kinds of reversible enzyme inhibitors. They are classified according to the effect of varying the concentration of the enzyme's substrate on the inhibitor.[2]

- In **competitive inhibition**, the substrate and inhibitor cannot bind to the enzyme at the same time, as shown in the figure on the left. This usually results from the inhibitor having an affinity for the active site of an enzyme where the substrate also binds; the substrate and inhibitor *compete* for access to the enzyme's active site. This type of inhibition can be overcome by sufficiently high concentrations of substrate (Vmax remains constant), i.e., by out-competing the inhibitor. However, the apparent Km will increase as it takes a higher concentration of the substrate to reach the Km point, or half the Vmax. Competitive inhibitors are often similar in structure to the real substrate (see examples below).

- In **uncompetitive inhibition**, the inhibitor binds only to the substrate-enzyme complex, it should not be confused with non-competitive inhibitors. This type of inhibition causes Vmax to decrease (maximum velocity decreases as a result of removing activated complex) and Km to decrease (due to better binding efficiency as a result of Le Chatelier's principle and the effective elimination of the ES complex thus decreasing the Km which indicates a higher binding affinity).

- In **mixed inhibition**, the inhibitor can bind to the enzyme at the same time as the enzyme's substrate. However, the binding of the inhibitor affects the binding of the substrate, and vice versa. This type of inhibition can be reduced, but not overcome by increasing concentrations of substrate. Although it is possible for mixed-type inhibitors to bind in the active site, this type of inhibition generally results from anallosteric effect where the inhibitor binds to a different site on an enzyme. Inhibitor binding to thisallosteric site changes the conformation (i.e., tertiary structure or three-dimensional shape) of the enzyme so that the affinity of the substrate for the active site is reduced.

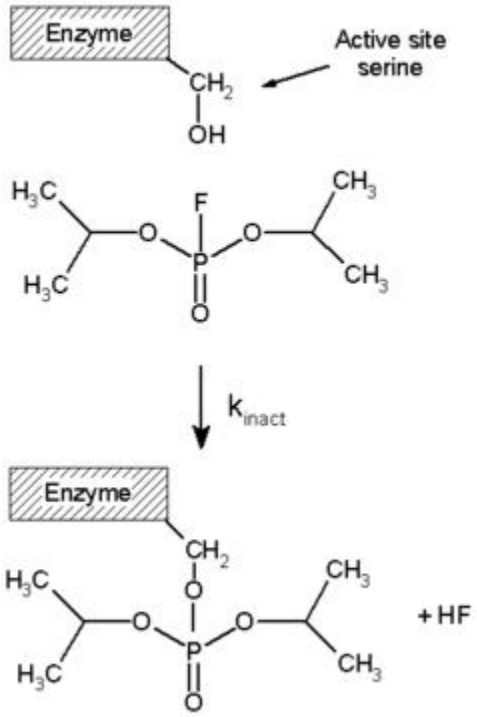
- Non-competitive inhibition is a form of mixed inhibition where the binding of the inhibitor to the enzyme reduces its activity but does not affect the binding of substrate. As a result, the extent of inhibition depends only on the concentration of the inhibitor. Vmax will decrease due to the inability for the reaction to proceed as efficiently, but Km will remain the same as the actual binding of the substrate, by definition, will still function properly.

As enzymes have evolved to bind their substrates tightly, and most reversible inhibitors bind in the active site of enzymes, it is unsurprising that some of these inhibitors are strikingly similar in structure to the substrates of their targets. An example of these substrate mimics are the protease inhibitors, a very successful class of antiretroviral drugs used to treat HIV.[12] The structure of ritonavir, a protease inhibitor based on a peptide and containing three peptide bonds, is shown on the right. As this drug resembles the protein that is the substrate of the HIV protease, it competes with this substrate in the enzyme's active site.

4. What is meant by irreversible inhibition
5. What are the different types of irreversible inhibition
6. What is meant by non-competitive inhibition
7. What is meant by competitive inhibition
8. Differentiate competitive inhibition and non-competitive inhibition
    1. What are the primary physicochemical considerations in preparing pharmaceutical solutions
    2. How temperature affects the pharmaceutical solutions
    3. PKa values
    4. How quinine was discovered.
    5. Give an example for accidental discoveries of drugs
    6. What is meant by a clinical trial.
    7. What for a clinical trial may be designed to do

    3. What are the different phases in the clinical trial.

Types of irreversible inhibition



Reaction of the irreversible inhibitordiisopropylfluorophosphate (DFP) with a serine protease

Irreversible inhibitors usually covalently modify an enzyme, and inhibition can therefore not be reversed. Irreversible inhibitors often contain reactive functional groups such asnitrogen mustards, aldehydes, haloalkanes, alkenes, Michael acceptors, phenyl sulfonates, or fluorophosphonates. These electrophilic groups react with amino acid side chains to form covalent adducts. The residues modified are those with side chains containing nucleophiles such as hydroxyl or sulfhydryl groups; these include the amino acids serine (as in DFP, right), cysteine, threonine or tyrosine.[16]

Irreversible inhibition is different from irreversible enzyme inactivation. Irreversible inhibitors are generally specific for one class of enzyme and do not inactivate all proteins; they do not function by destroying protein structure but by specifically altering the active site of their target. For example, extremes of pH or temperature usually cause denaturation of all protein structure, but this is a non-specific effect. Similarly, some non-specific chemical treatments destroy protein structure: for example, heating in concentrated hydrochloric acid will hydrolyse the peptide bonds holding proteins together, releasing free amino acids.[17]

Irreversible inhibitors display time-dependent inhibition and their potency therefore cannot be characterised by an IC_{50} value. This is because the amount of active enzyme at a given concentration of irreversible inhibitor will be different depending on how long the inhibitor is pre-incubated with the enzyme. Instead, $k_{obs}/[I]$ values are used,[18] where k_{obs} is the observed pseudo-first order rate of inactivation (obtained by plotting the log of % activity vs. time) and $[I]$ is the concentration of inhibitor. The $k_{obs}/[I]$ parameter is valid as long as the inhibitor does not saturate binding with the enzyme (in which case $k_{obs} = k_{inact}$).

Diisopropylfluorophosphate (DFP) is shown as an example of an irreversible protease inhibitor in the figure above right. The enzyme hydrolyses the phosphorus–fluorine bond, but the phosphate residue remains bound to the serine in the active site, deactivating it.[26] Similarly, DFP also reacts with the active site of acetylcholine esterase in the synapses of neurons, and consequently is a potent neurotoxin, with a lethal dose of less than 100 mg

The purpose (actually, I should say function) of enzymes is basically to catalyze the various reactions that must occur within the body. Like a true catalyst, each enzyme is in the end itself unchanged in the reaction it catalyzes, although it may undergo several changes during the execution of the reaction. A catalyst exerts a profound effect on the rate at which the reaction takes place, often increasing it by a factor of as much as one hundred thousand to a million. In many cases this amounts to the difference between reacting and not reacting. Thus, enzymes not only catalyze reactions, they are also the means that the body uses to control which reactions occur. In order to function, an enzyme must have a precise, three-dimensional structure. By subtly (and reversibly) altering the structure of an enzyme, the body can use the enzyme as a switch to turn on and off the reaction that it catalyzes.
Enzymes are generally named using an -ase ending.

Enzyme Function

In simple terms, an enzyme functions by binding to **one or more of the reactants** in a reaction. The reactants that bind to the enzyme are known as the **substrates** of the enzyme. The exact location on the enzyme where substrate binding takes place is called the **active site** of the enzyme. The shape of the active site just fits the shape of the substrate, somewhat like a lock fits a key. In this way only the correct substrate binds to the enzyme.

Once the substrate or substrates are bound to the enzyme, the enzyme can promote the desired reaction in some particular way. What that way is depends on the nature of the reaction and the nature of the enzyme. An enzyme may hold two substrate molecules in precisely the orientation needed for the reaction to occur. Or binding to the enzyme may weaken a bond in a substrate molecule that must be broken in the course of the reaction, thus increasing the rate at which the reaction can occur.

An enzyme may also **couple two different reactions**. Coupling an exothermic reaction with an endothermic one allows the enzyme to use the energy released by the exothermic reaction to drive the endothermic reaction. In fact, a large variety of enzymes couple many different endothermic reactions to the exothermic reaction in which ATP is converted by hydrolysis to ADP. In this way,

ATP serves as the molecular fuel that powers most of the energy-requiring processes of living things.

ENZYME INHIBITORS

This page looks at the effect of inhibitors on reactions involving enzymes. This is the third and final page talking about how enzymes function as catalysts. Please remember that this series of pages is written for 16 - 18 year old *chemistry* students. If you want something more advanced, you are looking in the wrong place.

Competitive and non-competitive inhibition

Competitive inhibitors

This is the most straightforward and obvious form of enzyme inhibition - and the name tells you exactly what happens.

The inhibitor has a similar shape to the usual substrate for the enzyme, and competes with it for the active site. However, once it is attached to the active site, nothing happens to it. It doesn't react - essentially, it just gets in the way.

Remember the general equation for an enzyme reacting with a substrate?

The equivalent equation for a competitive inhibitor looks like this:

The complex doesn't react any further to form products - but its formation is still *reversible*. It breaks up again to form the enzyme and the inhibitor molecule.

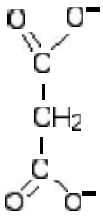
That means that if you increase the concentration of the substrate, the substrate can out-compete the inhibitor, and so the normal reaction can take place at a reasonable rate.

A simple example of this involves malonate ions inhibiting the enzyme succinate dehydrogenase. This enzyme catalyses the conversion of succinate ions to fumarate ions. The modern names are:

- malonate: propanedioate
- succinate: butanedioate
- fumarate: trans-butenedioate

The conversion that succinic dehydrogenase carries out is:

The reaction is inhibited by malonate ions which have a very similar shape to succinate ions.



The similar shape lets the malonate ions bind to the active site, but the lack of the CH_2-CH_2 bond in the centre of the ion stops any further reaction taking place.

The malonate ions therefore block the active site - but remember that this is reversible. The malonate ions will break away and free up the enzyme again. The malonate ions are in competition for the site - they aren't destroying it.

If the succinate ions have a greater concentration than the malonate ions, by chance they will get access to the site more often than the malonate ions. That means that you can overcome the effect of a competitive inhibitor by increasing the concentration of the substrate.

Non-competitive inhibitors

A non-competitive inhibitor doesn't attach itself to the active site, but attaches somewhere else on the enzyme. By attaching somewhere else it affects the structure of the enzyme and so the way the enzyme works. Because there isn't any competition involved between the inhibitor and the substrate, increasing the substrate concentration won't help.

If you look at various biochemistry sites on the web, you will find two explanations for this. We'll look at the simple, fairly obvious one in some detail in a minute. I want to have a brief word about the other one first.

"Pure" non-competitive inhibitors

This explanation says that the inhibitor doesn't affect the ability of the substrate to bond with the active site, but stops it reacting once it is there.

I found a couple of biochemistry sites which said that inhibitors working like this (which they describe as *pure* non-competitive inhibitors) are virtually unknown. As a non-biochemist, I don't know what the truth is about this - if you want to find out, you will probably have to do a biochemistry degree!

Other non-competitive inhibitors

The straightforward explanation (which would seem to apply to most enzymes) is that reaction with the inhibitor causes the shape of the active site to change. Remember that non-competitive inhibitors aren't attaching directly to the active site, but elsewhere on the enzyme.

The inhibitor attachs to a side group in the protein chain, and affects the way the protein folds into its tertiary structure. That in turn changes the shape of the active site. If the shape of the active site changes, then the substrate can't attach to it any more.

Some non-competitive inhibitors attach irreversibly to the enzyme, and therefore stop it working permanently. Others attach reversibly.

A relatively uncomplicated example of non-competitive inhibitors in a reasonably familiar situation is:

Heavy metal poisoning

You are probably aware that compounds containing heavy metals such as lead, mercury, copper or silver are poisonous. This is because ions of these metals are non-competitive inhibitors for several enzymes.

I'm going to take silver as a simple example.

Silver ions react with -SH groups in the side groups of cysteine residues in the protein chain:

cysteine residue in protein chain

There isn't enough electronegativity difference between silver and sulphur for a full ionic bond and so the bond can be considered as covalent.

If the cysteine residue is somewhere on the protein chain which affects the way it folds into its tertiary structure, then altering this group could have an effect on the shape of the active site, and so stop the enzyme from working.

The 2+ ions from, for example, mercury, copper or lead can behave similarly - also attaching themselves to the sulphur in place of the hydrogen.

Introduction

One of the primary physicochemical considerations in preparing pharmaceutical solutions is the solubility of the drug in a suitable solvent. **Solubility** may be defined as the maximum concentration of a substance that may be completely dissolved in a given solvent at a given temperature and pressure. When both solute and solvent are liquids, the term **miscibility** rather than solubility may be used to describe the affinity between the liquids.

The solubility of a substance may be described in a variety of ways. The USP/NF generally expresses the solubility in terms of the volume of solvent required to dissolve 1 gram of the drug at a specified temperature (eg. 1 g ASA in 300 ml H_2O, 5 ml ethanol at 25°C). Other references may use more subjective terms to describe solubility, such as those given in the following table from *Remington's*.

Descriptive terms	**Parts of solvent needed for 1 part solute**
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000

Practically insoluble or insoluble	> 10,000

Liquids which form a homogenous system when mixed in any proportion are said to be **miscible** (eg. water and ethanol). Those in which only certain volume ratios produce homogenous mixtures are said to be **miscible in certain proportions** (eg. water and chloroform). **Immiscible** liquids will not produce a homogenous solution in any proportions (eg. water and olive oil).

The aqueous solubility of all drugs is of interest to us, since it is only in the form of an aqueous solution that a drug can be absorbed into the general circulation to exert a therapeutic effect.

Temperature

The solubility of any substance is a function of temperature. Most substances are endothermic, absorbing heat in the process of dissolution. For these substances, an increase in temperature results in an increase in solubility. A few substances, such as calcium hydroxide and sodium carbenicillin, are exothermic and give off heat in the process of dissolution. The solubility of such substances would decrease with an increase in temperature. The application of this aspect of solubility is of limited use to us, since pharmaceutical solutions must be administered at or near room or body temperature. It is more a factor to be considered for product storage than for formulation.

Solute pKa, Solvent pH, and Solubility

According to the Henderson-Hasselbach equation, the relationship between pH, pKa, and relative concentrations of an acid and its salt is as follows:

$$pH = pKa + log\frac{[A^-]}{[HA]}$$

where $[A^-]$ is the molar concentration of the salt (dissociated species) and [HA] is the concentration of the undissociated acid. When the concentrations of salt and acid are equal, the pH of the system equals the pKa of the acid. As the pH decreases, the concentration of the molecular acid increases and that of the salt decreases. This has some interesting implications regarding the aqueous solubility of the acid, since the undissociated form is much less soluble than its salt. Of further interest, therapeutically, is the fact that it is the undissociated acid (HA) that more readily penetrates biological tissues to exert a therapeutic effect. Thus, in formulating the product, some balance must be struck between the more soluble salt form and the biologically active acid and factors other than pKa and pH must be considered (e.g. safety and comfort).

Changes in solubility brought about by alterations of solvent pH can be predicted by the pHp equation. The pHp is the pH below which an acid or above which a base will begin to precipitate.

$$pHp = pKa + \log\frac{S - S_0}{S_0} \qquad (for\ a\ weak\ acid)$$

$$pHp = pKw - pKb + \log\frac{S}{S - S_0} \qquad (for\ a\ weak\ base)$$

where,

S_o = the molar solubility of the undissociated acid or base
S = the molar concentration of the salt form of the drug initially added

Solute and Solvent Structure/Polarity

Solute molecules are held together by certain intermolecular forces (dipole-dipole, induced dipole-induced dipole, ion-ion, etc.), as are molecules of solvent. In order for dissolution to occur, these cohesive forces of like molecules must be broken and adhesive forces between solute and solvent must be formed.

The solubility of a drug in a given solvent is largely a function of the polarity of the solvent. Solvents may be considered polar, semi-polar or non-polar. Polar solvents will dissolve ionic and other polar solutes (i.e. those with an asymmetric charge distribution [like dissolves like]), whereas, non-polar solvents will dissolve non-polar molecules. Semi-polar solvents (eg. alcohols and ketones) may induce a certain degree of polarity in non-polar molecules and may thus act to improve the miscibility of polar and non-polar liquids. The relationship between polarity and solubility may be used in practice to alter the solubility of a drug in a pharmaceutical solution.

One approach is to **alter the polarity of the solute** by shifting it between its molecular (undissociated) and ionic (dissociated) states. A shift toward the ionic form improves solubility of the solute in water and other polar solvents. A shift toward the molecular species improves solute solubility in non-polar solvents. Such shifts may be produced by altering the pH of the solution (or using the salt form of the compound).

Another approach is to mix solvents of different polarities to **form a solvent system of optimum polarity to dissolve the solute**. Such solvents must, obviously, be miscible. This method is referred to as **solvent blending or cosolvency** and uses the dielectric constant as a guide to developing the cosolvent system. Since many solvents may be toxic when ingested, most solvent blends are limited to mixtures containing water, ethanol, glycerin, propylene glycol, polyethylene glycol 400 or sorbitol solution. The list is somewhat expanded for solutions for external application.

The dielectric constant (δ) of a compound is an index of its polarity. A series of solvents of increasing polarity will show a similar increase in dielectric constant.

Compound	**Dielectric constant, δ, @ 20°C**
N-methylformamide	190
Water	80
Sorbitol Solution USP (70% w/w)	62
Syrup USP	56
Glycerol (glycerin)	46
Methanol	33
Propylene glycol	32.1
Ethanol	25
n-Propyl alcohol	22
Acetone	21
Polyethylene glycol 400	12.4
Chloroform	5

Castor oil	4.6
Ethyl ether	4.3
Sucrose	3.3
Olive oil	3.1
Sesame oil	3.1
Benzene	2.2
Carbon tetrachloride	2.2
Octane	1.9

Solvents may be classified according to their dielectric constants as polar ($\delta > 50$), semi-polar ($\delta = 20 - 50$), or non-polar ($\delta = 1 - 20$).

The value of the dielectric constant for a mixture is obtained by multiplying the volume fraction of each solvent times its dielectric constant and summing.

$$A + B + \ldots = f_A\delta_A + f_B\delta_B + \ldots$$

There are many pharmaceutical substances which are non-polar or which are weak acids and bases whose ionized salt forms are unstable in solution. In order to dispense solutions of these substances, we must derive a solvent of appropriate polarity (or non-polarity).

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates.[1] The importance of natural products in modern medicine has been discussed in recent reviews and reports.[1-6] The value of natural products in this regard can be assessed using 3 criteria: (1) the rate of introduction of new chemical entities of wide structural diversity, including serving as templates

for semisynthetic and total synthetic modification, (2) the number of diseases treated or prevented by these substances, and (3) their frequency of use in the treatment of disease.

Approved Drugs

Apomorphine hydrochloride (**1**, Apokyn, Bertek, 2004), a short-acting dopamine D_1 and D_2 receptor agonist, is a potent dopamine receptor agonist used to treat Parkinson's disease, a chronic neurodegenerative disease caused by the loss of pigmented mesostriatal dopaminergic neurons linking the substantia nigra (pars compacta) to the neostriatum (caudate nucleus and putamen). Apomorphine is a derivative of morphine isolated from poppy (*Papaver somniferum*). Subcutaneous apomorphine is currently used for the management of sudden, unexpected and refractory levodopa-induced off states in fluctuating Parkinson's disease.[16]

Tiotropium bromide (**2**, Spiriva Handihaler, Boehringer Ingelheim, 2004) has been approved by the United States Food and Drug Administration (FDA) for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Tiotropium, a derivative of atropine from *Atropa belladonna*(Solanaceae) and related tropane alkaloids from other solanaceous plants, is a potent reversible nonselective inhibitor of muscarinic receptors. Tiotropium is structurally analogous to ipratropium, a commonly prescribed drug for COPD, but has shown longer-lasting effects.[17]

Nitisinone (**3**, Orfadin, Swedish Orphan, 2002) is a derivative of leptospermone, an important new class of herbicides from the bottlebrush plant (*Callistemon citrinus*), and exerts an inhibitory effect for *p*-hydroxyphenylpyruvate dioxygenase (HPPD) involved in plastoquinone synthesis.[18] This drug has been used successfully as a treatment of hereditary tyrosinaemia type 1 (HT-1), a severe inherited disease of humans caused by a deficiency of fumaryl acetoacetate hydrolase (FAH), leading to accumulation of fumaryl and maleyl acetoacetate, and progressive liver and kidney damage.[19]

Galantamine hydrobromide (**4**, Reminyl, Janssen, 2001) is an Amaryllidaceae alkaloid obtained from *Galanthus nivalis* that has been used traditionally in Bulgaria and Turkey for neurological conditions,[20,21] and was launched onto the market as a selective acetylcholinesterase inhibitor for Alzheimer's disease treatment, slowing the process of neurological degeneration by inhibiting acetylcholinesterase as well as binding to and modulating the nicotinic acetylcholine receptor.[5]

Arteether (**5**, Artecef, Artecef BV, 2000), an antimalarial agent, has been developed from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua*(Asteraceae), a plant used in traditional Chinese medicine as a remedy for chills and fevers. Other derivatives of artemisinin are in various stages of clinical development as antimalarial drugs in Europe.[5,22]

Drug Absorption, Distribution and Metabolism

Once the drug is administered, the Phamacokinetic phase or absorption begins. The route of administration, the solubility of the drug and the presence of inflammation influence the rate of absorption. Intravenous administration is the fastest, while oral injection is the slower. Water soluble drugs are absorbed more quickly.

The Phamacokinetic phase continues with the distribution of the drug. For a drug to be therapeutic a sufficient amount of the drug must be available in the system. Too much of the drug may cause a toxic effect, while too little will not do what it is suppose to do.

The next step in the Phamacokinetic phase is metabolism or biotransformation. Metabolism most often occurs in the liver. But may also occur in the kidneys, lungs, plasma and intestinal mucosa.

Lastly, the final phase of the Phamacokinetic process is excretion. Most often excretion occurs my the kidneys in urine. But drugs may also be eliminated through sweat, saliva, bile, breast milk, breathing and feces.

As discussed in the text, there are numerous factors that influence the effects of drugs. An example is an individual with uncontrolled diabetes and periodontal disease. An individual with uncontrolled diabetes is at higher risk for periodontal disease due to the body's decreased ability to effectively respond to inflammation. However, the therapeutic effect of insulin is decreased in the presence of inflammation. As you can imagine, without careful monitoring of the circulating drug, resolution of both diseases may be challenging.

The Phamacokinetic Phase is very clearly illustrated in these animations:

- Absorption
- Distribution
- Binding
- Excretion

To understand how drugs work, one must understand the concept of drug kinetics. In short, drug kinetics refers to the actions taken by the human body to deal with a medicine. These actions involve the processes of drug absorption into the body, distribution of that drug to various tissues, metabolism (or breakdown), and excretion (or elimination). Of the above processes, absorption is the most significant.

Absorption

Absorption is the process by which a drug passes from its site of administration into the circulation (bloodstream). The blood receives a drug from the site of administration and carries it to all the organs, including those on which the drug acts. The speed, ease, and degree of absorption are related to the route of administration. There are several sites at which drugs are commonly administered. They are as follows:

- Intravenous administration (IV) - IV refers to the injection of a drug directly into the blood, most commonly into a peripheral vein.

