

## DRUG DESIGN

optimizing target interactions

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## Drug Design: optimizing target interactions

- Once the lead compound has been discovered it can be used as the starting point for drug design.
- There are various aims in drug design:
  1. The drug should have a good selectivity for its target
  2. The drug should have a good level of activity for its target
  3. The drug should have minimum side effects
  4. The drug should be easily synthesized
  5. The drug should be chemically stable
  6. The drug should have acceptable pharmacokinetics properties
  7. The drug should be non-toxic

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## There are two important aspects in drug design and drug strategies to improve :

1. **Pharmacodynamics properties:** to optimize the interaction of the drug with its target.
  2. **Pharmacokinetics properties:** to improve the drug's ability to reach its target & to have acceptable lifetime.
- Pharmacodynamics and pharmacokinetics should have equal priority in influencing which strategies are used and which analogues are synthesized.

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## Structure Activity Relationships (SAR)

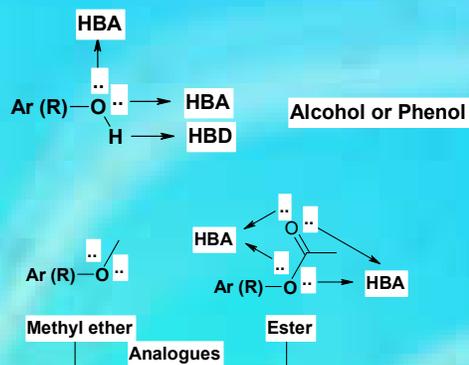
- This involves testing all analogues for biological activity and comparing them with the original compound.
- If an analogue shows a significant lower activity, then the group that has been modified must be important.
- If the activity remain similar, then the group is not essential.
- It may be possible to modify some lead compounds directly to the required analogues and other analogues may be prepared by total synthesis.

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## Binding Role of Different Functional Groups

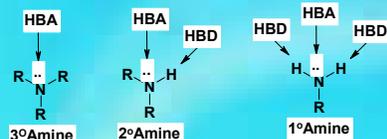
- 1-Functional groups such as alcohols, phenols, amines, esters, amides, carboxylic acids, ketones and aldehydes can interact with binding sites by means of hydrogen bonding.
- 2- Functional groups such as amines, (ionized) quaternary ammonium salts and carboxylic acid can interact with binding sites by ionic bond.

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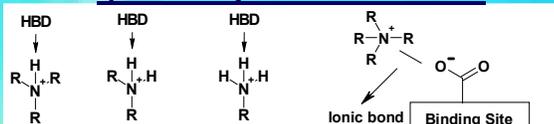


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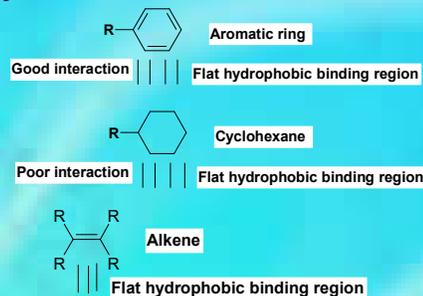
## Amines



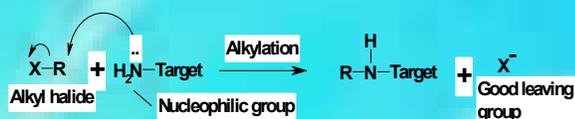
### Ionized amines and quaternary ammonium salts



- 3- Functional groups such as alkenes and aromatic rings can interact with binding sites by means of Van der Waals interactions.



- 4- Alkyl substituents and the carbon skeleton of the lead compound can interact with hydrophobic regions of binding site by means of Van der Waals interactions.
- 5- Interactions involving dipole moments or induced dipole moments may play a role in binding a lead compound to a binding site.
- 6- Reactive functional groups such as alkyl halides may lead to irreversible covalent bonds being formed between a lead compound and its target.
- E.g. alkylation of macromolecular target by alkyl halides



- The relevance of a functional group to binding can be determined by preparing analogues where the functional group is *modified or removed* in order to see whether activity is affected by such change.
- Some functional groups can be important to the activity of a lead compound for reasons other than target binding as they may play a role in the electronic or stereochemical properties of the compound or they may have an important pharmacokinetic role.
- Replacing a group in the lead compound with isostere (a group having the same valency) makes it easier to determine whether a particular property such as hydrogen bonding is important.
- In vitro testing procedures should be used to determine the SAR for target binding.
- The pharmacophore summarizes the important groups which are important in the binding of a lead compound to its target, as well as their relative positions in three dimensions (for a specific pharmacological activity).

## Drug Optimization: Strategies in drug design

### I-optimizing drug target interactions

- Drug optimization aims to maximize the interactions of a drug with its target binding site in order to improve activity, selectivity and to minimize side effects.
- Designing a drug that can be synthesized efficiently and cheaply is another priority.
- The aim of drug optimization can be achieved by different strategies or approaches on the lead compound SAR, such as:
  - 1-variation of substituents (alkyl and aromatic substitution)
  - 2- extension of structure (chain extension/contraction, ring expansion/contraction),
  - 3-ring variation,
  - 4-ring fusion,
  - 5-isosteres and bioisosteres,
  - 6-simplification of the structure,
  - 7- rigidification of the structure.
  - 8-Conformational blockers

## Drug Optimization:

### Strategies in drug design

#### I-optimizing drug target interactions

- 1-The length and size of alkyl substituents can be modified** to fill up on hydrophobic pockets in the binding site or to introduce selectivity for one target over another. Alkyl groups attached to heteroatoms are most easily modified.
- Aromatic substituents can be varied** in character and/or ring position.
- 2-Extension is a strategy** where extra functional groups are added to the lead compound in order to interact with extra binding region in binding site.

- **Chains connecting two important binding groups** can be modified in length in order to maximize the interactions of each group with the corresponding binding regions.
- **Rings linking important binding groups** can be expanded or contracted such that the binding groups bind efficiently with relevant binding regions.
- **3-Rings acting** as scaffold for important binding groups can be varied in order to give novel class of drugs which may have improved properties.
- **4-Rings can be fused** to existing