- Intramuscular injection (IM) - In an intermuscular injection, the drug is injected into the muscle. This type of injection may have erratic absorption. If suspended in an oil base, an IM medicine usually has a slow and even absorption. (i.e. penicillin IM)
- Subcutaneous injection (SQ, SC) - With a subcutaneous injection, the drug is injected just beneath the skin. A subcutaneous injection provides slower absorption than an IM. (i.e. insulin)
- Rectal administration - In this type of administration, the drug passes through the rectal lining (mucosa) into the blood. Absorption is highly variable and may cause irritation of the rectal mucosa. This route is mainly used for antinausea and antiemetic (antivomiting) drugs.
- Oral route - This is the most commonly used route of administration for drugs. It uses the oral lining (mucosa) and the gastrointestinal tract (GI).

o The oral mucosa administration includes sublingual (under the tongue) and buccal (in the cheek) methods. These methods provide convenient routes when rapid onset of action is required (i.e. sublingual nitroglycerin) and are convenient ways to administer drugs that are unstable in the gastointestinal environment.

o Absorption of drugs from the GI tract depends on the drug's ability to pass across intestinal cell membranes, withstand the highly acidic environment of the stomach, and resist destruction in the liver (first-pass effect). In most cases drugs pass through cell membranes of intestines by simple diffusion, from an area of high concentration (inside the lumen of the intestines) to an area of lower concentration (bloodstream). Active transport across the GI mucosa, very much like a shuttle system, is another way some substances are absorbed (i.e. Vitamin B12). Other factors that may affect absorption of drugs include food and other medications that may inactivate the drug.

Distribution

After the drug is absorbed, it is then distributed to various organs of the body. Distribution is influenced by how well each organ is perfused (supplied by blood), organ size, binding of the drug to various components of blood and tissues, and permeability of tissue membranes. The more fat-soluble a drug is, the higher its ability to pass across the cell membrane is. The blood-brain-barrier restricts passage of drugs from the blood into the central nervous system and cerebrospinal fluid. Protein binding (attachment of the drug to blood proteins) is an important consideration influencing drug distribution. Many drugs are bound to blood proteins such as serum albumin (the main blood protein) and are not available as active drugs.

Metabolism

Metabolism occurs via two types of reactions: phase I and phase II. The goal of metabolism is to change the active part of medications (also referred to as the functional group), making them more water-soluble and more readily excreted by the kidney. (ie. the body is trying to get rid of the "foreign" drug) Changing the molecular structure of drugs increases their water solubility and decreases their fat solubility, which speeds up the excretion of the drug in the urine. Phase I reactions involve oxidation, hydrolysis, and reduction. Oxidation and reduction processes make a molecule's charge more positive or negative than the original drug. Regardless of the positivity or negativity, a charged molecule is dissolvable in water. (blood serum is primarily water) These reactions take place primarily in the liver by enzymes known as the cytochrome p-450 enzyme system. Oxidative metabolism may result in formation of an active metabolite or inactive compound. Phase II reactions involve conjugation (which means adding another compound) to form glucuronides, acetates, or sulfates, by adding glucose, acetate, or sulfate molecules, respectively.

These reactions generally inactivate the pharmacologic activity of the drug and may make it more prone to elimination by the kidney.

Excretion

Excretion occurs primarily through the urine. Fecal excretion is seen with drugs that are not absorbed from the intestines or have been secreted in the bile (which is discharged into the intestines). Drugs may also be excreted in the expired air through the lungs, in the perspiration, or in breast milk. There are three processes by which drugs are eliminated through the urine: by pressure filtration of the drug through the kidney component called the Glomerulus, through active tubular secretion (like the shuttle system), and by passive diffusion from areas of high drug concentration to areas of lower concentration.

The above paragraphs explain what the human body does to the drug (pharmacokinetics). What the drug does to the body is called pharmacodynamics; this term refers to the action of the drug at the tissue-,cellular-, and molecular level. Pharmacodynamic processes are specific to and different for each drug.

Absorption/administration

For a compound to reach a tissue, it usually must be taken into the bloodstream - often via mucous surfaces like the digestive tract(intestinal absorption) - before being taken up by the target cells. Factors such as poor compound solubility, gastric emptying time, intestinal transit time, chemical instability in the stomach, and inability to permeate the intestinal wall can all reduce the extent to which a drug is absorbed after oral administration. Absorption critically determines the compound's bioavailability. Drugs that absorb poorly when taken orally must be administered in some less desirable way, like intravenously or by inhalation (e.g. zanamivir). Routes of administration is an important consideration.

Distribution

The compound needs to be carried to its effector site, most often via the bloodstream. From there, the compound may distribute into muscle and organs, usually to differing extents. After entry into the systemic circulation, either by intravascular injection or by absorption from any of the various extracellular sites, the drug is subjected to numerous distribution processes that tend to lower its plasma concentration.

Distribution is defined as the reversible transfer of a drug between one compartment to another. Some factors affecting drug distribution include regional blood flow rates, molecular size, polarity and binding to serum proteins, forming a complex. Distribution can be a serious problem at some natural barriers like the blood–brain barrier.

Metabolism

Compounds begin to break down as soon as they enter the body. The majority of small-molecule drug metabolism is carried out in the liver by redox enzymes, termed cytochrome P450 enzymes. As metabolism occurs, the initial (parent) compound is converted to new compounds called metabolites. When metabolites are pharmacologically inert, metabolism deactivates the administered dose of parent drug and this usually reduces the effects on the body. Metabolites may also be pharmacologically active, sometimes more so than the parent drug.

Excretion

Compounds and their metabolites need to be removed from the body via excretion, usually through the kidneys (urine) or in the feces. Unless excretion is complete, accumulation of foreign substances can adversely affect normal metabolism.

There are three main sites where drug excretion occurs. The kidney is the most important site and it is where products are excreted through urine. Biliary excretion or fecal excretion is the process that initiates in the liver and passes through to the gut until the products are finally excreted along with waste products or feces. The last main method of excretion is through the lungs e.g. anesthetic gases.

Excretion of drugs by the kidney involves 3 main mechanisms:

- Glomerular filtration of unbound drug.
- Active secretion of (free & protein-bound) drug by transporters e.g. anions such as urate, penicillin, glucuronide, sulfate conjugates) or cations such as choline, histamine.
- Filtrate 100-fold concentrated in tubules for a favorable concentration gradient so that it may be secreted by passive diffusion and passed out through the urine.

Lead molecules

A **lead compound** (i.e. the "leading" compound, not lead metal) in drug discovery is a chemical compound that has pharmacological orbiological activity and whose chemical structure is used as a starting point for chemical modifications in order to improve potency,selectivity, or pharmacokinetic parameters.

Lead compounds are often found in high-throughput screenings ("hits") or are secondary metabolites from natural sources.

Newly invented pharmacologically active moieties may have poor drug likeness and may require chemical modification to become drug-like enough to be tested biologically or clinically.

Modern drug discovery and development efforts typically emerge from basic research and then gradually move on to specific sequential tasks, which – if successful – culminate in a new drug for the treatment of a human disease. The overall pathway is structured by well-delineated milestones, which include selection of the drug target, identification of a lead compound, its modification to a compound suitable for toxicity testing in animals, and selection as drug candidate for clinical testing. Although the road is well mapped out, it is by no means easy or guaranteed to end in success. Even before the onset of human studies, a drug candidate suitable for clinical testing is expected to satisfy specific and demanding criteria. It must bind selectively to the receptor site on the target and elicit the desired functional response from the target molecule. It must have sufficient bioavailability and distribution within the body to reach the receptor site, and it must elicit the desired responses *in vivo*, in animal models of the human disease. Most importantly, a drug candidate suitable for testing in humans must pass a formal toxicity evaluation in animals, to demonstrate that humans participating in the clinical studies are exposed to minimal risks only.

Drug Discovery Screening

Once a biochemical or cell-based assay has been developed successfully, the lead identification, or screening, process begins. Primary screensidentify hits. Subsequently, confirmation screens and counter screens identify leads out of the pool of hits. This is commonly referred to as the "hit-to-lead" process. The success of drug discovery screening depends on the availability of compounds, as well as their quality and diversity. Efforts to synthesize, collect, and characterize compounds are an essential and costly part of drug discovery.

Primary Screens

The goals of primary screens are to minimize the number of false positives and maximize the number of confirmed hits. Typically, primary screens are run in multiplets (i.e., two, three, or more) of single compound concentrations. Readouts are expressed as percent activity in comparison to positive and negative controls. Hits are retested independently of the first assay. If

a compound exhibits the same activity within a statistically significant range, it is termed a confirmed hit. The next step is dose-response screening, typically referred to as a secondary screen.

Secondary Screens

In a secondary screen, a range of compound concentrations is tested in an assay to assess the concentration or dose dependence of the assay's readout. Typically, this dose-response is expressed as an IC50 in enzyme-, protein-, antibody-, or cell-based assays, or as an EC50 in *in vivo*experiments. The shape of a dose-response curve often provides information about the mechanism of action.

Confirmed hits are then profiled or run through a series of counterscreens. These assays usually include drug targets of the same protein or receptor family; for example, panels of GPCRs or kinases. These screens profile the action of a confirmed hit on a defined spectrum of biological target classes. Counterscreens can also be used to confirm mechanism of action.

Mechanism of Action

One of the goals throughout the discovery of novel drugs is to establish and confirm the mechanism of action. In an ideal scenario, the mechanism of action remains consistent from the level of molecular interaction of a drug molecule at the target site through the physiological response in a disease model.

Molecular Devices provides a range of bioanalytical systems to support primary and secondary screening, compound profiling, and mechanism of action studies.

Lead Optimization

Lead optimization is a complex, non-linear process. During this stage of drug discovery, the chemical structure of a confirmed hit is refined to improve its drug characteristics with the goal of producing a preclinical drug candidate.

Typically, confirmed hits are evaluated in secondary assays, and a set of related compounds, called analogs, are synthesized and screened. The testing of analog series results in quantitative information that correlates changes in chemical structure to biological and pharmacological data to establish structure-activity relationships (SARs).

Today, lead optimization often involves a series of standard assays to evaluate toxicity, including P450 inhibition, cytotoxicity assays, and hERG testing. Toxicity in these relatively simple *in vitro* assays flags hits or leads that could have potential safety concerns.

Another characteristic that lead optimization often evaluates is formulation. Formulation and delivery are closely linked. For example, a drug intended to be delivered via intramuscular injection might call for a different formulation than would one intended for oral delivery. Formulation problems and solutions feed back into the iterative lead optimization cycle.

Molecular Devices offers a range of products that are particularly well suited for lead optimization studies.

table 1

Desired properties for drug candidate taken for evaluation in formal animal toxicity studies.

Properties	**Details**
Chemical properties	Stable molecule

Properties	Details
	Nonproblematic synthesis with potential for scale-up
Pharmacological properties	Selective high-affinity binding to target binding site
	Selective and potent functional effect on target receptor molecule *in vitro*
	Effectiveness in animal model of targeted human indication
Pharmacokinetics	Adequate bioavailability for selected route of administration
	Adequate half-life and biodistribution for intended use
Safety and toxicity	Satisfactory profile for inhibition and induction of cytochrome P450 enzymes

Properties	Details
	Absence of obvious cardiac toxicity (hERG binding)

1. **How quinine was discovered.**
2. **Give an example for accidental discoveries of drugs**
3. What is meant by a clinical trial.
4. What for a clinical trial may be designed to do

3. What are the different phases in the clinical trial.

Accidental Discoveries

QUININE

The story behind the chance discovery of the anti-malarial drug quinine may be more legend than fact, but it is nevertheless a story worthy of note. The account that has gained the most currency credits a South American Indian with being the first to find a medical application for quinine. According to legend, the man unwittingly ingested quinine while suffering a malarial fever in a jungle high in the Andes. Needing desperately to quench his thirst, he drank his fill from a small, bitter-tasting pool of water. Nearby stood one or more varieties of cinchona, which grows from Colombia to Bolivia on humid slopes above 5,000 feet. The bark of the cinchona, which the indigenous people knew as *quina-quina,* was thought to be poisonous. But when this man's fever miraculously abated, he brought news of the medicinal tree back to his tribe, which began to use its bark to treat malaria.

A laborer scrapes the bark from a cinchona tree. The bark is then sundried and pulverized to make the drug quinine. EnlargePhoto credit: Corbis

Since the first officially noted use of quinine to fight malaria occurred in a community of Jesuit missionaries in Lima, Peru in 1630, historians have surmised that Indian tribes taught the missionaries how to extract the chemical quinine from cinchona bark. In any case, the Jesuits' use of quinine as a malaria medication was the first documented use of a chemical compound to successfully treat an infectious disease. To this day, quinine-based anti-malarials are widely used as effective treatments against the growth and reproduction of malarial parasites in humans.

SMALLPOX VACCINATION

In 1796, Edward Jenner, a British scientist and surgeon, had a brainstorm that ultimately led to the development of the first vaccine. A young milkmaid had told him how people who contracted cowpox, a harmless disease easily picked up during contact with cows, never got smallpox, a deadly scourge.

With this in mind, Jenner took samples from the open cowpox sores on the hands of a young dairymaid named Sarah Nelmes and inoculated eight-year-old James Phipps with pus he extracted from Nelmes' sores. The boy developed a slight fever and a few lesions but remained for the most part unscathed. A few months later, Jenner gave the boy another injection, this one containing smallpox. James failed to develop the disease, and the idea behind the modern vaccine was born.

A depiction of Edward Jenner vaccinating James Phipps, a boy of eight, on May 14, 1796EnlargePhoto credit: Corbis

X-RAYS

X-rays have become an important tool for medical diagnoses, but their discovery in 1895 by the German physicist Wilhelm Conrad Röntgen had little to do with medical experimentation. Röntgen was studying cathode rays, the phosphorescent stream of electrons used today in everything from televisions to fluorescent light bulbs. One earlier scientist had found that cathode rays can penetrate thin pieces of metal, while another showed that these rays could light up a fluorescent screen placed an inch or two away from a thin aluminum "window" in the glass tube.

Röntgen wanted to determine if he could see cathode rays escaping from a glass tube completely covered with black cardboard. While performing this experiment, Röntgen noticed that a glow appeared in his darkened laboratory several feet away from his cardboard-covered glass tube. At first he thought a tear in the paper sheathing was allowing light from the high-voltage coil inside the cathode-ray tube to escape. But he soon realized he had happened upon something entirely different. Rays of light were passing right through the thick paper and appearing on a fluorescent screen over a yard away.

Röntgen found that this new ray, which had many characteristics different from the cathode ray he had been studying, could penetrate solids and even record the image of a human skeleton on a photographic negative. In 1901, the first year of the Nobel Prize, Röntgen won for his accidental discovery of what he called the "X-ray," which physicians worldwide soon adopted as a standard medical tool.

ALLERGY

Charles Robert Richet, a French physiologist, made several experiments testing the reaction of dogs exposed to poison from the tentacles of sea anemones. Some of the dogs died from allergic shock, but others survived their reactions and made full recoveries.

Weeks later, because the recovered dogs seemed completely normal, Richet wasted no time in reusing them for more experiments. They were given another dose of anemone poison, this time much smaller than before. The first time the dogs' allergic symptoms, including vomiting, shock, loss of consciousness, and in some cases death, had taken several days to fully develop. But this time the dogs suffered such serious symptoms just minutes after Richet administered the poison.

Though Richet was puzzled by what had happened, he realized he could not disregard the unexpected result of his experiment. Later, he noted that his eventual conclusions about the dogs' affliction were "not at all the result of deep thinking, but of a simple observation, almost accidental; so that I have had no other merit than that of not refusing to see the facts which presented themselves before me, completely evident."

Richet's conclusions from his findings came to form the theoretical basis of the medical study and treatment of allergies. He eventually proved that there was a physiological state called anaphylaxis that was the antithesis of prophylaxis: When an allergic subject is exposed to an allergen a second time, he or she is even more sensitive to its effects than the first time. Instead of building immunity to the substance through exposure (prophylaxis), the allergic subject's immunity becomes greatly reduced.

In 1913 Richet received a Nobel Prize for his discovery and articulation of diseases of allergy.

INSULIN

Frederick G. Banting, a young Canadian doctor, and Professor John J.R. MacLeod of the University of Toronto shared a Nobel Prize in 1923 for their isolation and clinical use of insulin against diabetes. Their work with insulin followed from the chance discovery of the link between the pancreas and blood-sugar levels by two other doctors on the other side of the Atlantic decades earlier.

In 1889, German physicians Joseph von Mering and Oscar Minkowski removed the pancreas from a healthy dog in order to study the role of the pancreas in digestion. Several days after the dog's pancreas was removed, the doctors happened to notice a swarm of flies feeding on a puddle of the dog's urine. On testing the urine to determine the cause of the flies' attraction, the doctors realized that the dog was secreting sugar in its urine, a sign of diabetes. Because the dog had been healthy

prior to the surgery, the doctors knew that they had created its diabetic condition by removing its pancreas and thus understood for the first time the relationship between the pancreas and diabetes.

With more tests, von Mering and Minkowski concluded that a healthy pancreas must secrete a substance that controls the metabolism of sugar in the body. Though many scientists tried in vain to isolate the particular substance released by the pancreas after the Germans' accidental discovery, it was Banting and MacLeod who established that the mysterious substance was insulin and began to put it to use as the first truly valuable means of controlling diabetes.

PAP SMEAR

Dr. George Nicholas Papanicolaou's chance observation, while doing a genetic study, of cancer cells on a slide containing a specimen from a woman's uterus spawned the routine use of the so-called "Pap smear," a simple test that has saved millions of women from the ravages of uterine cancer.

In 1923, Papanicolaou undertook a study of vaginal fluid in women, in hopes of observing cellular changes over the course of a menstrual cycle. In female guinea pigs, Papanicolaou had already noticed cell transformation and wanted to corroborate the phenomenon in human females. It happened that one of Papanicolaou's human subjects was suffering from uterine cancer.

Upon examination of a slide made from a smear of the patient's vaginal fluid, Papanicolaou was astonished to discover that abnormal cancer cells could be plainly observed under a microscope. "The first observation of cancer cells in the smear of the uterine cervix," he later wrote, "gave me one of the greatest thrills I ever experienced during my scientific career." Papanicolaou quickly realized that doctors could administer a simple test to gather a sample of vaginal fluid and test it for early signs of uterine and other cancers.

PENICILLIN

The identification of penicillium mold by Dr. Alexander Fleming in 1928 is one of the best-known stories of medical discovery, not only because of its accidental nature, but also because penicillin has remained one of the most important and useful drugs in our arsenal, and its discovery triggered invaluable research into a range of other invaluable antibiotic drugs.

While researching the flu in the summer of 1928, Dr. Fleming noticed that some mold had contaminated a flu culture in one of his petri dishes. Instead of throwing out the ruined dish, he decided to examine the moldy sample more closely.

Fleming had reaped the benefits of taking time to scrutinize contaminated samples before. In 1922, Fleming had accidentally shed one of his own tears into a bacteria sample and noticed that the spot where the tear had fallen was free of the bacteria that grew all around it. This discovery peaked his curiosity. After conducting some tests, he concluded that tears contain an antibiotic-like enzyme that could stave off minor bacterial growth.

Six years later, the mold Fleming observed in his petri dish reminded him of this first experience with a contaminated sample. The area surrounding the mold growing in the dish was clear, which told Fleming that the mold was lethal to the potent staphylococcus bacteria in the dish. Later he noted, "But for the previous experience, I would have thrown the plate away, as many bacteriologists have done before."

Instead, Fleming took the time to isolate the mold, eventually categorizing it as belonging to the genus *penicillium.* After many tests, Fleming realized that he had discovered a non-toxic antibiotic substance capable of killing many of the bacteria that cause minor and severe infections in humans and other animals. His work, which has saved countless lives, won him a Nobel Prize in 1945.

KEEP THAT MIND OPEN

For all you would-be Nobel Prize-winners, remember the one trait that tied all these lucky strikers together: openmindedness. As the American physicist Joseph Henry once noted, "The seeds of great discoveries are constantly floating around us, but they only take root in minds well prepared to receive them."

1. What is meant by a clinical trial.
2. What for a clinical trial may be designed to do
3. What are the different phases in the clinical trial.

Clinical trials often involve patients with specific health conditions who then benefit from receiving otherwise unavailable treatments. In early phases, participants are healthy volunteers who receive financial incentives for their inconvenience. During dosing periods, study subjects typically remain on site at the unit for durations of one to 40 nights, and occasionally longer, although this is not always the case.

Usually, one or more pilot experiments are conducted to gain insights for design of the clinical trial to follow. In medical jargon,effectiveness is how well a treatment works in practice and

efficacy is how well it works in a clinical trial. In the US, the elderly comprise only 14% of the population, but they consume over one-third of drugs.[1] Despite this, they are often excluded from trials because their more frequent health issues and drug use produce unreliable data. Women, children, and people with unrelated medical conditions are also frequently excluded.[2]

In coordination with a panel of expert investigators (usually physicians well known for their publications and clinical experience), the sponsor decides what to compare the new agent with (one or more existing treatments or a placebo), and what kind of patients might benefit from the medication or device. If the sponsor cannot obtain enough patients with this specific disease or condition at one location, then investigators at other locations who can obtain the same kind of patients to receive the treatment would be recruited into the study.

During the clinical trial, the investigators: recruit patients with the predetermined characteristics, administer the treatment(s), and collect data on the patients' health for a defined time period. These patients are volunteers and they are not paid for participating in clinical trials. These data include measurements like vital signs, concentration of the study drug in the blood, and whether the patient's health improves or not. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.

Some examples of what a clinical trial may be designed to do:

- Assess the safety and effectiveness of a new medication or device on a specific kind of patient (e.g., patients who have been diagnosed with Alzheimer's disease)
- Assess the safety and effectiveness of a different dose of a medication than is commonly used (e.g., 10-mg dose instead of 5-mg dose)
- Assess the safety and effectiveness of an already marketed medication or device for a new indication, i.e. a disease for which the drug is not specifically approved
- Assess whether the new medication or device is more effective for the patient's condition than the already used, standard medication or device ("the gold standard" or "standard therapy")
- Compare the effectiveness in patients with a specific disease of two or more already approved or common interventions for that disease (e.g., device A vs. device B, therapy A vs. therapy B)

While most clinical trials compare two medications or devices, some trials compare three or four medications, doses of medications, or devices against each other.

Except for very small trials limited to a single location, the clinical trial design and objectives are written into a document called aclinical trial protocol. The protocol is the 'operating manual' for

the clinical trial and ensures the researchers in different locations all perform the trial in the same way on patients with the same characteristics. (This uniformity is designed to allow the data to be pooled.) A protocol is always used in multicenter trials.

Because the clinical trial is designed to test hypotheses and rigorously monitor and assess what happens, clinical trials can be seen as the application of the scientific method, and specifically the experimental step, to understanding human or animal biology.

The most commonly performed clinical trials evaluate new drugs, medical devices (like a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before the national regulatory authority[3] approves marketing of the drug or device, or a new dose of the drug, for use on patients

One way of classifying clinical trials is by the way the researchers behave.

- In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.
- In an interventional study, the investigators give the research subjects a particular medicine or other intervention. Usually, they compare the treated subjects to subjects who receive no treatment or standard treatment. Then the researchers measure how the subjects' health changes.

Another way of classifying trials is by their purpose. The U.S. National Institutes of Health (NIH) organizes trials into five different types:[13]

- **Prevention trials** look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
- **Screening trials** test the best way to detect certain diseases or health conditions.
- **Diagnostic trials** are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- **Treatment trials** test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- **Quality of life trials** (supportive care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.
- **Compassionate use trials** or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy exists, or a patient who has already attempted and failed all other standard

treatments and whose health is so poor, he does not qualify for participation in randomized clinical trials.[14] Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

A fundamental distinction in evidence-based medicine is between observational studies and randomized controlled trials. Types of observational studies in epidemiology, such as the cohort study and the case-control study, provide less compelling evidence than the randomized controlled trial. In observational studies, the investigators only observe associations (correlations) between the treatments experienced by participants and their health status or diseases. However, under certain conditions, causal effects can be inferred from these studies.

Under the right conditions, a randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.

Currently, some Phase 2 and most Phase 3 drug trials are designed as randomized, double-blind, and placebo-controlled.

- **Randomized**: Each study subject is randomly assigned to receive either the study treatment or a placebo.
- **Blind**: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment is being given to any given subject. This 'blinding' is to prevent biases, since if a physician knew which patient was getting the study treatment and which patient was getting the placebo, he/she might be tempted to give the (presumably helpful) study drug to a patient who could more easily benefit from it. In addition, a physician might give extra care to only the patients who receive the placebos to compensate for their ineffectiveness. A form of double-blind study called a "double-dummy" design allows additional insurance against bias or placebo effect. In this kind of study, all patients are given both placebo and active doses in alternating periods of time during the study.
- **Placebo-controlled**: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Although the term "clinical trials" is most commonly associated with the large, randomized studies typical of Phase 3, many clinical trials are small. They may be "sponsored" by single physicians or a small group of physicians, and are designed to test simple questions. In the field of rare diseases, sometimes the number of patients might be the limiting factor for a clinical trial. Other clinical trials require large numbers of participants (who may be followed over long periods of

time), and the trial sponsor is a private company, a government health agency, or an academic research body such as a university.

Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases 0, 1, 2, and 3, it will usually be approved by the national regulatory authority for use in the general population.

1. What are the different phases in the clinical trial.

- Phase 0: Pharmacodynamics and Pharmacokinetics
- Phase 1: Screening for safety
- Phase 2: Establishing the testing protocol
- Phase 3: Final testing
- Phase 4: Postapproval studies

Each phase has a different purpose and helps scientists answer a different question:

In Phase 0 trials are the first-in-human trials. Single subtherapeutic doses of the study drug are given to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[18]

In Phase 1 trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase 2 trials, the experimental treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

In Phase 3 trials, the treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

In Phase 4 trials, postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use.

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive preclinical studies.

S.No	Question	Option 1	Option 2	Option 3	Option 4	Answer
	UNIT-II					
1	All substances that are not nutrients, which enters the body through ingestion, inhalation or absorption is called	xenobiotics	Toxic substances	Herbal drugs	narcotics	xenobiotics
2	All substances that are not nutrients, which enters the body through ingestion, inhalation or absorption is called	Exogenous compound	Toxic substances	Herbal drugs	narcotics	Exogenous compound
3	Drugs are also xenobiotics by virtue of their	lipophilicity	lyophilicity	Solubility in water	toxicity	lipophilicity
4	The enzymaticbiotransformation of water insoluble lipophilic non-polar drug into polar water soluble product is called	Drug metabolism	Drug excretion	Drug intake	Drug hydrolysis	Drug metabolism
5	Drug biotransformation is a	Detoxification process	Toxification process	Absorption process	Desorbtion process	Detoxification process
6	The principle site of drug metabolism is	liver	brain	mouth	Large intestine	liver
7	Example for phase I metabolic reactions	Oxidative reactions	Glucuronic acid conjugation	Sulfate conjugation	Acetylation	Oxidative reactions
8	The reaction which increase the polarity of molecules	Oxidative reactions	Glucuronic acid conjugation	Sulfate conjugation	Acetylation	Oxidative reactions

9	The reaction which increase the polarity of molecules	Reductive reactions	Glucuronic acid conjugation	Sulfate conjugation	Acetylation	Reductive reactions
10	The reaction which increase the polarity of molecules	Hydrolytic reactions	Glucuronic acid conjugation	Sulfate conjugation	Acetylation	Hydrolytic reactions
11	Example for phase II metabolic reactions	Oxidative reactions	Reductive reactions	Hydrolytic reactions	Glucuronic acid conjugation	Glucuronic acid conjugation
12	Example for phase II metabolic reactions	Oxidative reactions	Reductive reactions	Hydrolytic reactions	Sulfate conjugation	Sulfate conjugation
13	Example for phase II metabolic reactions	Oxidative reactions	Reductive reactions	Hydrolytic reactions	Acetylation	Acetylation
14	The reaction which increase the polarity of the polar metabolite	Oxidative reactions	Reductive reactions	Hydrolytic reactions	methylation	Methylation
15	The reaction which increase the polarity of the polar metabolite	Oxidative reactions	Reductive reactions	Hydrolytic reactions	Conjugation with glycine, glutamine and other amino acids	Conjugation with glycine, glutamine and other amino acids
16	The reaction which increase the polarity of the polar metabolite	Oxidative reactions	Reductive reactions	Hydrolytic reactions	Glutathione or mercapturic acid conjugation	Glutathione or mercapturic acid conjugation

17	The chemical messenger acetylcholine is related to the receptor	Cholinergic receptor	Dopaminergic receptor	GABA receptor	Adrenergic receptor	Cholinergic receptor
18	The chemical messenger dopamine is related to the receptor	Cholinergic receptor	Dopaminergic receptor	GABA receptor	Adrenergic receptor	Dopaminergic receptor
19	The chemical messenger amino butyric acid is related to the receptor	Cholinergic receptor	Dopaminergic receptor	GABA receptor	Adrenergic receptor	GABA receptor
20	The chemical messenger epinephrineis related to the receptor	Cholinergic receptor	Dopaminergic receptor	GABA receptor	Adrenergic receptor	Adrenergic receptor
21	The chemical messenger for Cholinergic receptor is	acetylcholine	dopamine	amino butyric acid	Cholinergic	acetylcholine
22	The chemical messenger for Dopaminergic receptor is	acetylcholine	dopamine	amino butyric acid	Cholinergic	dopamine
23	The chemical messenger for GABA receptor receptor is	acetylcholine	dopamine	amino butyric acid	Cholinergic	amino butyric acid
24	The chemical messenger for Adrenergic receptor receptor receptor is	acetylcholine	dopamine	amino butyric acid	Cholinergic	Cholinergic
25	The strongest bond involved in drug receptor interaction is	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Covalent bond
26	The ability of the drug to receptor binding increases as the drug molecule diffuses closure to the receptor	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Ionic bond

27	A weak bond and broke easily	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Hydrogen bond
28	Interaction between non-polar organic molecules	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Hydrophobic interaction
29	Hydrophobic interation between the drug and the receptor	Interaction between non-polar organic molecules	A weak bond and broke easily	The ability of the drug to receptor binding increases as the drug molecule diffuses closure to the receptor	The strongest bond involved in drug receptor interaction is	Interaction between non-polar organic molecules
30	Hydrogen bond between the drug and the receptor	Interaction between non-polar organic molecules	A weak bond and broke easily	The ability of the drug to receptor binding increases as the drug molecule diffuses closure to the receptor	The strongest bond involved in drug receptor interaction is	A weak bond and broke easily
31	Ionic bond between the drug and the receptor	Interaction between non-polar organic molecules	A weak bond and broke easily	The ability of the drug to receptor binding increases as	The strongest bond involved in drug	The ability of the drug to receptor binding

				the drug molecule diffuses closure to the receptor	receptor interaction is	increases as the drug molecule diffuses closure to the receptor
32	Covalent bond between the drug and the receptor	Interaction between non-polar organic molecules	A weak bond and broke easily	The ability of the drug to receptor binding increases as the drug molecule diffuses closure to the receptor	The strongest bond involved in drug receptor interaction is	The strongest bond involved in drug receptor interaction is
33	Between the drug and the receptor binding the presence of nonpolar molecules, the surrounding water molecules will be	In high energy state	In low energy state	In polarized state	Non polarized state	In high energy state
34	Hydrophobic interaction in drug-receptor molecules is a	Reversible type of bonding that liberates energy	Irreversible type of bonding that liberates energy	Reversible type of bonding that absorbs energy	irreversible type of bonding that absorbs energy	Reversible type of bonding that liberates energy
35	Since many drugs contain hydroxyl and amino groups, the type of bond formed with the receptor is	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Hydrogen bond

36	Since many drugs contain carboxyl and carbonyl groups, the type of bond formed with the receptor is	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Hydrogen bond
37	For a higher drug receptor interaction, the essential requirement is	Covalent bond	Ionic bond	Hydrogen bond	Hydrophobic interaction	Hydrogen bond
38	In the past, most drugs have been discovered by identifying the active ingredient from	Traditional medicines	vegetables	fruits	grains	Traditional medicines
39	The leaves of Ocimum sanctum for the cure of common cold can be attributed to the	Religious believes of the Hindus	Accidental discovery	Real discovery process	Random drug discovery	Religious believes of the Hindus
40	Which step is not involved in the drug discovery process	Identification of the candidates	synthesis	characterization	cloning	clonig
41	Desirable characteristics of a lead molecule	Desired biological activity	High toxicity	Absorption difficulties	insolubility	Desired biological activity
42	Desirable characteristics of a lead molecule	Desired pharmacological activity	High toxicity	Absorption difficulties	insolubility	Desired pharmacological activity
43	undesirable characteristics of a lead molecule	Desired pharmacological activity	Desired biological activity	Good metabolic propety	High toxicity	High toxicity
44	undesirable characteristics of a lead molecule	Desired pharmacological activity	Desired biological activity	Good metabolic propety	insolubility	insolubility

45	undesirable characteristics of a lead molecule	Desired pharmacological activity	Desired biological activity	Good metabolic property	Absorption difficulties	Absorption difficulties
46	The structure of the lead compounds are modified by synthesis to amplify the	Desired activity	toxicity	Absorption difficulties	insolubility	Desired activity
47	The structure of the lead compounds are modified by synthesis to amplify the	Minimize the unwanted properties	toxicity	Absorption difficulties	insolubility	Minimize the unwanted properties
48	The structure of the lead compounds are modified by synthesis to amplify the	Minimize the unwanted properties	toxicity	Absorption difficulties	insolubility	Minimize the unwanted properties
49	Pharmacophore is	The collection of relevant groups responsible for drug-receptor interaction	Functional group	The group which does not interact with receptor	The group present away from the receptor	The collection of relevant groups responsible for drug-receptor interaction
50	The geometric arrangement of the pharmacophore is called	Functional group	Pharmacophoric pattern	Lattice plane	Braveis lattice	Pharmacophoric pattern
51	The collection of relevant groups responsible for drug-receptor interaction is called	Pharmacophore	Functional group	Lead molecule	Pharmacophore pattern	Pharmacophore
52	The position of the complimentary structure on the receptor is called	Receptor map	ligand	Binding site	Functional moiety	Receptor map

53	The activity of the drug ca be correlated to its structure in term of its functional groups to the	lipophilicity	stereochemistry	Melting point	stability	lipophilicity
54	The activity of the drug ca be correlated to its structure in term of its functional groups to the	Electronic features	stereochemistry	Melting point	stability	Electronic features
55	The activity of the drug ca be correlated to its structure in term of its functional groups to the	Stearic features	stereochemistry	Melting point	stability	Stearic features
56	A variety of conformations of the drug molecule can be generated using	Molecular mechanics	Molecular dynamics	Molecular docking	Molecular graphing	Molecular mechanics
57	Molecular dynamics programme heats the molecule to	800-900K	373K	500K	425K	800-900K
58	Using molecular dynamics program heating the molecule to 800-90K, it allows the molecule to	Undergo bond stretching and bond rotation	melt	vaporise	sublimate	Undergo bond stretching and bond rotation
59	Combinatorial chemistry can be used to	Synthesis a large number of compounds simuntaneously	Synthesise One molecule at a time	Different conformers of a molecule	Compounds with specific stereochemistry	Synthesis a large number of compounds simuntaneously
60	Combinatorial chemistry results in	Multi complex mixture	Single pure compound	Few compounds in a greener way	Different conformers of a molecule	Multi complex mixture

UNIT-III

SYLLABUS

Drug transport mechanism and absorption processes, pharmacodynamic and pharmacokinetic aspects, prodrugs and bioactivation, receptor theories and receptor models, drug receptor interactions drug design, physiochemical principles and basis of drug design, different methods of drug design

DRUG ABSORPTION, DISTRIBUTION AND EXCRETION

To produce its characteristic effect, a drug must be present in appropriate concentration at its site of action. Although this process is clearly dependent upon the concentration of drug administered, the concentration ultimately attained depends upon the rate of its absorption, distribution, binding (or localization) in tissues, biotransformations, and excretion.

It is best to consider these events as four phases in the lifetime of a drug. They are not always occurring in vivo in this order.

1. Pharmacokinetic Phase (absorption and distribution): the physicochemical events that permit a drug to reach its target.

2. Pharmacodynamic Phase: the interaction of the drug with its receptor and the biochemical effects of this interaction.

3. Metabolism Phase (biotransformation): chemical changes to the drug molecule imparted by enzymes and other biological agents. May complete wholly with pharmacokinetic phase.

4. Excretion Phase: the termination of drug action

1. PHARMACOKINETIC PHASE (absorption and distribution)

(A) Absorption:

- Absorption, regardless of the route of administration, is dependent upon drug solubility. Drugs given as aqueous solutions are more rapidly absorbed than oils, suspensions or solid form because they mix more readily. Drugs given in a solid form (pills) are dependent upon the rate of *dissolution*, which may be a limiting factor.

- The *concentration* of a drug influences its rate of absorption. Drugs injected (or administered) in high concentration are absorbed more quickly than those at lesser concentrations.

- The *route of administration* markedly affects drug uptake. Some routes of administration are summarized below:

ROUTE	ABSORPTION PATTERN	LIMITATIONS/PRECAUTIONS/UTILITY
Enteral (oral)	variable	Absorption potentially erratic. Absorption potentially incomplete.
Parenteral (non-oral) - 3 major types		
Intravenous (i.v.)	Absorption circumvented	Immediate Effects. Increased risk of adverse effects.

Subcutaneous (sub cut or s.c.)	Prompt from aqueous soln. Slow and sustained (suspension)	Not suitable for large volume. Possible pain, edema.
Intramuscular (i.m.)	Prompt from aqueous soln. Slow and sustained (suspension)	Overweight or emaciated patients exhibit unusual patterns of absorption.

Some additional notes on absorption and routes of administration:

- *oral ingestion of drugs:* Most drug absorptions from the gastrointestinal (GI) tract occurs via passive processes and is favored when the drug is non-ionized (more lipophilic or greasy form). Any factor that accelerates gastric emptying will be likely to increase the rate of drug absorption.
- *Intravenous*: The assets of i.v. injection are accuracy and immediacy not possible through other routes. Liabilities include the fact that there is no retreat from i.v. drug administration: constant monitoring is usually employed.
- *Intramuscular*: Most common, insulin. However, penicillin, owing to solubility and the fact that slow absorption is desired, is injected as an oily suspension into muscle (gluteus maximus).
- *Intra-arterial*: when localized effect into target organ is warranted
- *Intrathecal*: drug injected into spinal arachnoid space (CNS drugs - esp. birthing)
- *Intraperitoneal*: thorax cavity offers a large absorbing surface; danger of infection and first pass (through the blood) losses.

(B) Distribution: After a drug is absorbed into the bloodstream it is distributed into /interstitial and cellular fluids. In the first few minutes, the drug is usually distributed to high blood flow organs (heart, liver, kidney, brain, etc.). Delivery to muscle, skin and fat is slower but less reversible (outflow/min). Lipid insoluble drugs are restricted in their distribution and hence, their sites of action. Drugs may accumulate in tissues in high concentration as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

The distribution of drugs to the CNS from the bloodstream is unique. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores; thereby restricting bulk aqueous flow. Thus, organic acids and bases only slowly diffuse into the brain. Strongly ionized agents such as quaternary amines or the penicillins are normally unable to enter the CNS from circulation. Important!

Many drugs accumulate in muscle and other tissues: **cellular reservoirs.** For example, during administration of the anti-malarial drug quinacrine, the concentration in the liver may be 1000x that in the plasma. Fat is the most stable reservoir because it not only serves as an organic solvent

but it has very low blood flow.

BIOTRANSFORMATION

Many drugs are lipid soluble weak organic acids and bases that are not readily eliminated from the body. Drug metabolites are usually more polar and less lipid soluble than the parent material and this enhances their excretion, and lowering their volume of distribution. There are several chemical reactions causing the biotransformation of drugs classified as Phase-I and Phase-II reactions.

Phase - I: reactions convert the parent material to a more polar metabolite by oxidation, reduction or hydrolysis.

Phase - II: usually synthetic or conjugation reactions and, involve coupling between the drug or its metabolite and an endogenous substrate (e.g., glucuronic acid, sulfuric acid, acetic acid or an amino acid.

One of the most important systems for biotransformation is the *hepatic microsomal drug-metabolizing system*. The endoplasmic reticulum of the liver has a network of enzymes called **microsomes**. The microsomes catalyze the oxidation of drugs (via mixed function oxidases or monooxygenases) as well as glucuronide conjugation. Drug metabolism, owing to its strong relationship with organic chemistry shall be the emphasis of this class although classical medicinal chemistry would provide a more equal distribution of the aforementioned areas.

METABOLISM

In the following pages some representative metabolic transformations will be presented. This summary is by no means definitive nor exhaustive. Clearly, there are major pathways that seems to occur more than others. And, although the intention of metabolism or biotransformation is to aid the excretion of a drug, it is not always consistent that the drug is changed to an "innocuous form." Frequently a process termed "*metabolic activation*" occurs leading to a more active form of the drug. This more active form may act either at the intended target as a more or less potent form, or an alternative one causing a side effect at another target site.

Excretion: the kidney is the most important organ for elimination of drugs. Substances excreted in the feces are mainly unabsorbed orally ingested compounds or metabolites excreted in the bile and not reabsorbed from the intestine. Excretory organs, eliminate polar compounds more efficiently than substances with high lipid solubility. There are four major types of enzyme-mediated metabolic reactions:

1. Hydrolysis

2. Oxidation

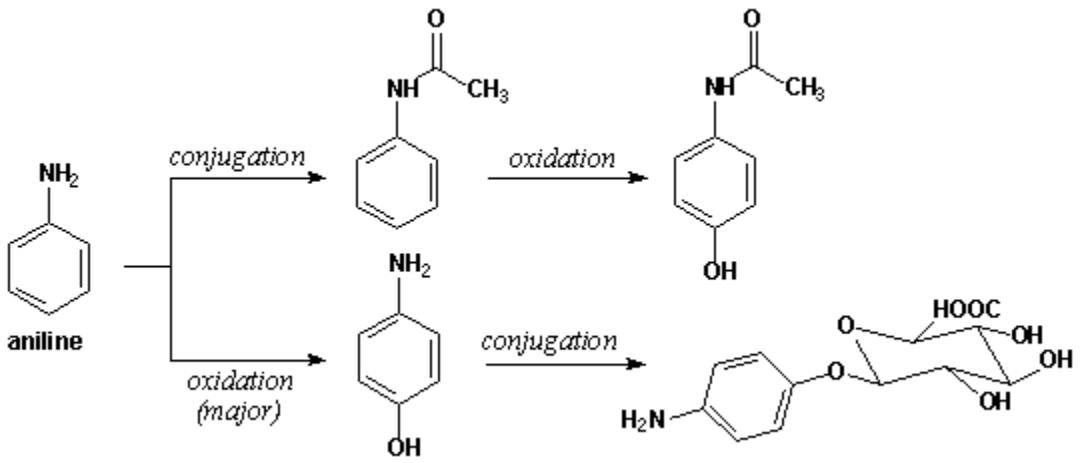
3. Reduction

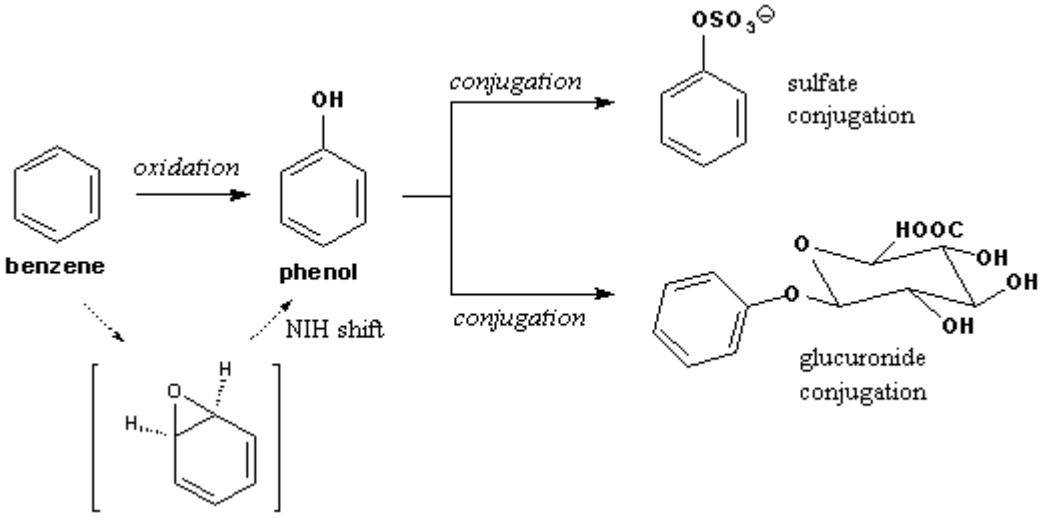
4. Conjugation

They occur most frequently in the soluble, mitochondrial or microsomal fractions of the liver. *Hydrolysis, oxidation and reduction* are chemically precise transformations whereas *conjugation* may include a diversity of changes including: N- or O-alkylation, esterification, and acylation. Conjugation usually involves the combination of a drug with a highly polar or ionic endogenous moiety, the product of which possesses greater water solubility.

A drug is often metabolized in more than one way and very often there are sequential and/or parallel reaction pathways.

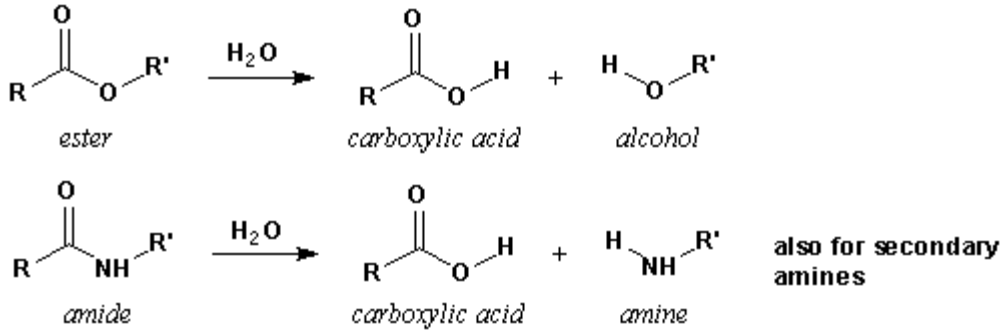
Example 1. benzene



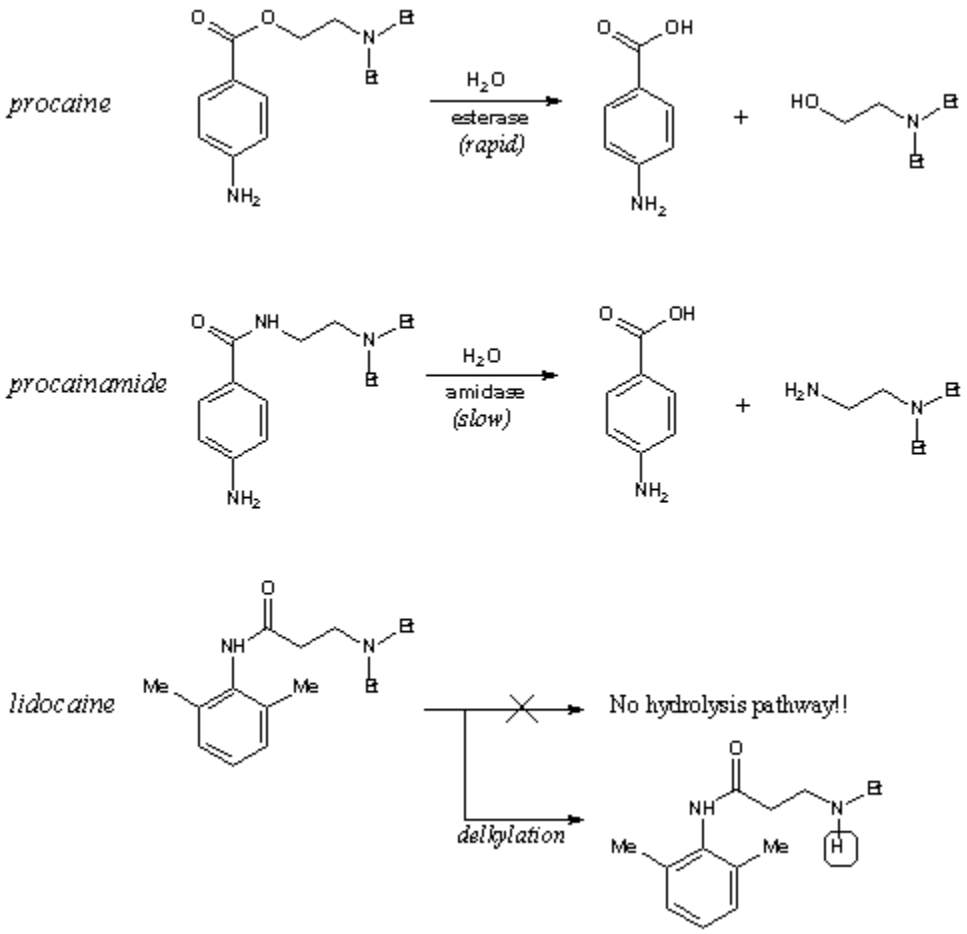


Example 2. aniline

1. Hydrolysis: (reaction of water with substrate resulting in breaking scissile carbon-heteroatom bonds): Usually an ester or amide hydrolyzes. The reaction is frequently enzyme - mediated although serum pH may cause reaction. Carboxylic (and phosphoric) esters afford a carboxylic acid and alcohol (1:1 molar equiv.). Carboxamides (and phosphoramides) afford the acid and one equivalent of the amine.

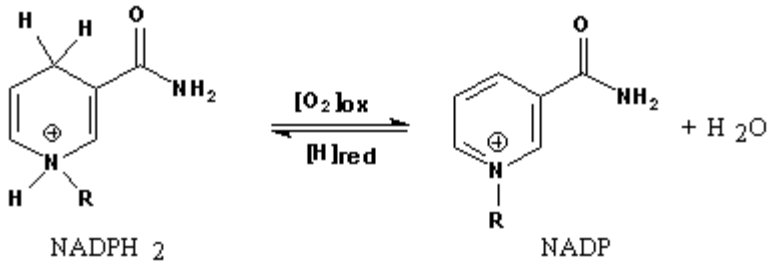


Some examples of how hydrolysis plays a role in medicinal chemistry is shown below.



2.

Oxidations. There are several possible oxidation routes involved in metabolism most of which are mediated by microsomes. Examples are used to represent each type of transformation. Note that although oxidation would seem to imply the addition of oxygen, that is not always the case. Oxidation refers to the change in oxidation state of the substrate.



Microsomal-mediated Oxidations **Non-microsomal-mediated Oxidations**

1. aromatic hydroxylation 8. amine oxidation -> to aldehydes and ketones

2. aliphatic oxidation -> alcohols, ketones, acids 9. alcohol/aldehyde oxidation

3. N-dealkylation -> alkyl oxidation

4. O- and S-dealkylation

5. epoxidation

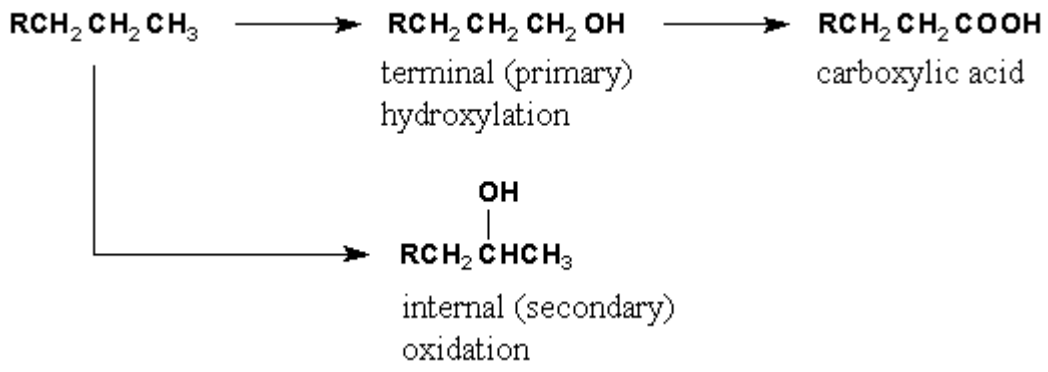
6. N-oxidation -> formation of hydroxylamine, amine oxides

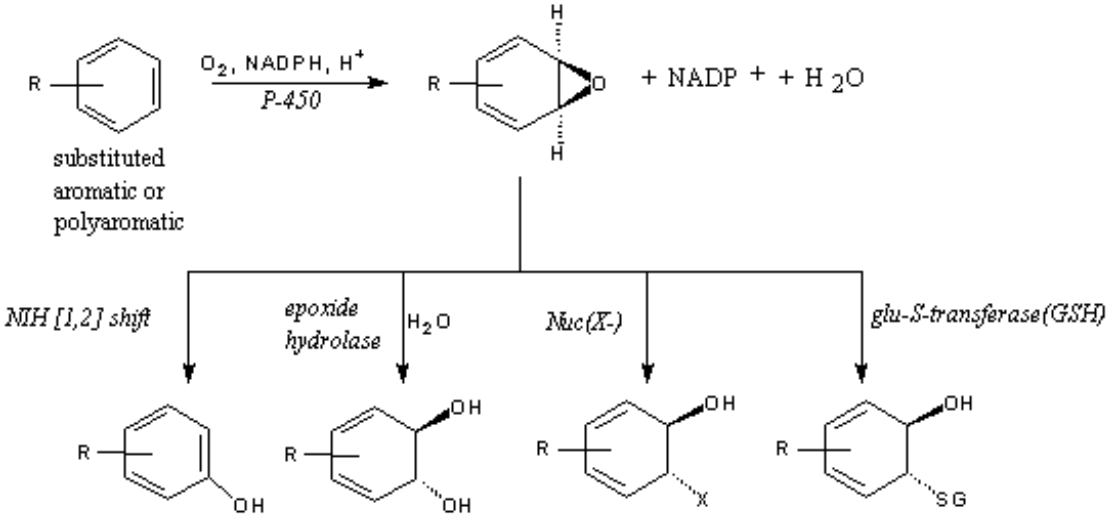
7. S-oxidation -> formation of sulfoxides and/or sulfones

Microsomal Oxidations: Most oxidations in the microsomal fraction require $NADPH_2$/NADP as co-factor and are catalyzed by the P-450 oxidase system.

EXAMPLES (OXIDATIVE METABOLISM):

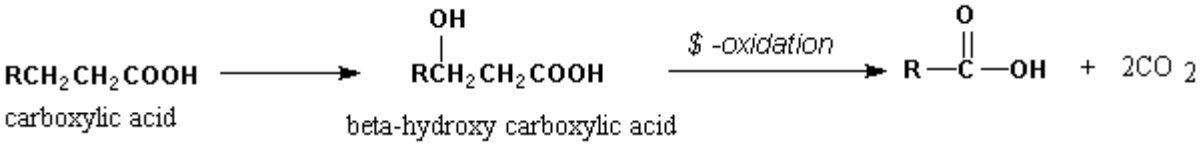
1. **Aromatic hydroxylation**



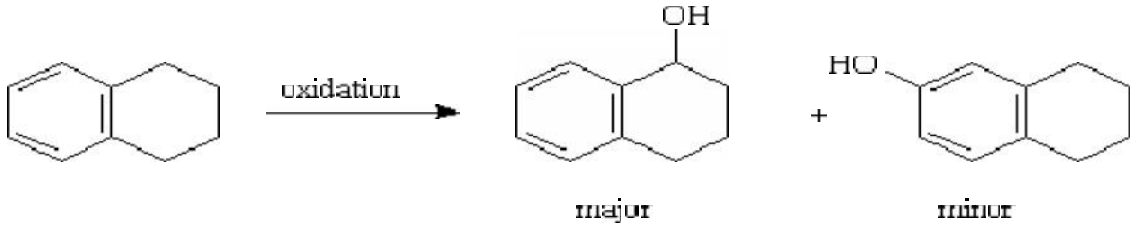


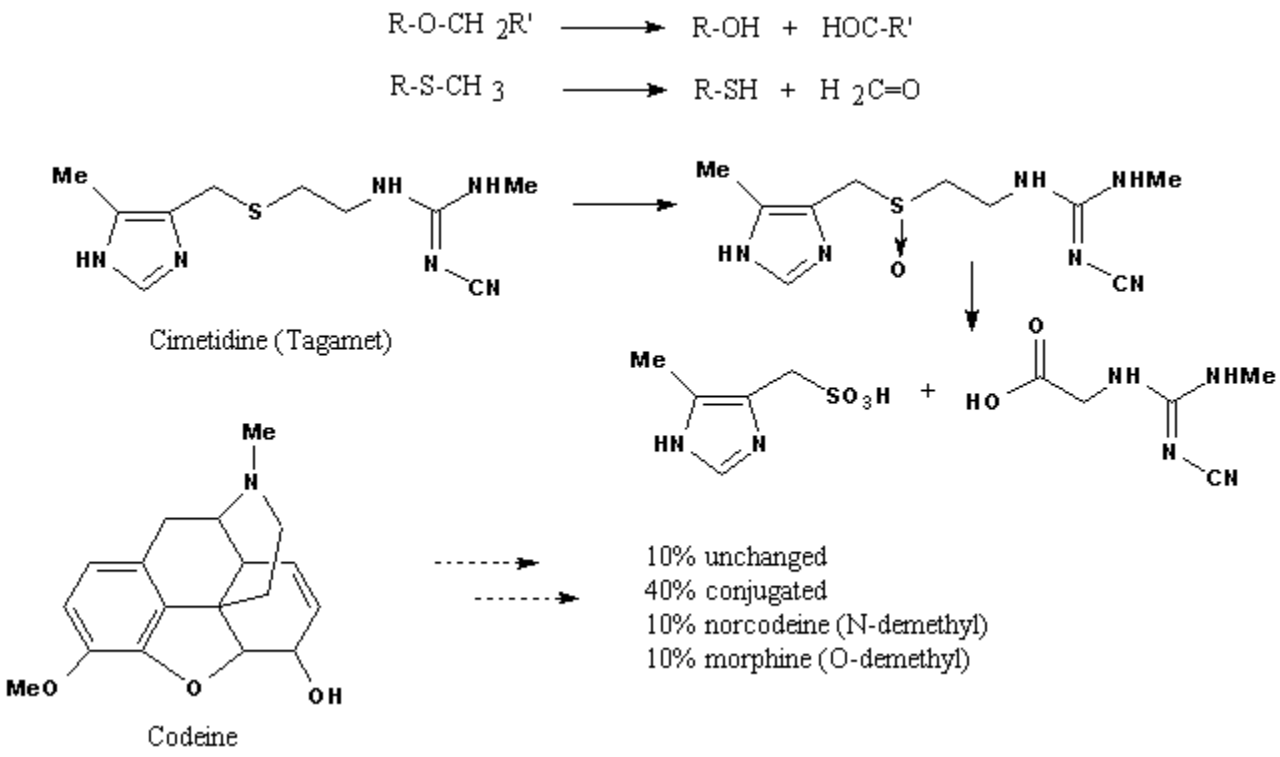
2. **Aliphatic oxidation**

Once a terminal acid is formed, the carbon beta () to the carbonyl is oxidized -> "clipping."

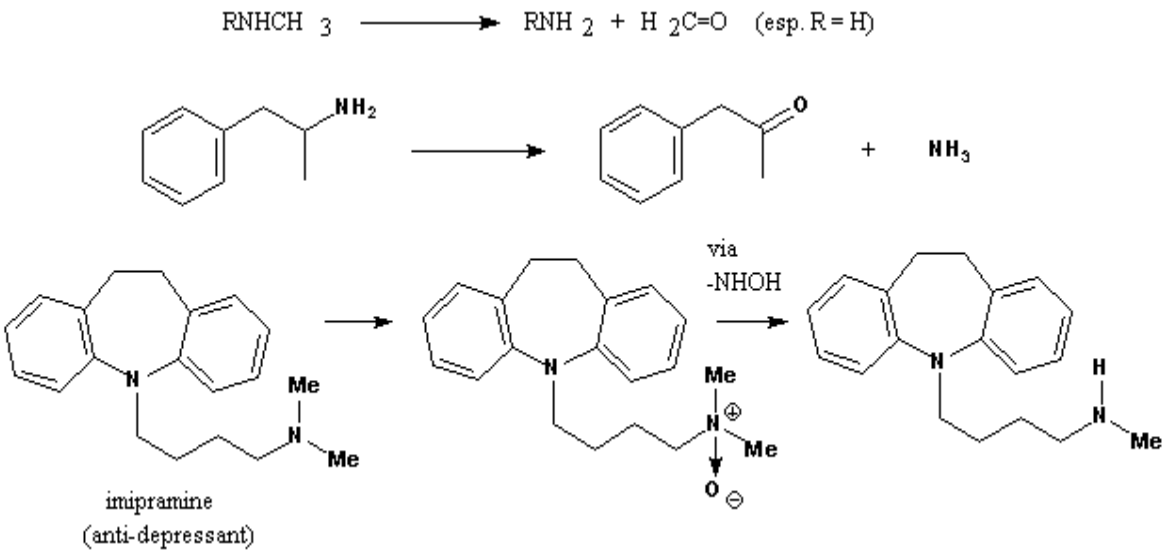


If there is a choice between aromatic and aliphatic, the aliphatic is more easily oxidized.



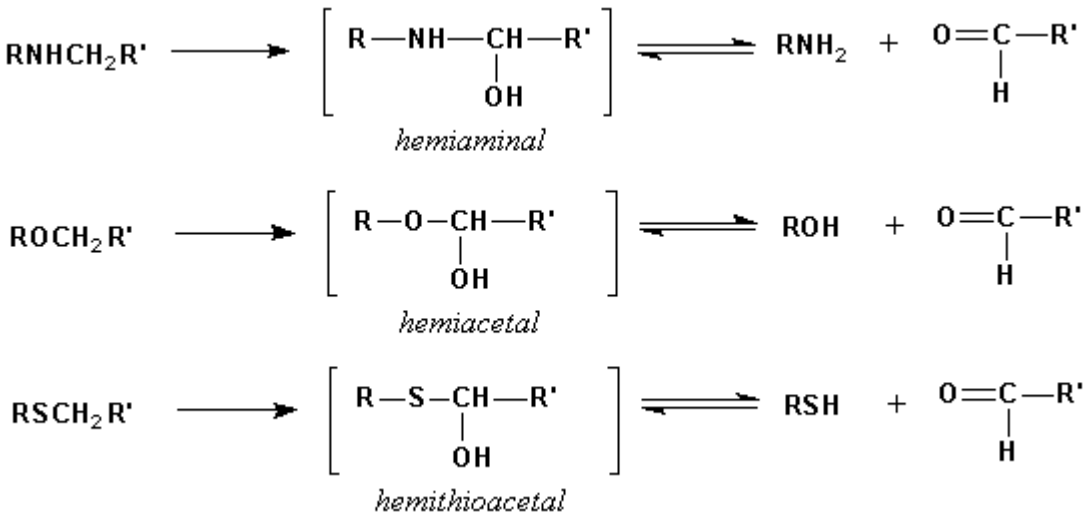


3. **N-Dealkylation**

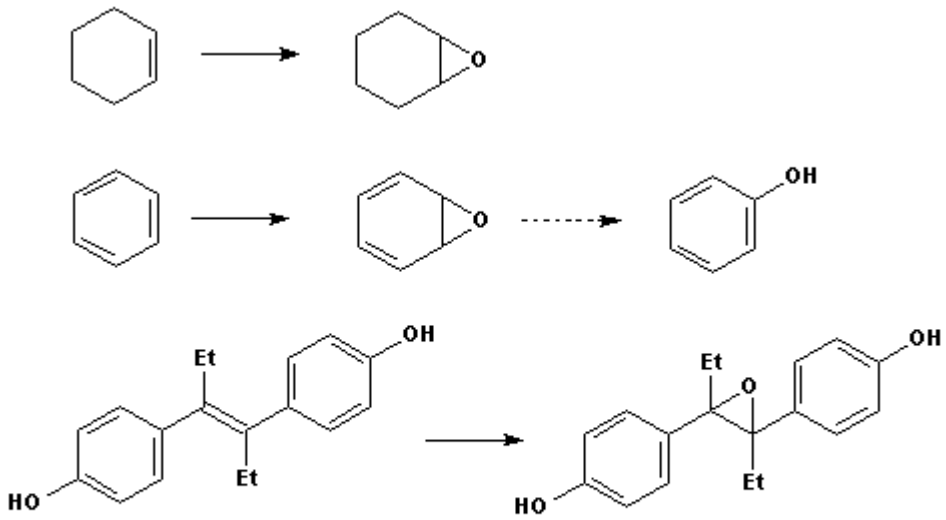


4. **O- and S-dealkylation**

General Mechanism of Dealkylation - hydroxylation, elimination process

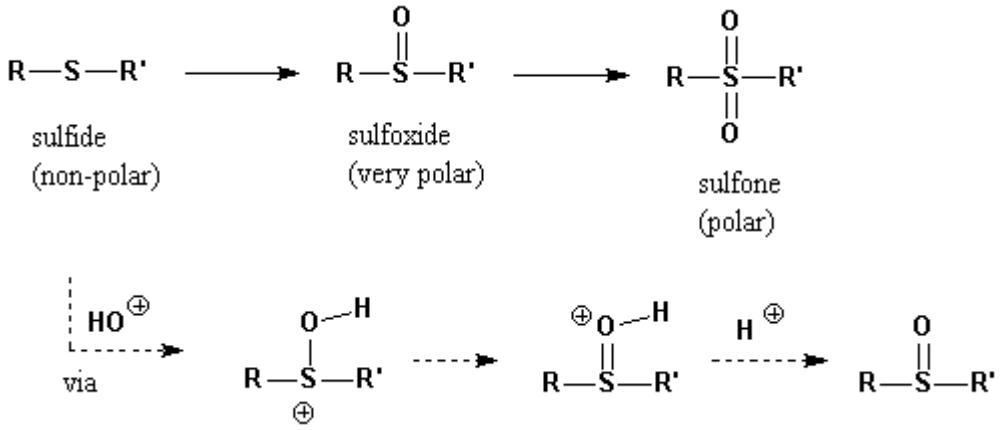


5. **Epoxidation**

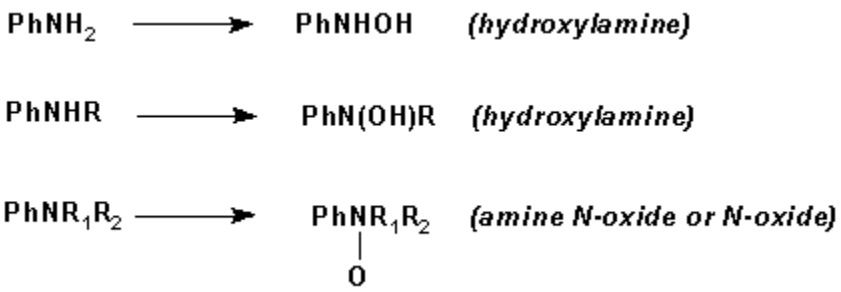


diethylstilbestrol (DES)
potent estrogen
post-coital contraception

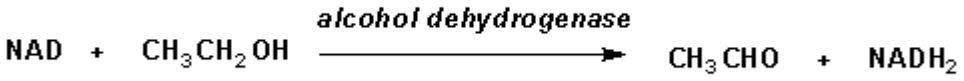
DES-epoxide
(carcinogenic)



6. **N-Oxidation**



7. **S-Oxidation**



UNIT-IV

SYLLABUS

Electronic effects; Hammett equation, Lipophilicity effects; Hansch equation, Steric Effects; Taft Equation; Experimental and theoretical approaches for the determination of physico-chemical parameters, parameter inter-dependence; linearity versus non-linearity; The importance of biological data in the correct form; Molecular docking and dynamics: Rigid docking, flexible docking and manual docking.

MOLECULAR MODELLING

Structure-based design and discovery of protein ligands has emerged as a new tool in medicinal chemistry. In particular, the knowledge of the three-dimensional structure of a protein can be used to derive new protein ligands with improved binding properties (i.e. new drugs). Within this approach we need algorithms and methods to solve the following questions: What is the binding affinity of a novel ligand towards a particular receptor? What are the best conformations of a ligand to the binding site? What are the similarities of different ligands with respect to their recognition capabilities? With which orientation will a ligand bind to the active site?

Molecular Dynamics

We apply molecular dynamics (MD) extensively using the AMBER and GROMACS suite of programs. MD is used to simulate the stability of protein dimers and of drug-protein complexes throughout time. We apply MD also to analyze the binding free energy of these complexes, employing the MMPBSA approximation.

Homology Modelling

Homology modelling refers to a set of methods that aim to predict the 3D structure of unknown

proteins by comparing their sequences with known proteins, for which the crystal structure is available (the template). After refinement, applying usually molecular dynamics, the predicted model can be used for drug design purposes.

Virtual Screening

Virtual Screening (VS) refers to the process of predicting new chemical entities that would eventually inhibit a target (protein) related to some disease. VS could enhance the hit ratio discovery as compared to classical high throughput screening, speeding up the process of drug design.

Introduction

• Powerful desktop and super computers has helped chemists to predict the structures and the values of **properties of known, unknown, stable and unstable molecular species using mathematical equations.**

• Mathematical methods used to obtain and solve the equations is well known and so in most cases it is possible to obtain a reliable estimate of the accuracy of the results.

• In some cases the calculated values are believed to be more accurate than the experimentally determined figures because of the higher degree of **experimental error** in the experimental work.

• Graphics packages that convert the data for the structure of a chemical species into a variety of easy to understand **visual formats** have also been developed

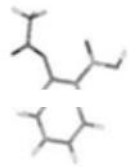
• Medicinal Chemist can visualize the three dimensional shapes of both the ligands and their target sites.

Docking

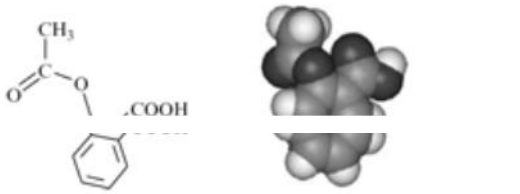
• Sophisticated computational chemistry packages also allow the medicinal chemist to evaluate the interactions between a compound and its target site before synthesizing that compound

• Only synthesize and test the most promising of the compounds, which considerably increases the chances of discovering a potent drug. It also significantly reduces the cost of development.

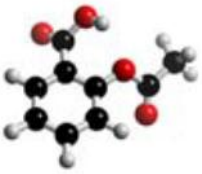
• Drug rely on computational chemist to make the necessary calculations and graphic conversions.

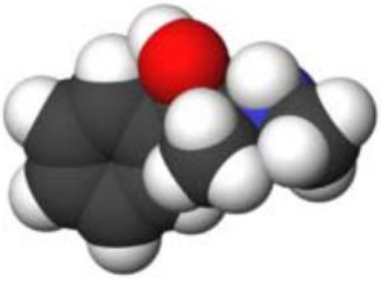


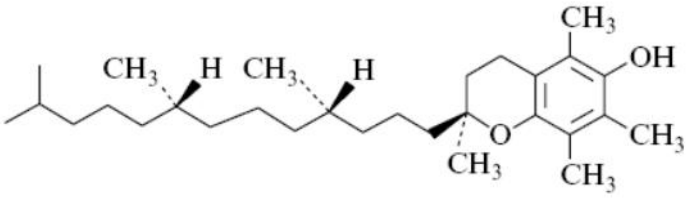
Stick model of aspirin.

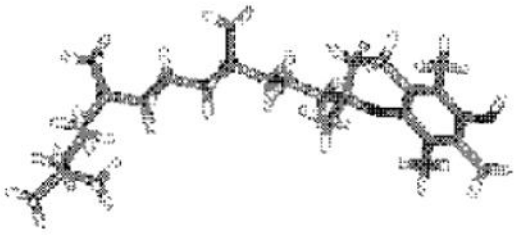


(b) Space fill model model of aspirin (CPK model)

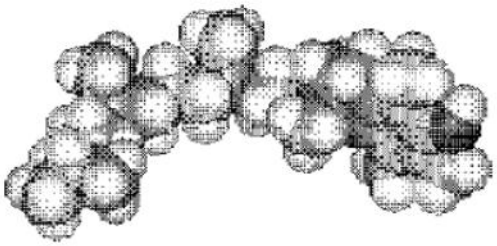




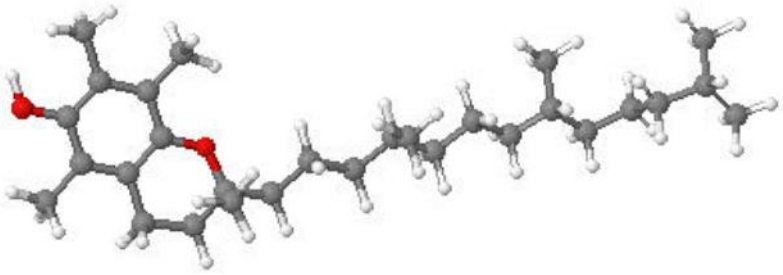




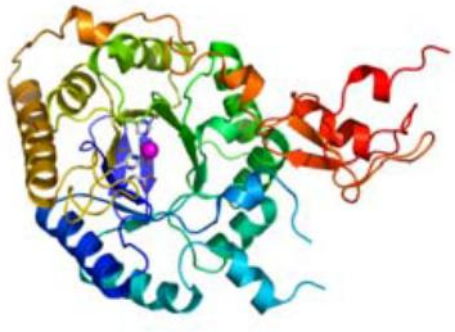
(c) Stick model of Vitamin E.



(d) Space fill model model of vitamin E.



• The three dimensional shapes of both ligand and target site may be determined by X-ray crystallography or computational methods.



• The three dimensional shapes of both ligand and target site may be determined.

• Most common computational methods are based on either molecular or quantum mechanics and produce equations for the total energy of the structure.

Molecular Models

• Most calculations are based on a frozen molecule at 0 K in a vacuum and so do not take into account that the structure is vibrating (temperature) or the influence of the medium (solvent) in which the chemical species is found.

• Calculations taking these factors into account would undoubtedly give a more realistic picture of the structure.

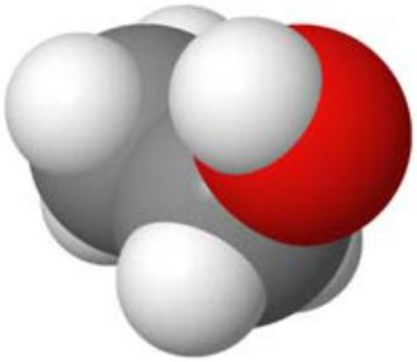
• Quantum mechanics calculations are more expensive to carry out because they require considerable more computing power and time than molecular mechanics calculations.

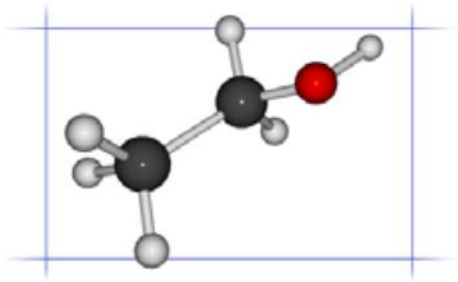
• Molecular mechanics is the more useful source of the large structures of interest to the medicinal chemist.

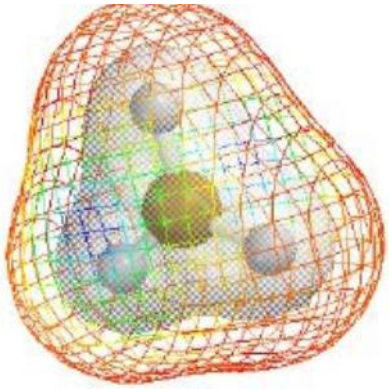
• Time and expense structures are often built up using information obtained from databases, such as the Cambridge (organic) and Brookhaven (biological) databases.

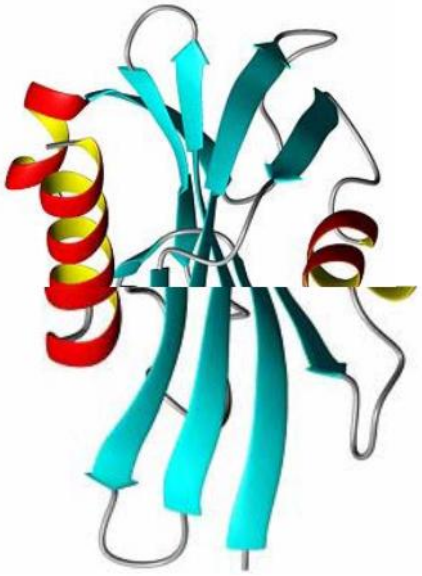
Computer Graphics

• In molecular modeling the data produced are converted into visual images on a computer screen by graphics packages. These images may be displayed as space fill, CPK (Corey–Pauling–Koltun), stick, ball and stick, mesh and ribbon.









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• Ribbon representations are usually used to depict large molecules, such as nucleic acids and proteins.

• Molecular mechanics is the more popular of the methods used to obtain molecular models as it is simpler to use and requires considerably less computing time to produce a model.

It assumes that the total potential energy ($\boldsymbol{E}_{\text{Total}}$) of a molecule is given by the sum of all the energies of the attractive and repulsive forces between the atoms in the structure.

• $\boldsymbol{E}_{\text{Total}}$ is expressed mathematically by equations, known as force fields.

$\boldsymbol{E}_{\text{Stretching}}$ is the bond stretching energy

$\boldsymbol{E}_{\text{Bend}}$ is the bond energy due to changes in bonding angle

$\boldsymbol{E}_{\text{Torsion}}$ is the bond energy due to changes in the conformation of a bond

$\boldsymbol{E}_{\text{vd}}$ W is the total energy contribution due to van der Waals forces

$\boldsymbol{E}_{\text{Coulombic}}$ the electrostatic attractive and repulsive forces operating in the molecule between atoms carrying a partial or full charge.

Creating Models

• Unlike molecular mechanics, the quantum mechanical approach to molecular modeling does not require the use of parameters similar to those used in molecular mechanics

• Electrons and all material particles exhibit wavelike properties

• Wave motions to be applied to electrons, atomic and molecular structure

Docking

• The three dimensional structures produced on a computer screen may be manipulated on the screen to show different views of the structures.

• Superimpose the three dimensional structure of a potential drug on its possible target site (Docking).

• It enables the medicinal chemist to evaluate the fit of potential drugs (ligands) to their target site.

• Color code to indicate the nature of the atoms and functional groups present in the three dimensional structures also enables the medicinal chemist to investigate the binding of the ligand to the target site.

Prodrug - a pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation Ideally, conversion occurs as soon as the desired goal for designing the prodrug is achieved. Prodrugs and soft drugs are opposite:

• a prodrug is inactive - requires metabolism to give active form

• a soft drug is active - uses metabolism to promote excretion

S.No	Question	Option 1	Option 2	Option 3	Option 4	Answer
	UNIT-IV					
1	In the QSAR studies, among the following one of them is a liphophilic parameter	Partition coefficient	Molar refractivity	Taft's steric constant	Molecular weight	Partition coefficient
2	In the QSAR studies, among the following one of them is a liphophilic parameter	Chromatographic parameter	Molar refractivity	Taft's steric constant	Molecular weight	Chromatographic parameter
3	In the QSAR studies, among the following one of them is a liphophilic parameter	Pi-substitution constant	Molar refractivity	Taft's steric constant	Molecular weight	Pi-substitution constant
4	One among the following is a polarizability parameter in QSAR	Pi-substitution constant	Molar refractivity	Taft's steric constant	Molecular weight	Molar refractivity
5	One among the following is a polarizability parameter in QSAR	Pi-substitution constant	Molar volume	Taft's steric constant	Molecular weight	Molar volume
6	One among the following is a polarizability parameter in QSAR	Pi-substitution constant	Parachor	Taft's steric constant	Molecular weight	Parachor
7	An electronic parameter in QSAR studies	Hammet constant	Parachor	Taft's steric constant	Molecular weight	Hammet constant
8	An electronic parameter in QSAR studies	Field and resonance parameters	Parachor	Taft's steric constant	Molecular weight	Field and resonance parameters

9	An electronic parameter in QSAR studies	Spectroscopic data	Parachor	Taft's steric constant	Molecular weight	Spectroscopic data
10	An electronic parameter in QSAR studies	Charge transfer constat	Parachor	Taft's steric constant	Molecular weight	Charge transfer constant
11	An electronic parameter in QSAR studies	Dipole moment	Parachor	Taft's steric constant	Molecular weight	Dipole moment
12	An electronic parameter in QSAR studies	Quantum chemical parameters	Parachor	Taft's steric constant	Molecular weight	Quantum chemical parameters
13	An example for a steric parameter	Quantum chemical parameters	Parachor	Taft's steric constant	Molecular weight	Taft's steric constant
14	An example for a steric parameter	Quantum chemical parameters	Parachor	Vander waals radii	Molecular weight	Vander waals radii
15	Partition coefficient is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Liphophilic parameter
16	Chromatographic parameters is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Liphophilic parameter
17	Pi-substitution constant is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Liphophilic parameter
18	Molar refractivity is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Polarazability parameter

19	Molar volume is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Polarazability parameter
20	Parachor is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Polarazability parameter
21	Hammett constant is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Electronic parameter
22	Field and resonance measurements is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Electronic parameter
23	Properties derived fron spectral data is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Electronic parameter
24	Charge transfer constant is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Electronic parameter
25	Dipole moment is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Electronic parameter
26	Quantum chemical measurements are	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Electronic parameter
27	Taft’s steric constant is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Stearic parameter
28	Vanderwaals radii is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Stearic parameter

29	Partitioning of a compound between an aqueous and non-aqueous phase is a	Liphophilic parameter	Polarazability parameter	Electronic parameter	Steric parameter	Liphophilic parameter
30	In determining the partition coefficient n-octanol/water system has more advantages because	Octanol have a long alkyl chain and a polar hydroxyl group	Octanol has a short alkyl chain	Octanol has a non polar hydroxyl group	Octanol has polar alkyl chain	Octanol have a long alkyl chain and a polar hydroxyl group
31	In determining the partition coefficient n-octanol/water system has more advantages because	Octanol has a low vapour pressure	Octanol has a short alkyl chain	Octanol has a non polar hydroxyl group	Octanol has polar alkyl chain	Octanol has a low vapour pressure
32	In determining the partition coefficient n-octanol/water system has more advantages because	Octanol is UV transparent	Octanol has a short alkyl chain	Octanol has a non polar hydroxyl group	Octanol has polar alkyl chain	Octanol is UV transparent
33	One of the disadvantages in determining the chromatographic parameter R_M is	Compounds need not to be pure	Only traces of materials needed	Several compounds can be estimated simultaneously	Lack of precision and reproducibi ity	Lack of precision and reproducibiity
34	One of the disadvantages in determining the chromatographic parameter R_M is	Compounds need not to be pure	Only traces of materials needed	Several compounds can be estimated simultaneously	Use of different solvent system renders deviation	Use of different solvent system renders deviation
35	The drugs which are more readily transported through membranes are	Non-polar drug	Polar drug	Drugs in their ionized form	Polar drug in its	Non-polar drug

					ionized form	
36	The drugs which are more readily transported through membranes are	Polar non-ionised drug	Polar drug	Drugs in their ionized form	Polar drug in its ionized form	Polar non-ionised drug
37	Ribbon presentation is used for	Nucleic acid and protein	Smaller molecules	ligands	Charged molecules	Nucleic acid and protein
38	The image type used to display the molecular graphics	Ball and stick	Coral draw	paint	Bright and dull	Ball and stick
39	The image type used to display the molecular graphics	Mesh	Coral draw	paint	Bright and dull	Mesh
40	The image type used to display the molecular graphics	Colour scheme	Coral draw	paint	Bright and dull	Colour scheme

UNIT-V

SYLLABUS

Molecular forces and binding energetic, enzyme inhibitors - modes of inhibition and general approaches. Antibacterial drugs - major drug classes and drug resistance, antiviral drugs- major drug classes and drug resistance, anticancer drugs- major cancer drug targets, major drug classes and drug resistance.

Enzyme Inhibitor

An **enzyme inhibitor** is a molecule which binds to enzymes and decreases their activity. Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance, many drugs are enzyme inhibitors. They are also used as herbicides and pesticides. Not all molecules that bind to enzymes are inhibitors; *enzyme activators* bind to enzymes and increase their enzymatic activity, while enzyme substrates bind and are converted to products in the normal catalytic cycle of the enzyme.

The binding of an inhibitor can stop a substrate from entering the enzyme'sactive site and/or hinder the enzyme from catalyzing its reaction. Inhibitor binding is either reversible or irreversible. Irreversible inhibitors usually react with the enzyme and change it chemically (e.g. via covalent bond formation). These inhibitors modify key amino acid residues needed for enzymatic activity. In contrast, reversible inhibitors bind non-covalently and different types of inhibition are produced depending on whether these inhibitors bind to theenzyme, the enzyme-substrate complex, or both.

Many drug molecules are enzyme inhibitors, so their discovery and improvement is an active area of research in biochemistry and pharmacology. A medicinal enzyme inhibitor is often judged by its specificity (its lack of binding to other proteins) and its potency (its dissociation constant, which

indicates the concentration needed to inhibit the enzyme). A high specificity and potency ensure that a drug will have few side effects and thus low toxicity.

Enzyme inhibitors also occur naturally and are involved in the regulation of metabolism. For example, enzymes in a metabolic pathwaycan be inhibited by downstream products. This type of negative feedback slows the production line when products begin to build up and is an important way to maintain homeostasis in a cell. Other cellular enzyme inhibitors are proteins that specifically bind to and inhibit an enzyme target. This can help control enzymes that may be damaging to a cell, like proteases or nucleases. A well-characterised example of this is the ribonuclease inhibitor, which binds to ribonucleases in one of the tightest known protein–protein interactions.[1]Natural enzyme inhibitors can also be poisons and are used as defences against predators or as ways of killing prey.

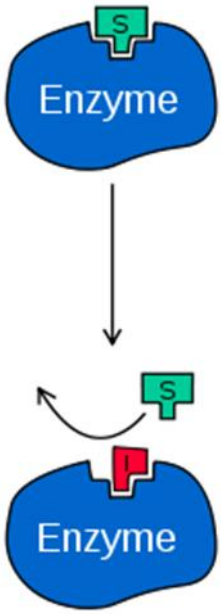
1. What is meant by an enzyme inhibitor.
2. What are enzyme activators
3. How the Reversible inhibitors bind to enzymes
4. How many kinds of reversible inhibitors are available
5. What are enzymes. Give examples
6. What is meant by irreversible inhibition
7. What are the different types of irreversible inhibition
8. What is meant by **non-competitive inhibition**
9. What is meant by **competitive inhibition**
10. **Differentiate competitive inhibition and non-competitive inhibition**
    a. What are the primary physicochemical considerations in preparing pharmaceutical solutions
    b. How temperature affects the pharmaceutical solutions
    c. PKa values
    d. How quinine was discovered.
    e. Give an example for accidental discoveries of drugs
    f. What is meant by a clinical trial.

g. What for a clinical trial may be designed to do

3. What are the different phases in the clinical trial.

Types of reversible inhibitors

Reversible inhibitors bind to enzymes with non-covalent interactions such as hydrogen bonds, hydrophobic interactions and ionic bonds. Multiple weak bonds between the inhibitor and the active site combine to produce strong and specific binding. In contrast to substratesand irreversible inhibitors, reversible inhibitors generally do not undergo chemical reactions when bound to the enzyme and can be easily removed by dilution or dialysis.



Competitive inhibition: substrate (S) and inhibitor (I) compete for the active site.

There are four kinds of reversible enzyme inhibitors. They are classified according to the effect of varying the concentration of the enzyme's substrate on the inhibitor.[2]

- In **competitive inhibition**, the substrate and inhibitor cannot bind to the enzyme at the same time, as shown in the figure on the left. This usually results from the inhibitor having an affinity for the active site of an enzyme where the substrate also binds; the substrate and inhibitor *compete* for access to the enzyme's active site. This type of inhibition can be overcome by sufficiently high concentrations

of substrate (Vmax remains constant), i.e., by out-competing the inhibitor. However, the apparent Km will increase as it takes a higher concentration of the substrate to reach the Km point, or half the Vmax. Competitive inhibitors are often similar in structure to the real substrate (see examples below).

- In **uncompetitive inhibition**, the inhibitor binds only to the substrate-enzyme complex, it should not be confused with non-competitive inhibitors. This type of inhibition causes Vmax to decrease (maximum velocity decreases as a result of removing activated complex) and Km to decrease (due to better binding efficiency as a result of Le Chatelier's principle and the effective elimination of the ES complex thus decreasing the Km which indicates a higher binding affinity).

- In **mixed inhibition**, the inhibitor can bind to the enzyme at the same time as the enzyme's substrate. However, the binding of the inhibitor affects the binding of the substrate, and vice versa. This type of inhibition can be reduced, but not overcome by increasing concentrations of substrate. Although it is possible for mixed-type inhibitors to bind in the active site, this type of inhibition generally results from anallosteric effect where the inhibitor binds to a different site on an enzyme. Inhibitor binding to thisallosteric site changes the conformation (i.e., tertiary structure or three-dimensional shape) of the enzyme so that the affinity of the substrate for the active site is reduced.

- Non-competitive inhibition is a form of mixed inhibition where the binding of the inhibitor to the enzyme reduces its activity but does not affect the binding of substrate. As a result, the extent of inhibition depends only on the concentration of the inhibitor. Vmax will decrease due to the inability for the reaction to proceed as efficiently, but Km will remain the same as the actual binding of the substrate, by definition, will still function properly.

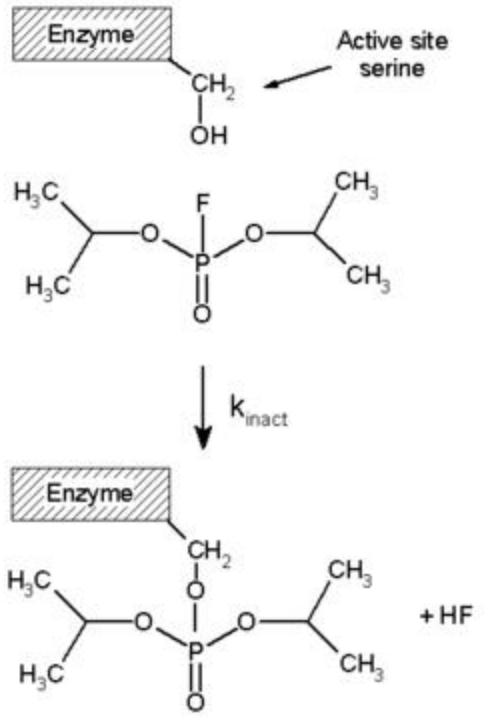
As enzymes have evolved to bind their substrates tightly, and most reversible inhibitors bind in the active site of enzymes, it is unsurprising that some of these inhibitors are strikingly similar in structure to the substrates of their targets. An example of these substrate mimics are the protease inhibitors, a very successful class of antiretroviral drugs used to treat HIV.[12] The structure of ritonavir, a protease inhibitor based on a peptide and containing three peptide bonds, is shown on the right. As this drug resembles the protein that is the substrate of the HIV protease, it competes with this substrate in the enzyme's active site.

1. What is meant by irreversible inhibition

2. What are the different types of irreversible inhibition
3. What is meant by non-competitive inhibition
4. What is meant by competitive inhibition
5. Differentiate competitive inhibition and non-competitive inhibition
    1. What are the primary physicochemical considerations in preparing pharmaceutical solutions
    2. How temperature affects the pharmaceutical solutions
    3. PKa values
    4. How quinine was discovered.
    5. Give an example for accidental discoveries of drugs
    6. What is meant by a clinical trial.
    7. What for a clinical trial may be designed to do

    3. What are the different phases in the clinical trial.

Types of irreversible inhibition



Reaction of the irreversible inhibitordiisopropylfluorophosphate (DFP) with a serine protease

Irreversible inhibitors usually covalently modify an enzyme, and inhibition can therefore not be reversed. Irreversible inhibitors often contain reactive functional groups such asnitrogen mustards, aldehydes, haloalkanes, alkenes, Michael acceptors, phenyl sulfonates, or fluorophosphonates. These electrophilic groups react with amino acid side chains to form covalent adducts. The residues modified are those with side chains containing nucleophiles such as hydroxyl or sulfhydryl groups; these include the amino acids serine (as in DFP, right), cysteine, threonine or tyrosine.[16]

Irreversible inhibition is different from irreversible enzyme inactivation. Irreversible inhibitors are generally specific for one class of enzyme and do not inactivate all proteins; they do not function by destroying protein structure but by specifically altering the active site of their target. For example, extremes of pH or temperature usually cause denaturation of all protein structure, but this is a non-specific effect. Similarly, some non-specific chemical treatments destroy protein structure: for example, heating in concentrated hydrochloric acid will hydrolyse the peptide bonds holding proteins together, releasing free amino acids.[17]

Irreversible inhibitors display time-dependent inhibition and their potency therefore cannot be characterised by an IC_{50} value. This is because the amount of active enzyme at a given concentration of irreversible inhibitor will be different depending on how long the inhibitor is pre-incubated with the enzyme. Instead, $k_{obs}/[I]$ values are used,[18]wherek_{obs} is the observed pseudo-first order rate of inactivation (obtained by plotting the log of % activity vs. time) and $[I]$ is the concentration of inhibitor. The $k_{obs}/[I]$ parameter is valid as long as the inhibitor does not saturate binding with the enzyme (in which case $k_{obs} = k_{inact}$).

Diisopropylfluorophosphate (DFP) is shown as an example of an irreversible protease inhibitor in the figure above right. The enzyme hydrolyses the phosphorus–fluorine bond, but the phosphate residue remains bound to the serine in the active site, deactivating it.[26] Similarly, DFP also reacts with the active site of acetylcholine esterase in the synapses of neurons, and consequently is a potent neurotoxin, with a lethal dose of less than 100 mg

The purpose (actually, I should say function) of enzymes is basically to catalyze the various reactions that must occur within the body. Like a true catalyst, each enzyme is in the end itself unchanged in the reaction it catalyzes, although it may undergo several changes during the execution of the reaction. A catalyst exerts a profound effect on the rate at which the reaction takes place, often increasing it by a factor of as much as one hundred thousand to a million. In many cases this amounts to the difference between reacting and not reacting. Thus, enzymes not only catalyze reactions, they are also the means that the body uses to control which reactions occur. In order to function, an enzyme must have a precise, three-dimensional structure. By subtly (and reversibly) altering the structure of an enzyme, the body can use the enzyme as a switch to turn on and off the reaction that it catalyzes.
Enzymes are generally named using an -ase ending.

Enzyme Function

In simple terms, an enzyme functions by binding to **one or more of the reactants** in a reaction. The reactants that bind to the enzyme are known as the **substrates** of the enzyme. The exact location on the enzyme where substrate binding takes place is called the **active site** of the enzyme. The shape of the active site just fits the shape of the substrate, somewhat like a lock fits a key. In this way only the correct substrate binds to the enzyme.

Once the substrate or substrates are bound to the enzyme, the enzyme can promote the desired reaction in some particular way. What that way is depends on the nature of the reaction and the nature of the enzyme. An enzyme may hold two substrate molecules in precisely the orientation needed for the reaction to occur. Or binding to the enzyme may weaken a bond in a substrate molecule that must be broken in the course of the reaction, thus increasing the rate at which the reaction can occur.

An enzyme may also **couple two different reactions**. Coupling an exothermic reaction with an endothermic one allows the enzyme to use the energy released by the exothermic reaction to drive the endothermic reaction. In fact, a large variety of enzymes couple many different endothermic reactions to the exothermic reaction in which ATP is converted by hydrolysis to ADP. In this way,

ATP serves as the molecular fuel that powers most of the energy-requiring processes of living things.

ENZYME INHIBITORS

This page looks at the effect of inhibitors on reactions involving enzymes. This is the third and final page talking about how enzymes function as catalysts. Please remember that this series of pages is written for 16 - 18 year old *chemistry* students. If you want something more advanced, you are looking in the wrong place.

Competitive and non-competitive inhibition

Competitive inhibitors

This is the most straightforward and obvious form of enzyme inhibition - and the name tells you exactly what happens.

The inhibitor has a similar shape to the usual substrate for the enzyme, and competes with it for the active site. However, once it is attached to the active site, nothing happens to it. It doesn't react - essentially, it just gets in the way.

Remember the general equation for an enzyme reacting with a substrate?

The equivalent equation for a competitive inhibitor looks like this:

The complex doesn't react any further to form products - but its formation is still *reversible*. It breaks up again to form the enzyme and the inhibitor molecule.

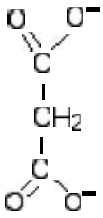
That means that if you increase the concentration of the substrate, the substrate can out-compete the inhibitor, and so the normal reaction can take place at a reasonable rate.

A simple example of this involves malonate ions inhibiting the enzyme succinate dehydrogenase. This enzyme catalyses the conversion of succinate ions to fumarate ions. The modern names are:

- malonate: propanedioate
- succinate: butanedioate
- fumarate: trans-butenedioate

The conversion that succinic dehydrogenase carries out is:

The reaction is inhibited by malonate ions which have a very similar shape to succinate ions.



The similar shape lets the malonate ions bind to the active site, but the lack of the CH_2-CH_2 bond in the centre of the ion stops any further reaction taking place.

The malonate ions therefore block the active site - but remember that this is reversible. The malonate ions will break away and free up the enzyme again. The malonate ions are in competition for the site - they aren't destroying it.

If the succinate ions have a greater concentration than the malonate ions, by chance they will get access to the site more often than the malonate ions. That means that you can overcome the effect of a competitive inhibitor by increasing the concentration of the substrate.

Non-competitive inhibitors

A non-competitive inhibitor doesn't attach itself to the active site, but attaches somewhere else on the enzyme. By attaching somewhere else it affects the structure of the enzyme and so the way the enzyme works. Because there isn't any competition involved between the inhibitor and the substrate, increasing the substrate concentration won't help.

If you look at various biochemistry sites on the web, you will find two explanations for this. We'll look at the simple, fairly obvious one in some detail in a minute. I want to have a brief word about the other one first.

"Pure" non-competitive inhibitors

This explanation says that the inhibitor doesn't affect the ability of the substrate to bond with the active site, but stops it reacting once it is there.

I found a couple of biochemistry sites which said that inhibitors working like this (which they describe as *pure* non-competitive inhibitors) are virtually unknown. As a non-biochemist, I don't know what the truth is about this - if you want to find out, you will probably have to do a biochemistry degree!

Other non-competitive inhibitors

The straightforward explanation (which would seem to apply to most enzymes) is that reaction with the inhibitor causes the shape of the active site to change. Remember that non-competitive inhibitors aren't attaching directly to the active site, but elsewhere on the enzyme.

The inhibitor attachs to a side group in the protein chain, and affects the way the protein folds into its tertiary structure. That in turn changes the shape of the active site. If the shape of the active site changes, then the substrate can't attach to it any more.

Some non-competitive inhibitors attach irreversibly to the enzyme, and therefore stop it working permanently. Others attach reversibly.

A relatively uncomplicated example of non-competitive inhibitors in a reasonably familiar situation is:

Heavy metal poisoning

You are probably aware that compounds containing heavy metals such as lead, mercury, copper or silver are poisonous. This is because ions of these metals are non-competitive inhibitors for several enzymes.

I'm going to take silver as a simple example.

Silver ions react with -SH groups in the side groups of cysteine residues in the protein chain:

cysteine residue in protein chain

There isn't enough electronegativity difference between silver and sulphur for a full ionic bond and so the bond can be considered as covalent.

If the cysteine residue is somewhere on the protein chain which affects the way it folds into its tertiary structure, then altering this group could have an effect on the shape of the active site, and so stop the enzyme from working.

The 2+ ions from, for example, mercury, copper or lead can behave similarly - also attaching themselves to the sulphur in place of the hydrogen.

S.No	Question	Option 1	Option 2	Option 3	Option 4	Answer
	UNIT-V					
1	Antineoplastic agents are the drugs used in the treatment of	cancer	Bacterial infection	Viral infection	Central nervous system	cancer
2	Antineoplastic agents are the drugs used in the treatment of	Malignancy	Bacterial infection	Viral infection	Central nervous system	Malignancy
3	Antineoplastic agents are the drugs used in the treatment of	tumor	Bacterial infection	Viral infection	Central nervous system	Tumor
4	Antineoplastic agents are the drugs used in the treatment of	carcinoma	Bacterial infection	Viral infection	Central nervous system	carcinoma
5	Antineoplastic agents are the drugs used in the treatment of	Sarcoma	Bacterial infection	Viral infection	Central nervous system	Sarcoma
6	Antineoplastic agents are the drugs used in the treatment of	Leukemia	Bacterial infection	Viral infection	Central nervous system	Leukemia
7	A new and diseased form of tissue growth is called	neoplasm	Plasma membrane	Golgi bodies	mitichondria	neoplasm
8	An alkylating agent used to treat neoplasms	Nitrogen mustards	Pyrimidine analogues	Mitomycin	Vinca alkaloids	Nitrogen mustards
9	An alkylating agent used to treat neoplasms	Alkyl sulfonates	Pyrimidine analogues	Mitomycin	Vinca alkaloids	Alkyl sulfonates
10	An alkylating agent used to treat neoplasms	Nitroso ureas	Pyrimidine analogues	Mitomycin	Vinca alkaloids	Nitroso ureas
11	An alkylating agent used to treat neoplasms	Ethylimine	Pyrimidine analogues	Mitomycin	Vinca alkaloids	Ethylimine

12	An alkylating agent used to treat neoplasms	Methyl hydrazines	Pyrimidine analogues	Mitomycin	Vinca alkaloids	Methyl hydrazines
13	An antimetaboite used to treat neoplasms	Methyl hydrazines	Pyrimidine analogues	Mitomycin	Vinca alkaloids	Pyrimidine analogues
14	An antimetaboite used to treat neoplasms	Methyl hydrazines	Purine analogues	Mitomycin	Vinca alkaloids	Purine analogues
15	An antimetaboite used to treat neoplasms	Methyl hydrazines	Folic acid analogues	Mitomycin	Vinca alkaloids	Folic acid analogues
16	An antibiotics used to treat neoplasms	Methyl hydrazines	Purine analogues	Anthracyclines	Vinca alkaloids	Anthracyclines
17	An antibiotics used to treat neoplasms	Methyl hydrazines	Purine analogues	Bleomycin	Vinca alkaloids	Bleomycin
18	An antibiotics used to treat neoplasms	Methyl hydrazines	Purine analogues	Mitomycin	Vinca alkaloids	Mitomycin
19	A plant product used to treat neoplasm	Methyl hydrazines	Purine analogues	Mitomycin	Vinca alkaloids	Vinca alkaloids
20	A plant product used to treat neoplasm	Methyl hydrazines	Purine analogues	Mitomycin	Vincristine	Vincristine
21	A plant product used to treat neoplasm	Methyl hydrazines	Purine analogues	Mitomycin	Vincristine	Vinblastine
22	A plant product used to treat neoplasm	Methyl hydrazines	Purine analogues	Mitomycin	Taxol	Taxol
23	A plant product used to treat neoplasm	Methyl hydrazines	Purine analogues	Mitomycin	Etoposide	Etoposide

24	A radiotherapeutic agent used to treat cancer	Chromic phosphate P 32	Purine analogues	Mitomycin	Etoposide	Chromic phosphate P 32
25	An inorganic complex used to treat cancer	Chromic phosphate P 32	Purine analogues	Mitomycin	cisplatin	cisplatin
26	Antiviral drug which belongs to purine nucleoside	Acyclovir	Iodoxuridine	Methisazone	Rimantadine	Acyclovir
27	Antiviral drug which belongs to pyrimidine nucleoside	Acyclovir	Iodoxuridine	Methisazone	Rimantadine	Iodoxuridine
28	Antiviral drug which belongs to Thiosemicarbazone class	Acyclovir	Iodoxuridine	Methisazone	Rimantadine	Methisazone
29	Antiviral drug which belongs to Adamantane amine class	Acyclovir	Iodoxuridine	Methisazone	Rimantadine	Rimantadine
30	Which class of antiviral drug Acyclovir belongs to	purine nucleoside	pyrimidine nucleoside	Thiosemicarbazone	Adamantane amine	purine nucleoside
31	Which class of antiviral drug Iodoxuridine belongs to	purine nucleoside	pyrimidine nucleoside	Thiosemicarbazone	Adamantane amine	pyrimidine nucleoside
32	Which class of antiviral drug Methisazone belongs to	purine nucleoside	pyrimidine nucleoside	Thiosemicarbazone	Adamantane amine	Thiosemicarbazone
33	Which class of antiviral drug Rimantadine belongs to	purine nucleoside	pyrimidine nucleoside	Thiosemicarbazone	Adamantane amine	Adamantane amine
34	Convulsant respiratory stimulants	Act on the brain system and spinal cord	Effect on mental function and behavious	Mood elevating	Effect thought pattern and perception	Act on the brain system and spinal cord

35	Psychomotor stimulants	Act on the brain system and spinal cord	Effect on mental function and behavious	Mood elevating	Effect thought pattern and perception	Effect on mental function and behavious
36	Antidepressant drugs	Act on the brain system and spinal cord	Effect on mental function and behavious	Mood elevating	Effect thought pattern and perception	Mood elevating
37	Psycho mimetic drugs	Act on the brain system and spinal cord	Effect on mental function and behavious	Mood elevating	Effect thought pattern and perception	Effect thought pattern and perception
38	Act on the brain system and spinal cord	Convulsant respiratory stimulants	Psychomotor stimulants	Antidepressant drugs	Psycho mimetic drugs	Convulsant respiratory stimulants
39	Effect on mental function and behavious	Convulsant respiratory stimulants	Psychomotor stimulants	Antidepressant drugs	Psycho mimetic drugs	Psychomotor stimulants
40	Mood elevating	Convulsant respiratory stimulants	Psychomotor stimulants	Antidepressant drugs	Psycho mimetic drugs	Antidepressant drugs
41	Effect thought pattern and perception	Convulsant respiratory stimulants	Psychomotor stimulants	Antidepressant drugs	Psycho mimetic drugs	Psycho mimetic drugs
42	Act on the brain system and spinal cord	Analeptics	Psychomotor stimulants	Antidepressant drugs	Psycho mimetic drugs	Analeptics

Reg. No…… **[18CHP105B]**

KARPAGAM UNIVERSITY

(Under Section 3 of UGC Act 1956)
COIMBATORE-641 021

(For the candidates admitted from 2018 & Onwards)

M.Sc., DEGREE EXAMINATION

I SEMESTER
INTERNAL TEST – I
CHEMISTRY

MEDICINAL CHEMISTRY

Time: 2 Hours **Maximum : 50 marks**

PART A **20 x 1 =20 marks**
Answer all Questions

1. Analgesics function is to
   a) **Relieve pain** b) Reduce elevated body temperatures
   c) To treat inflammation & mild pain d) To treat Bacterial infection
2. Antipyretics are used to
   a) Relieve pain b) **Reduce elevated body temperatures**
   c) To treat inflammation & mild pain d) To treat Bacterial infection
3. Anti-inflammatory drugs are used to
   a) Relieve pain b) Reduce elevated body temperatures
   c) **To treat inflammation & mild pain** d) To treat bacterial infection
4. Antibacterial agents function is to
   a) Relieve pain b) Reduce elevated body temperatures
   c) To treat inflammation & mild pain d) **To treat Bacterial infection**
5. A binding site means
   a) **The area of a macromolecular target that is occupied by a drug when it binds**
   b) The portion of the drug to which a drug target binds
   c) The functional groups used by a drug in binding to a drug target
   d) The bonds involved in binding a drug to its target

6. To treat viral infections,

a) Analgesics b) Antipyretics c) Anti-inflammatory drugs d) **Anti viral agents**

7. Example for analgesics,

a) **Aspirin** b) Chloramphenicol c) Sulphonamides, d) Diazepam

8. A weak bond and broke easily,

a) Covalent bond b) Ionic bond c) **Hydrogen bond** d) Hydrophobic interaction

9. p-amino phenol on treatment with acetic anhydride and acetic acid gives,

a) **paracetamol** b) Chloramphenicol c) Ibuprofen d) Acyclovir

10. Ibuprofen is prepared from,

a) **Isobutyl benzene**, b) p-nitro phenol c) Salicyclic acid d) Phenacetin

11. Ibuprofen is used to treat,

a) **Rheumatoid arthritis** b) Elevated body temperature

c) Blood pressure d) Diabetes

12. An example of a sulphonamide antibacterial agent

a) **Sulfadiazine** b) Ofloxacin c) Nitrofurazone d) Methenamine

13. The strongest bond involved in drug receptor interaction is,

a) **Covalent bond** b) Ionic bond c) Hydrogen bond d) Hydrophobic interaction

14. Interaction between non-polar organic molecules

a) Covalent bond b) Ionic bond c) Hydrogen bond d) **Hydrophobic interaction**

15. Pharmacodynamics involves the study of following EXCEPT:

a) Biological and therapeutic effects of drugs b) Drug interactions

c) **Absorption and distribution of drugs** d) Mechanisms of drug action

16. Oxidation, reduction or hydrolysis is

a) **Metabolic transformation (phase I)** b) Metabolic transformation (phase II)

c) Metabolic transformation (phase III) d) Metabolic transformation (phase IV)

17. Pharmacokinetic Phase is

a) **Adsorption and distribution** b) Hydrolysis c) Elimination d) Adsorption

18. The drug is usually distributed to high blood flow organs (heart, liver, kidney, brain, etc.)

a) **First few minutes** b) Immediately c) First few seconds d) One hour

19. Metabolism Phase is?

a) Oxidation b) **Biotransformation** c) Reduction d) Cumulative effect

20. Interacts with the receptor and initiates changes in cell function that substance is called

a) Rate of absorption b) Hydrolysis c) Insulin d) **Agonist**

PART B

Answer All the Questions **3 x 2 = 6 marks**

21. Give the types of Prodrug.

22. What is antiviral drugs and give one example with their chemical structure.

23. Write at least four names of receptor models

PART C

Answer All the Questions **3 x 8 = 24 marks**

24. a. What are analgesics? Explain the synthesis of Aspirin and Paracetamol.

OR

b. What are antibiotics? Write brief notes on Chloramphenicol.

25. a. What are antipyretics? Give suitable examples. Explain the synthesis of Ibuprofen.

OR

b. Explain the computer aided drug design process.

26. a. Write notes on Pharmacokinetics and Pharmacodynamics

OR

b. write notes on oxidation, reduction, hydrolysis and conjugations with examples.

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I SEMESTER
INTERNAL TEST – I
CHEMISTRY

MEDICINAL CHEMISTRY

Time: 2 Hours **Maximum : 50 marks**

PART A **20 x 1 =20 marks**

Answer all Questions

1. a) **Relieve**
2. b) **Reduce elevated body temperatures**
3. c) **To treat inflammation & mild pain**
4. d) **To treat Bacterial infection**
5. a) **The area of a macromolecular target that is occupied by a drug when it binds**
6. d) **Anti viral agents**
7. a) **Aspirin**
8. c) **Hydrogen bond**
9. a) **paracetamol**
10. a) **Isobutyl benzene**
11. a) **Rheumatoid**
12. a) **sulfadiazine**
13. a) **Covalent bond**
14. d) **Hydrophobic interaction**
15. c) **Absorption and distribution of drugs**
16. a) **Metabolic transformation (phase I)**
17. a) **adsorption and** c) **distribution**

18. a) **first few minutes**

19. b) **biotransformation**

20. d) **agonist**

PART B

Answer All the Questions **3 x 2 = 6 marks**

21. Give the types of Prodrug.

Table 1: Classification of prodrugs

Type	Bioactivation site	Subtype	Tissue location of bioactivation	Examples
Type I	Intracellular	Type IA	Therapeutic target tissues/cells	Acyclovir, 5-fluorouracil, cyclophosphamide, diethylstilbestrol diphosphate, L-dopa, 6-mercaptopurine, mitomycin C, zidovudine
Type I	Intracellular	Type IB	Metabolic tissues (liver, GI mucosal cell,lung etc.)	Carbamazepine, captopril, carisoprodol, heroin, molsidomine,paliperidone, phenacetin, primidone, psilocybin, sulindac,fursultiamine
Type II	Extracellular	Type IIA	GI fluids	Lisdexamfetamine, loperamide oxide, oxyphenisatin, sulfasalazine
Type II	Extracellular	Type IIB	Systemic circulation and Other Extracellular Fluid Compartments	Acetylsalicylate, bacampicillin, bambuterol, chloramphenicol

				succinate, dihydropyridine pralidoxime, dipivefrin, fosphenytoin
Type II	Extracellular	Type IIC	Therapeutic Target Tissues/Cells	ADEPTs, GDEPs, VDEPs

22. What is antiviral drugs and draw the chemical structure of one of them.

Antiviral drugs are a class of medication used specifically for treating viral infections rather than bacterial ones. Most antivirals are used for specific viral infections, while a **broad-spectrum antiviral** is effective against a wide range of viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasiticdrugs, or antiviral drugs based on monoclonal antibodies. Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Natural antivirals are produced by some plants such as eucalyptus and Australian tea trees.

23. Write at least four names of receptor models

There are **4 types of receptors**: ligand-gated channels, enzyme-linked **receptor**, G-protein linked **receptor**, and intracellular **receptor**. The cell membrane does not let any hydrophilic molecules go through, and so it requires specific ligand gated channels for their movement.

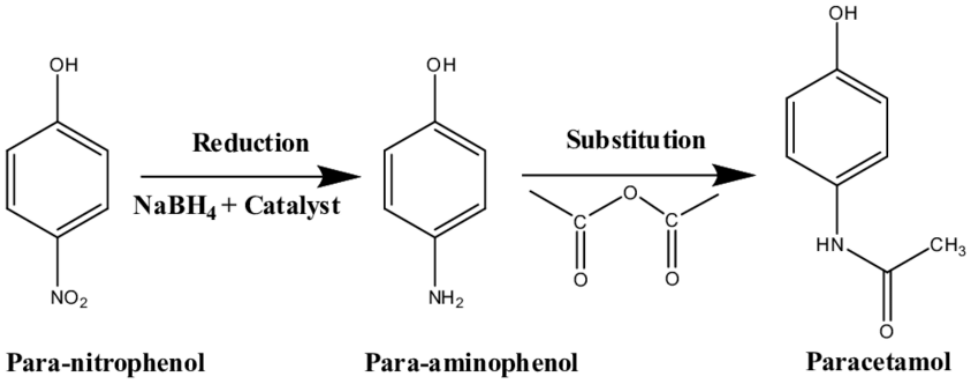
PART C

Answer All the Questions **3 x 8 = 24 marks**

24. a. What are analgesics? Explain the synthesis of Aspirin and paracetamol.

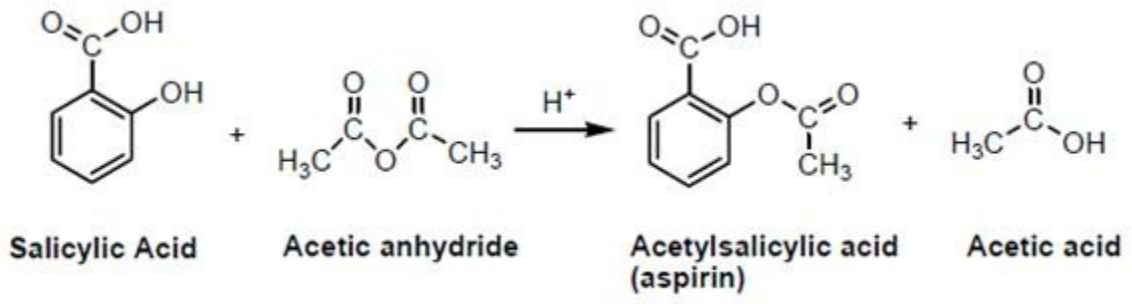
Analgesics are compounds used to reduce pain, antipyretics are compounds used to reduce fever. One popular drug that does both is aspirin, another is acetaminophen which is often used by people who have unwanted, harmful side effects to aspirin. Acetaminophen, which can be synthesized from p-aminophenol, is probably best recognized under the trade name Tylenol. The Merck Index, which is an encyclopedia of chemicals, drugs, and biologicals, lists the following information under

acetaminophen: large monoclinic prisms from water, mp 169-170.5, very slightly sol in cold water, considerably more sol in hot water. Sol in methanol, ethanol, dimethylformamide, acetone, ethyl acetate. Practically insol in petr ether, pentane.



Aspirin is one of the milder and least expensive pain relievers available. Today, Americans spend about $2 billion a year for non-prescription pain relievers. This figure mainly reflects purchase of 16,000 tons of aspirin tablets or 80 million tablets a year. Unlike many other formulations, the production of hard aspirin tablets only requires four ingredients: the active ingredient (acetylsalicylic acid), a lubricant such as hydrogenated vegetable oil, corn starch, and water. From the time of ancient Greeks to the present, acetylsalicylic acid or its parent - salicylic acid - has been used to relieve pain and symptoms of illness. In the early 1800s, salicin, a glycoside of salicylic acid, was found in the bark of a willow tree, *Salix alba*. Salicylic acid was found in the flowers of that tree. Although salicylic acid is a good pain reliever, its acidic properties cause irritation in the moist membranes of the mouth, throat, and stomach. In 1875, the sodium salt of salicylic acid was used because it is less sour to the taste. However, it still caused gastric discomfort problems. In 1893, Felix Hoffman Jr., a chemist working for the Bayer Laboratories in Germany, discovered a practical route for synthesizing an ester derivative of salicylic acid, acetylsalicylic acid. Acetylsalicylic acid does not have the bad taste and stomach problems of salicylic acid. Once acetylsalicylic acid is absorbed from the intestine, it is converted back to salicylic acid. It enters the bloodstream where it interferes with the synthesis of prostaglandins and irreversibly binds to an enzyme called cyclooxygenase 2. Prostaglandins and cyclooxygenase 2 are involved in generating a pain signal and inflaming the painful area. Salicylic acid interferes with

prostaglandins production and cyclooxygenase 2 activity, so there is less pain and inflammation. Bayer called its new product "aspirin," the name being derived from "a" for acetyl, and the root "-spir", from the Latin name *Spiraea ulmaria*, the meadow sweet flower, from which salicylic acid had been isolated. In this experiment, Le Chatelier's principle and esterification of the phenolic hydroxyl group of salicylic acid will be used to synthesize aspirin. Unlike the original Bayer Laboratory synthesis, acetic anhydride is used instead of acetyl chloride. Acetic anhydride is preferred because it is less hazardous to use and less expensive than acetyl chloride. In industry, the acetic acid produced in this reaction can be recovered and converted back into acetic anhydride. The reaction that is used for the synthesis is shown below. This reaction uses an excess of acetic anhydride, sulfuric acid as a catalyst, and heat to push the equilibrium toward the products. Water is added to quench the reaction, destroy the excess acetic anhydride, and cause crude aspirin to crystallize. The isolation will be carried out based on the solubility of the starting materials, product, and byproducts. In water, acetic anhydride slowly converts to acetic acid, and acetic acid, sulfuric acid, and water are infinitely miscible. Aspirin and salicylic acid are poorly soluble in cold water.



OR

b. What is antibiotics? Write brief notes on Chloramphenicol.

Chloramphenicol is a broad spectrum, effective and well-tolerated antibiotic - a simple neutral nitrobenzene derivative. However due to its propensity to cause blood dyscrasias in humans, the drug has been banned from use in food animals and is used with caution in companion animals. Chloramphenicol inhibits microbial protein synthesis by binding to the 50 S subunit of the 70 S

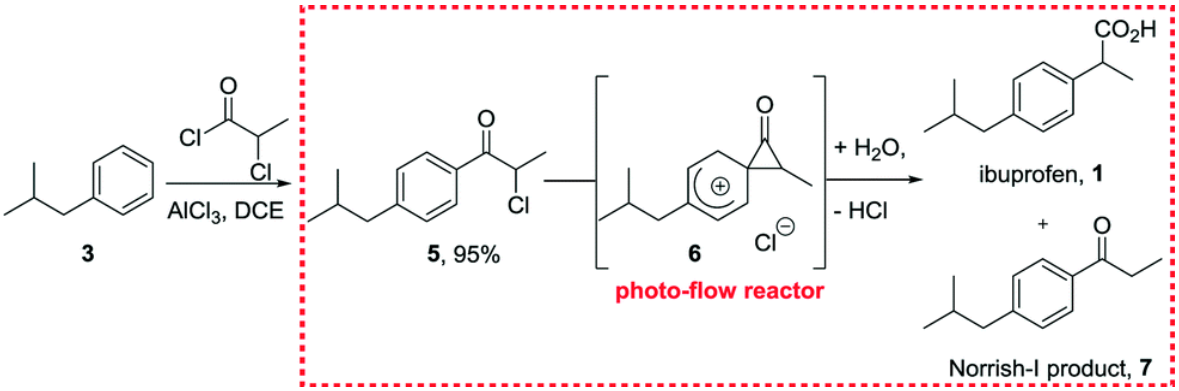
ribosome and inhibiting the action of peptidyl transferase, thus preventing peptide bond formation. This mechanism also prevents the binding of aminoacyl transfer RNA to the peptidyl transferase active site. The drug is primarily bacteriostatic but can be bactericidal in high concentrations against some bacteria. Chloramphenicol can be used orally as a neutral tasting palmitate and parenterally as a water soluble sodium succinate. The drug is lipid soluble, heat stable and ninety percent of the chemical is excreted in the urine. In addition to hematological disturbances, the drug also can cause gastrointestinal and neurological effects and Gray syndrome, a life-threatening condition of newborns. About half of plasma chloramphenicol is bound to albumin. The free portion, however, diffuses well into all tissues, including the central nervous system. The highest concentrations are found in the kidney, liver and bile. Significant levels are also found in body fluids such as cerebrospinal fluid and aqueous humor. Chloramphenicol does not reach effective concentrations in unaffected joints; however the drug does reach therapeutic levels in the presence of septic arthritis. Chloramphenicol never reaches effective levels in the prostate, even in the presence of significant infection or abscessation. Chloramphenicol is metabolized in the liver and is biotransformed primarily by glucuronide conjugation. In cats, a genetic deficiency in glucuronyl transferase activity may lead to considerably extended plasma half lives, therefore dosage should be adjusted accordingly. The very young (less than four weeks of age) of many species lack microsomal enzyme capabilities and plasma half lives can be profoundly extended, although foals are not affected. Two related antibiotics, thiamphenicol and its derivative, florfenicol, were developed by substituting a methyl sulfonyl group for the nitrophenol group that characterizes chloramphenicol. Thiamphenicol and florfenicol are both safer compounds; the former is less effective than chloramphenicol and the latter is more effective than chloramphenicol against some pathogens and is approved for use in cattle. Thiamphenicol and Florfenicol exhibit the same mechanism of action as the parent compound. Florfenicol penetrates the milk of lactating cows, but does not penetrate the CSF and aqueous humor to the same extent as chloramphenicol. Chloramphenicol can produce two distinctive types of bone marrow suppression. Reversible, dose dependent suppression occurs in humans. At a daily dose of 50 mg/kg for three weeks, this reversible condition is also demonstrated in cats. Dogs will experience only a milder suppression at even higher doses. Due to interference with mRNA and protein synthesis in rapidly multiplying cells, similar suppression is seen in neonatal animals receiving adult dosages of the drug. In humans a second more serious

irreversible, non-dose related aplastic anemia also occurs - often appearing after the drug is discontinued. This condition results in pancytopenia, bone marrow hypoplasia or aplasia, secondary infection and hemorrhagic diathesis. This non-reversible dyscrasia will occur in approximately one in 25,000 to one in 40,000 patients administered the drug. In order to eliminate the chance of such a condition resulting from food consumption, use of chloramphenicol is prohibited in food animals in the United States and several other countries. These blood dyscrasias seem to be related to the presence in chloramphenicol of the nitro group, therefore these conditions are not associated with the use of florfenicol or thiamphenicol. Use of chloramphenicol has also been associated with additional undesirable physical effects. Hypersensitivity in dogs and cats may result in yet another manifestation of aplastic anemia. Gastrointestinal disturbances have occurred in non-ruminants, cats may exhibit anorexia and depression when duration of therapy exceeds one week and use in calves has resulted in malabsorptive disorders. Chloramphenicol has demonstrated adverse effect on structure and function of reproductive organs in rats. Due to interference with protein synthesis, excessive topical use may interfere with healing. Interactions with vaccines and other drugs are additional concerns. Chloramphenicol interferes with the anamnestic immune response; therefore vaccines should never be administered to people or animals while chloramphenicol is being administered. Chloramphenicol may prolong the duration of action of several drugs, including pentobarbital, codeine, phenobarbital, phenytoin, NSAIDs and coumarins. When used in combination with sulfamethoxypyridazine, hepatic damage may result. Chloramphenicol interferes with the actions of several bactericidal drugs, such as penicillins, cephalosporins and aminoglycosides and in most circumstances, concurrent use of these drugs should be avoided. Use of the drug with other antibacterials that target the 50 S ribosomal subunit, lincosamides and macrolides, should be avoided. In veterinary medicine, safe use of the drug can be assured if chloramphenicol is not overdosed, if dosages are reduced in neonates and patients with impaired liver function or bone marrow suppression and if the duration of therapy is limited to a maximum of one week.

25. a. What are antipyretics? Give suitable examples. Explain the synthesis of ibuprofen.

Ibuprofen is a medication in the nonsteroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever, and inflammation. This includes painful menstrual periods, migraines,

and rheumatoid arthritis. It may also be used to close a patent ductus arteriosus in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.



Common side effects include heartburn and a rash.[6]Compared to other NSAIDs, it may have fewer side effects such as gastrointestinal bleeding.[7] It increases the risk of heart failure, kidney failure, and liver failure. At low doses, it does not appear to increase the risk of heart attack; however, at higher doses it may. Ibuprofen can also worsen asthma. While it is unclear if it is safe in early pregnancy, it appears to be harmful in later pregnancy and therefore is not recommended. Like other NSAIDs, it works by inhibiting the production of prostaglandins by decreasing the activity of the enzyme cyclooxygenase. Ibuprofen might be a weaker anti-inflammatory agent than other NSAIDs.

Ibuprofen was discovered in 1961 by Stewart Adams and initially marketed as **Brufen**. It is available under a number of trade names, including **Advil**and **Motrin**. It was first marketed in 1969 in the United Kingdom and in the United States in 1974. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. It is available as a generic medication. The wholesale cost in the developing world is between 0.01 and 0.04 USD per dose. In the United States it costs about 0.05 USD per dose.

OR

b. Explain the computer aided drug design process.

Computer-aided drug design

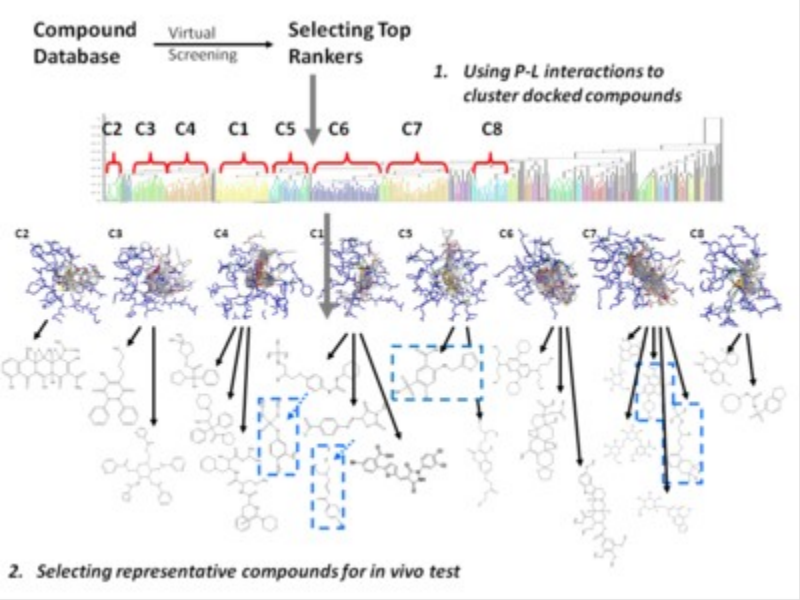
Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically activemolecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-basedscoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural netsor other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.[15][16]

Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized. The reality however is that present computational methods are imperfect and provide at best only qualitatively accurate estimates of affinity. Therefore in practice it still takes several iterations of design, synthesis, and testing before an optimal molecule is discovered. On the other hand, computational methods have accelerated discovery by reducing the number of iterations required and in addition have often provided more novel small molecule structures.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or ligand-based design)
2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
3. lead optimization optimization of other pharmaceutical properties while maintaining affinity



Flowchart of a Usual Clustering Analysis for Structure-Based Drug Design

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used to analysis. For structure-based drug design, several post-screening analysis focusing on protein-ligand interaction has been developed for improving enrichment and effectively mining potential candidates:

- Consensus scoring[17][18]
- Selecting candidates by voting of multiple scoring functions
- May lose the relationship between protein-ligand structural information and scoring criterion
- Geometric analysis
- Comparing protein-ligand interactions by visually inspecting individual structures
- Becoming intractable when the number of complexes to be analyzed increasing
- Cluster analysis[19][20]
- Represent and cluster candidates according to protein-ligand 3D information
- Needs meaningful representation of protein-ligand interactions.

26. a. write notes on Pharmacokinetics and Pharmacodynamics

It is best to consider these events as four phases in the lifetime of a drug. They are not always occurring *in vivo* in this order.

1. *Pharmacokinetic Phase* (absorption and distribution): the physicochemical events that permit a drug to reach its target.

2. *Pharmacodynamic Phase*: the interaction of the drug with its receptor and the biochemical effects of this interaction.

3. *Metabolism Phase* (biotransformation): chemical changes to the drug molecule imparted by enzymes and other biological agents. May complete wholly with pharmacokinetic phase.

4. *Excretion Phase*: the termination of drug action

---

1. PHARMACOKINETIC PHASE (absorption and distribution)

(A)Absorption:

- Absorption, regardless of the route of administration, is dependent upon drug solubility. Drugs given as aqueous solutions are more rapidly absorbed than oils, suspensions or solid form because they mix more readily. Drugs given in a solid form (pills) are dependent upon the rate of *dissolution*, which may be a limiting factor.

- The *concentration* of a drug influences its rate of absorption. Drugs injected (or administered) in high concentration are absorbed more quickly than those at lesser concentrations.

- The *route of administration* markedly affects drug uptake. Some routes of administration are summarized below:

ROUTE	ABSORPTION PATTERN	LIMITATIONS/PRECAUTIONS/UTILITY
Enteral (oral)	variable	Absorption potentially erratic. Absorption potentially incomplete.
Parenteral (non-oral) - 3 major types		
Intravenous (i.v.)	Absorption circumvented	Immediate Effects. Increased risk of adverse effects.
Subcutaneous (sub cut or s.c.)	Prompt from aqueous soln. Slow and sustained (suspension)	Not suitable for large volume. Possible pain, edema.
Intramuscular (i.m.)	Prompt from aqueous soln. Slow and sustained (suspension)	Overweight or emaciated patients exhibit unusual patterns of absorption.

Some additional notes on absorption and routes of administration:

- *oral ingestion of drugs:* Most drug absorptions from the gastrointestinal (GI) tract occurs via passive processes and is favored when the drug is non-ionized (more lipophilic or

greasy form). Any factor that accelerates gastric emptying will be likely to increase the rate of drug absorption.

- *Intravenous*: The assets of i.v. injection are accuracy and immediacy not possible through other routes. Liabilities include the fact that there is no retreat from i.v. drug administration: constant monitoring is usually employed.

- *Intramuscular*: Most common, insulin. However, penicillin, owing to solubility and the fact that slow absorption is desired, is injected as an oily suspension into muscle (gluteus maximus).

- *Intra-arterial*: when localized effect into target organ is warranted

- *Intrathecal*: drug injected into spinal arachnoid space (CNS drugs - esp. birthing)

- *Intraperitoneal*: thorax cavity offers a large absorbing surface; danger of infection and first pass (through the blood) losses.

(B) Distribution: After a drug is absorbed into the bloodstream it is distributed into /interstitial and cellular fluids. In the first few minutes, the drug is usually distributed to high blood flow organs (heart, liver, kidney, brain, etc.). Delivery to muscle, skin and fat is slower but less reversible (outflow/min). Lipid insoluble drugs are restricted in their distribution and hence, their sites of action. Drugs may accumulate in tissues in high concentration as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

The distribution of drugs to the CNS from the bloodstream is unique. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores; thereby restricting bulk aqueous flow. Thus, organic acids and bases only slowly diffuse into the brain. Strongly ionized agents such as quaternary amines or the penicillins are normally unable to enter the CNS from circulation. Important!

Many drugs accumulate in muscle and other tissues: **cellular reservoirs.** For example, during administration of the anti-malarial drug quinacrine, the concentration in the liver may be 1000x that in the plasma. Fat is the most stable reservoir because it not only serves as an organic solvent

but it has very low blood flow.

BIOTRANSFORMATION

Many drugs are lipid soluble weak organic acids and bases that are not readily eliminated from the body. Drug metabolites are usually more polar and less lipid soluble than the parent material and this enhances their excretion, and lowering their volume of distribution. There are several chemical reactions causing the biotransformation of drugs classified as Phase-I and Phase-II reactions.

Phase - I: reactions convert the parent material to a more polar metabolite by oxidation, reduction or hydrolysis.

Phase - II: usually synthetic or conjugation reactions and, involve coupling between the drug or its metabolite and an endogenous substrate (e.g., glucuronic acid, sulfuric acid, acetic acid or an amino acid.

One of the most important systems for biotransformation is the *hepatic microsomal drug-metabolizing system*. The endoplasmic reticulum of the liver has a network of enzymes called **microsomes**. The microsomes catalyze the oxidation of drugs (via mixed function oxidases or monooxygenases) as well as glucuronide conjugation. Drug metabolism, owing to its strong relationship with organic chemistry shall be the emphasis of this class although classical medicinal chemistry would provide a more equal distribution of the aforementioned areas.

OR

b. write notes on oxidation, reduction, hydrolysis and conjugations with examples.

METABOLISM

In the following pages some representative metabolic transformations will be presented. This summary is by no means definitive nor exhaustive. Clearly, there are major pathways that seems to occur more than others. And, although the intention of metabolism or biotransformation is to

aid the excretion of a drug, it is not always consistent that the drug is changed to an "innocuous form." Frequently a process termed "*metabolic activation*" occurs leading to a more active form of the drug. This more active form may act either at the intended target as a more or less potent form, or an alternative one causing a side effect at another target site.

Excretion: the kidney is the most important organ for elimination of drugs. Substances excreted in the feces are mainly unabsorbed orally ingested compounds or metabolites excreted in the bile and not reabsorbed from the intestine. Excretory organs, eliminate polar compounds more efficiently than substances with high lipid solubility. There are four major types of enzyme-mediated metabolic reactions:

1. Hydrolysis

2. Oxidation

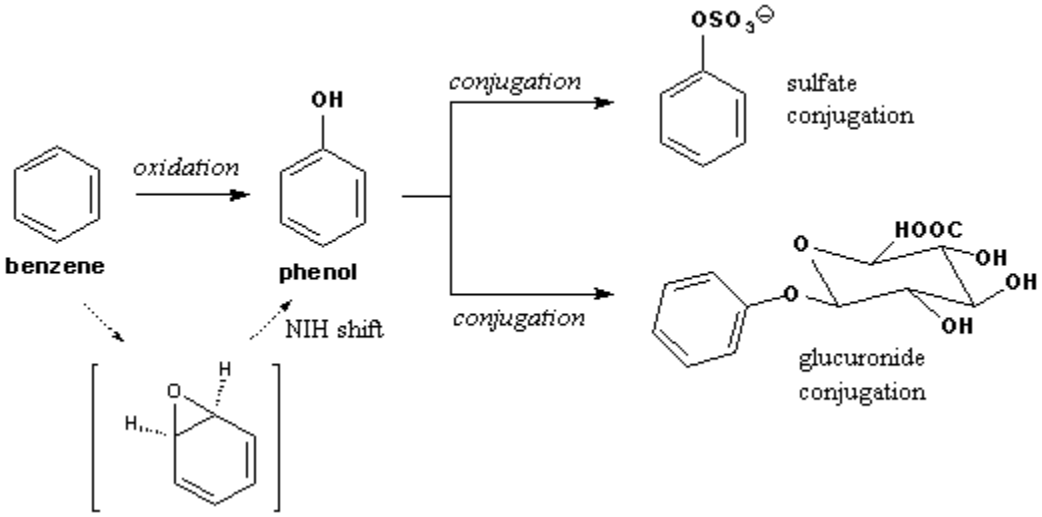
3. Reduction

4.Conjugation

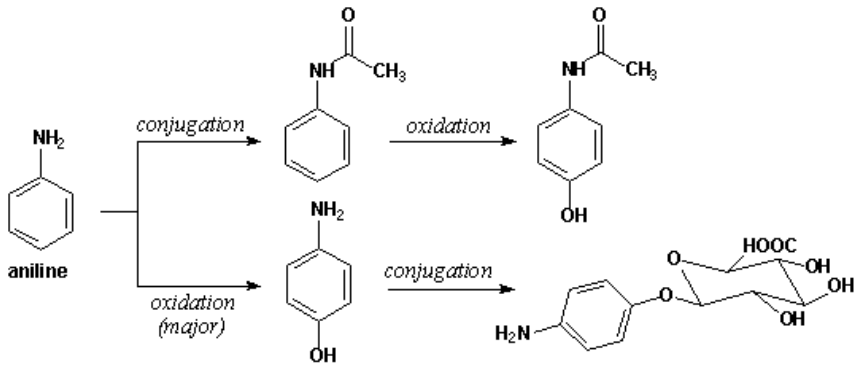
They occur most frequently in the soluble, mitochondrial or microsomal fractions of the liver. *Hydrolysis, oxidation and reduction* are chemically precise transformations whereas *conjugation* may include a diversity of changes including: N- or O-alkylation, esterification, and acylation. Conjugation usually involves the combination of a drug with a highly polar or ionic endogenous moiety, the product of which possesses greater water solubility.

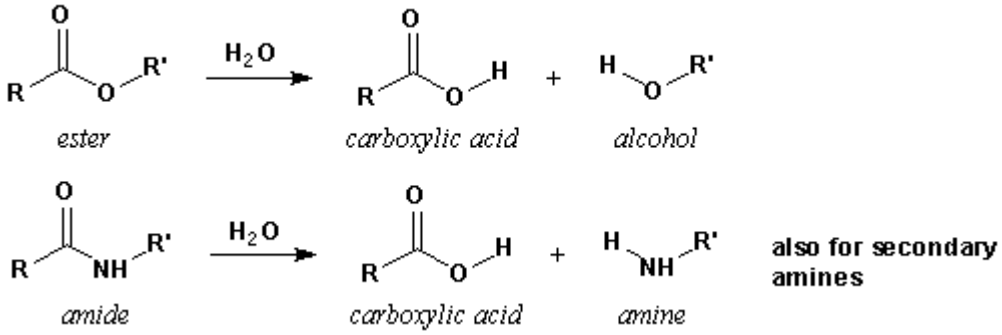
A drug is often metabolized in more than one way and very often there are sequential and/or parallel reaction pathways.

Example 1. benzene



Example 2. aniline

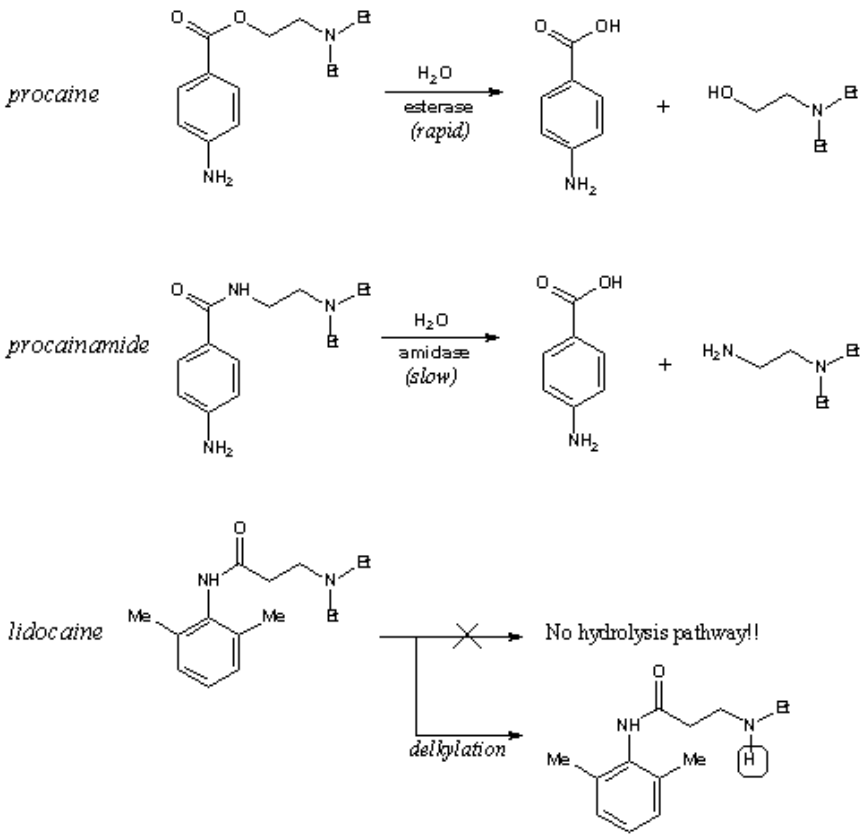




1. **Hydrolysis**

: (reaction of water with substrate resulting in breaking scissile carbon-heteroatom bonds) Usually an ester or amide hydrolyzes. The reaction is frequently enzyme - mediated although serum pH may cause reaction. Carboxylic (and phosphoric) esters afford a carboxylic acid and alcohol (1:1 molar equiv.). Carboxamides (and phosphoramides) afford the acid and one equivalent of the amine.

Some examples of how hydrolysis plays a role in medicinal chemistry is shown below.



2. Oxidations.

There are several possible oxidation routes involved in metabolism most of which are mediated by microsomes. Examples are used to represent each type of transformation. Note that although oxidation would seem to imply the addition of oxygen, that is not always the case. Oxidation refers to the change in oxidation state of the substrate.

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KARPAGAM UNIVERSITY

(Under Section 3 of UGC Act 1956)
COIMBATORE-641 021

(For the candidates admitted from 2018 & Onwards)

M.Sc., DEGREE EXAMINATION

I SEMESTER
INTERNAL TEST – II
CHEMISTRY

MEDICINAL CHEMISTRY

Time: 2 Hours **Maximum: 50 marks**

PART A **20 x 1 =20 marks**

Answer all Questions

1. In the past, most drugs have been discovered by identifying the active ingredient from

   a) vegetables b) fruits c) grains d) Traditional medicines

2. Combinatorial chemistry results in

   a) Multi complex mixture b) Single pure compound

   c) Few compounds in greener way d) Different conformers of a molecule

3. Drugs are also xenobiotics by virtue of their

   a) lipophilicity b) lyophilicity c) Solubility in water d) toxicity

4. The enzymatic biotransformation of water insoluble lipophilic non-polar drug into polar water soluble product is called,

   a) Drug metabolism b) Drug excretion c) Drug intake d) Drug hydrolysis

5. In the QSAR studies, among the following one of them is a liphophilic parameter,

   a) Partition coefficient b) Molar refractivity

   c) Taft's steric constant d) Molecular weight

6. In the QSAR studies, among the following one of them is a liphophilic parameter

   a) Chromatographic parameter b) Molar refractivity

   c) Taft's steric constant d) Molecular weight

7. In the QSAR studies, among the following one of them is a liphophilic parameter,

a) Pi-substitution constant b) Molar refractivity

c) Taft's steric constant d) Molecular weight

8. One among the following is a polarizability parameter in QSAR,

a) Pi-substitution constant b) Molar refractivity

c) Taft's steric constant d) Molecular weight

9. The ability of the drug to receptor binding increases as the drug molecule diffuses closure to the receptor,

a) Covalent bond b) Ionic bond c) Hydrogen bond d) Hydrophobic interaction

10. Drugs are also xenobiotics by virtue of their

a) lipophilicity b) lyophilicity c) Solubility in water d) toxicity

11. The enzymatic biotransformation of water insoluble lipophilic non-polar drug into polar water soluble product is called,

a) Drug metabolism b) Drug excretion c) Drug intake d) Drug hydrolysis

12. An example for a steric parameter

a) Quantum chemical parameters b) Parachor c) Vander waals radii d) Molecular weight

13. Ribbon presentation is used for

a) Nucleic acid and protein b) Smaller molecules

c) ligands d) Charged molecules

14. Hammett constant is a

a) Liphophilic parameter b) Polarazability parameter

c) Electronic parameter d) Steric parameter

15. Since many drugs contain hydroxyl and amino groups, the type of bond formed with the receptor is

a) Covalent bond b) Ionic bond c) Hydrogen bond d) Hydrophobic interaction

16. A variety of conformations of the drug molecule can be generated using

a) Molecular mechanics b) Molecular dynamics

c) Molecular docking d) Molecular graphing

17. The structure of the lead compounds are modified by synthesis to amplify the

a) Minimize the unwanted properties b) toxicity

c) Absorption difficulties d) insolubility

18. Taft's steric constant is a

a) Liphophilic parameter b) Polarizability parameter

c) Electronic parameter d) Steric parameter

19. The collection of relevant groups responsible for drug-receptor interaction is called

a) Pharmacophore b) Functional group c) Lead molecule d) Prodrug

20. 16. One among the following is a polarizability parameter in QSAR,

a) Pi-substitution constant b) Molar refractivity

c) Taft's steric constant d) Molecular weight

PART B

Answer All the Questions **3 x 2 = 6 marks**

21. What is a lead molecule?

22. Write the four distinct categories of drug discovery processes.

23. Briefly explain about the Taft's steric factor (Es).

PART C

Answer All the Questions **3 x 8 = 24 marks**

24. a. Explain the method of drug discovery screening.

OR

b. What is a clinical trial? Give an account of clinical trials.

25. a. Explain in detail about the electronic effects, Hammet equation and steric effects in QSAR studies.

OR

b. What is meant by rigid docking, flexible docking and manual docking?

26. a. Explain in detail about the experimental and theoretical approaches for the determination of physic-chemical parameters in drug design.

OR

b. Describe the molecular docking and dynamics used in the drug discovery.

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CHEMISTRY

MEDICINAL CHEMISTRY

Time: 2 Hours **Maximum : 50 marks**

PART A **20 x 1 =20 marks**

Answer all Questions

1. d) **Traditional medicines**

2. **a) Multi complex mixture**

3. a) **lipophilicity**

4. a) **Drug metabolism**

5. a) **Partition coefficient**

6. a) **Chromatographic parameter**

7. a) **Pi-substitution constant**

8. b) **Molar refractivity**

9. b) **Ionic bond**

10. a) **lipophilicity**

11. a) **Drug metabolism**

12. c) **Vander waals radii**

13. a) **Nucleic acid and protein**

14. **c) Electronic parameter**

15. **c) Hydrogen bond**

16. **a) Molecular mechanics**

17. **a) Minimize the unwanted properties**

18. **d) Steric parameter**

19. **a) Pharmacophore**

20. **b) Molecular refractivity**

PART B

Answer All the Questions **3 x 2 = 6 marks**

21. What is a lead molecule?

A **lead compound** (i.e. the "leading" compound, not lead metal) in drug discovery is a chemical compound that has pharmacological orbiological activity and whose chemical structure is used as a starting point for chemical modifications in order to improve potency,selectivity, or pharmacokinetic parameters.

22. Write the four distinct category of drug discovery processes.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or ligand-based design)

2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)

3. lead optimization optimization of other pharmaceutical properties while maintaining affinity

4. biopharmaceutical or pharmacokinetic properties of the drug

23. Briefly explain about the Taft's steric factor (Es).

The Taft equation is a linear free energy relationship (LFER) used in physical organic chemistry in the study of reaction mechanisms and in the development of quantitative structure activity relationships for organic compounds. It was developed by Robert W. Taft in 1952 as a

modification to the Hammett equation. While the Hammett equation accounts for how field, inductive, and resonance effects influence reaction rates, the Taft equation also describes the steric effects

PART C

Answer All the Questions **3 x 8 = 24 marks**

24. a. Explain the method of drug discovery screening.

Rational drug discovery

In contrast to traditional methods of drug discovery, which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value. In order for a biomolecule to be selected as a drug target, two essential pieces of information are required. The first is evidence that modulation of the target will have therapeutic value. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states. The second is that the target is "drugable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

Once a suitable target has been identified, the target is normally cloned and expressed. The expressed target is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.

The search for small molecules that bind to the target is begun by screening libraries of potential drug compounds. This may be done by using the screening assay (a "wet screen"). In addition, if the structure of the target is available, a virtual screen may be performed of candidate drugs. Ideally the candidate drug compounds should be "drug-like", that is they should possess properties that are predicted to lead to oral bioavailability, adequate chemical and metabolic stability, and minimal toxic effects. Several methods are available to estimate druglikeness such as Lipinski's Rule of Five and a range of scoring methods such as Lipophilic efficiency. Several methods for predicting drug metabolism have been proposed in the scientific literature, and a

recent example is SPORCalc.[14] Due to the complexity of the drug design process, two terms of interest are still serendipity and bounded rationality. Those challenges are caused by the large chemical space describing potential new drugs without side-effects.

Computer-aided drug design

Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it. Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.[15][16]

Ideally the computational method should be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized. The reality however is that present computational methods are imperfect and provide at best only qualitatively accurate estimates of affinity. Therefore in practice it still takes several iterations of design, synthesis, and testing before an optimal molecule is discovered. On the other hand, computational methods have accelerated discovery by reducing the number of iterations required and in addition have often provided more novel small molecule structures.Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or ligand-based design)
2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)

3. lead optimization optimization of other pharmaceutical properties while maintaining affinity

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used to analysis. For structure-based drug design, several post-screening analysis focusing on protein-ligand interaction has been developed for improving enrichment and effectively mining potential candidates:

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  - Selecting candidates by voting of multiple scoring functions
  - May lose the relationship between protein-ligand structural information and scoring criterion
- Geometric analysis
  - Comparing protein-ligand interactions by visually inspecting individual structures
  - Becoming intractable when the number of complexes to be analyzed increasing
- Cluster analysis[19][20]
  - Represent and cluster candidates according to protein-ligand 3D information
  - Needs meaningful representation of protein-ligand interactions.

Examples

A particular example of rational drug design involves the use of three-dimensional information about biomolecules obtained from such techniques as X-ray crystallography and NMR spectroscopy. Computer-aided drug design in particular becomes much more tractable when there is a high-resolution structure of a target protein bound to a potent ligand. This approach to drug discovery is sometimes referred to as structure-based drug design. The first unequivocal

example of the application of structure-based drug design leading to an approved drug is the carbonic anhydrase inhibitor dorzolamide, which was approved in 1995.[21][22]

Another important case study in rational drug design is imatinib, a tyrosine kinase inhibitor designed specifically for the bcr-abl fusion protein that is characteristic for Philadelphia chromosome-positive leukemias (chronic myelogenous leukemia and occasionally acute lymphocytic leukemia). Imatinib is substantially different from previous drugs for cancer, as most agents of chemotherapy simply target rapidly dividing cells, not differentiating between cancer cells and other tissues.

OR

b. What is clinical trials? Give an account of clinical trials.

Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases 0, 1, 2, and 3, it will usually be approved by the national regulatory authority for use in the general population.

There are different phases in the clinical trial.

- Phase 0: Pharmacodynamics and Pharmacokinetics
- Phase 1: Screening for safety
- Phase 2: Establishing the testing protocol
- Phase 3: Final testing
- Phase 4: Post approval studies

Each phase has a different purpose and helps scientists answer a different question:

In Phase 0 trials are the first-in-human trials. Single subtherapeutic doses of the study drug are given to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[18]

In Phase 1 trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase 2 trials, the experimental treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

In Phase 3 trials, the treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

In Phase 4 trials, post marketing studies delineate additional information, including the treatment's risks, benefits, and optimal use.

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive preclinical studies.

25. a. Explain in detail about the electronic effects, Hammet equation and steric effects in QSAR studies.

The Hammett equation (and its extended forms) has been one of the most widely used means forthe study and interpretation of organic reactions and their mechanisms. Ever since the Hammett equation was developed, there were several hundreds of redox, condensation, disproportionation,nucleophilic and electrophilic substitution, and addition reactions with meta- and para-substituted benzene derivatives in the literature, for which the Hammett reaction (ρ) constants were reported.

Hammett's success in treating the electronic effect of substituents on the rates and equilibria of organic reactions led Taft to apply the same principles to steric and inductive and resonance effects.

The Hammett equation correlates rates and equilibria for many reactions of compounds

Containing substituted phenyl groups. It was noted in the 1933 that there is a linear relationship between the acid strengths of substituted benzoic acids and the rates of many other chemical reactions, e.g., the rates of hydrolysis of substituted ethyl benzoates.

Hammett plotted log k for hydrolysis of esters against log K for ionization of the acids, a straight line was obtained.

The term structure–activity relationship (SAR) is now used to describe Ehrlich’s approach to drug discovery, which consisted of synthesizing and testing a series of structurally related

compounds Attempts to quantitatively relate chemical structure to biological action were first initiated in the 19th century.
In 1960 Hansch and Fujita devised a method that successfully incorporated quantitative measurements into SAR determinations.
The technique is referred to as QSAR (quantitative structure–activity relationships).
One of its most successful uses has been in the development in the 1970s of the antiulcer agents cimetidine and ranitidine.Both SARs and QSARs are important parts of the foundations of medicinal chemistry.

Cimetidine and Ranitidine is a histamine H2-receptor antagonist that inhibits the production of acid in the stomach.The H2-receptor antagonists are a class of drugs used to block the action of histamine on parietal cells in the stomach, decreasing the production of acid histamine

Langley (1905) proposed that so called receptive substances in the body could accept either a stimulating compound, which would cause a biological response, or a non-stimulating compound, which would prevent a biological response. It is now universally accepted that the binding of a chemical agent, referred to as a ligand, to a so called receptor sets in motion a series of biochemical events that result in a biological or pharmacological effect.
Furthermore, a drug is most effective when its structure or a significant part of its structure, both as regards molecular shape and electron distribution (stereoelectronic structure), is complementary with the stereo electronic structure of the receptor responsible for the desired biological action.The section of the structure of a ligand that binds to a receptor is known as its pharmacophore. Side effects - drug binds to either the receptor responsible for the desired biological response or undesired receptors.Human carboxylesterase 1 (hCE1) is a broad-spectrum drug metabolism enzyme found in abundance in liver, the central organ for xenobiotic detoxification.

OR

b. What is meant by rigid docking, flexible docking and manual docking?

Rigid-body docking *vs*. flexible docking

If the bond angles, bond lengths and torsion angles of the components are not modified at any stage of complex generation, it is known as *rigid body docking*. A subject of speculation is whether or not rigid-body docking is sufficiently good for most docking. When substantial conformational change occurs within the components at the time of complex formation, rigid-

body docking is inadequate. However, scoring all possible conformational changes is prohibitively expensive in computer time. Docking procedures which permit conformational change, or *flexible docking* procedures, must intelligently select small subset of possible conformational changes for consideration.

MANUAL DOCKING: Dock or fit a molecule in the binding site Binding group on the ligand and binding site are known, defined by the operator.

26. a. Explain in detail about the experimental and theoretical approaches for the determination of physic-chemical parameters in drug design

A successful drug candidate has the right attributes to reach and bind its molecular target and has the desired duration of action. Binding to the target can be optimised by designing the proper three-dimensional arrangement of functional groups. Each chemical entity also has, through its structure, physicochemical and biopharmaceutical properties. These are generally related to processes such as dissolution, oral absorption, uptake into the brain, plasma protein binding, distribution, and metabolism. Therefore fine-tuning of the physicochemical properties has an important place in lead optimization.

Physicochemical properties in relation to drug action

In general, when a drug molecule enters the body, it will interact with one or more biopolymers found in the extracellular fluid, in the cell membrane, and within cells. The type and the extent of this interaction will depend on the kind and number of chemically reactive functional groups and the polarity of the drug molecule. The drug-protein interaction does not involve covalent bonds that are relatively stable at body temperatures. Instead, weak forces such as ionic bonds, hydrogen bonds, Van der Waals forces, dipole-ion, and dipole-dipole forces are involved. The partition coefficient P, produced because of the presence of drug through lipid membranes/water system found in the body, is given by P = [drug] lipid /[drug] water , the Hansch equation. A biological response is produced by the interaction of a drug with a functional or an organized group of molecules, which may be called the biological receptor site.

The hydrophobic bond

This is a concept used to explain attractive interactions between nonpolar regions of the receptor and the drug. Explanations such as the isopropyl moiety of the drug fits into a hydrophobic cleft on the receptor composed of the hydrocarbon side chains of the amino acids valine, isoleucine,

and leucine are commonly used to explain why a nonpolar substituent at a particular position on the drug molecule is important for activity. Also, the polypeptide chain is considered to be the primary level of protein structure and the folding of the polypeptide chains into a specified structure maintained through hydrogen bonding interactions (intramolecular) .

Hydrogen bond

Among the secondary forces, hydrogen bonding that occurs over short distances (2.5-2.7 E) is one of the most important forces that affects the physical property of the compound. The important hydrogen bonding groups are -OH, -NH, which can form either intermolecular or intramolecular hydrogen bonds. Some examples are water, salicylic acid, and o-nitrophenol. The antipyretic and antirheumatic effects of salicylic acid are because of its prostaglandin synthase-inhibitory effect.

Chelation

The compounds that are obtained by donating electrons to a metal ion with the formation of a ring structure are called chelates (e.g. copper-chelate) [Figure 1]; the compounds capable of forming a ring structure with a metal are termed ligands. In this example, the ligand is a mercaptoamino acid that donates electrons to the Cu 2+ ion .

Chelation can be used for sequestration of metal ions , stabilization of drugs , and elimination of toxic metals from intact organisms and also for improvement of metal absorption. An important example of chelating agents is the radioactive transition state artificial metal, technetium (99m Tc), for albumin injection used as radiotracers in diagnostic nuclear medicine practice .

Surface activity

Four different types of surface-active agents can be recognized: (a) anionic compounds, for example salt of bile acids, salts of sulfate or phosphate esters of alcohols and salts of sulfonic acids; (b) cationic compounds, for example high-molecular-weight aliphatic amines and quaternary ammonium derivatives; (c) nonionic compounds, for example polyoxyethylene ethers and glycol esters of fatty acids; and (d) amphoteric surfactants

The surface-active molecules can be formed at the surface of water or at the interface of polar and nonpolar liquids with the nonpolar portion of the molecule oriented toward the nonpolar liquid and the polar groups toward the polar liquids. Three different types of forces are involved in the orientations of surface-active molecules, namely, Van der Waals, hydrogen bonds, and ion dipoles

Charge transfer interaction

In these interactions, electrons are not fully transferred; rather, electron density is distributed between molecules the same way as in covalent bond. The molecule that accepts electron density is called the acceptor and the molecule that donates electron density is called the donor The charge transfer interactions are weak in comparison with the covalent bonding because each of the molecules involved in the interaction already has its primary valence requirements satisfied. The commonly known examples of charge transfer complexes are aromatic molecules. The contribution of charge transfer interactions toward drug activity has been determined in terms of molecular orbital calculations. The calculations of the energy for the highest occupied molecular orbital and the lowest empty one of actinomycin and of various purines have shown them to be in accordance with the observed electron-accepting and electron-donating properties of the respective compounds. The interactions of Cu, Pd, and Ni chelates of 8-hydroxyquinoline with various electron acceptors support charge transfer as a possible mechanism of action of these compounds

OR

b. Describe molecular docking and dynamics used in the drug discovery.

MOLECULAR MODELLING

Structure-based design and discovery of protein ligands has emerged as a new tool in medicinal chemistry. In particular, the knowledge of the three-dimensional structure of a protein can be used to derive new protein ligands with improved binding properties (i.e. new drugs). Within this approach we need algorithms and methods to solve the following questions: What is the binding affinity of a novel ligand towards a particular receptor? What are the best conformations of a ligand to the binding site? What are the similarities of different ligands with respect to their recognition capabilities? With which orientation will a ligand bind to the active site?

Molecular Dynamics

We apply molecular dynamics (MD) extensively using the AMBER and GROMACS suite of programs. MD is used to simulate the stability of protein dimers and of drug-protein complexes throughout time. We apply MD also to analyze the binding free energy of these complexes, employing the MMPBSA approximation.

Homology Modelling

Homology modelling refers to a set of methods that aim to predict the 3D structure of unknown proteins by comparing their sequences with known proteins, for which the crystal structure is available (the template). After refinement, applying usually molecular dynamics, the predicted model can be used for drug design purposes.

Virtual Screening

Virtual Screening (VS) refers to the process of predicting new chemical entities that would eventually inhibit a target (protein) related to some disease. VS could enhance the hit ratio discovery as compared to classical high throughput screening, speeding up the process of drug design.

Introduction

• Powerful desktop and super computers has helped chemists to predict the structures and the values of **properties of known, unknown, stable and unstable molecular species using mathematical equations.**

• Mathematical methods used to obtain and solve the equations is well known and so in most cases it is possible to obtain a reliable estimate of the accuracy of the results.

• In some cases the calculated values are believed to be more accurate than the experimentally determined figures because of the higher degree of **experimental error** in the experimental work.

• Graphics packages that convert the data for the structure of a chemical species into a variety of easy to understand **visual formats** have also been developed

• Medicinal Chemist can visualize the three dimensional shapes of both the ligands and their target sites.

Docking

• Sophisticated computational chemistry packages also allow the medicinal chemist to evaluate the interactions between a compound and its target site before synthesizing that compound

• Only synthesize and test the most promising of the compounds, which considerably increases the chances of discovering a potent drug. It also significantly reduces the cost of development.

• Drug rely on computational chemist to make the necessary calculations and graphic conversions.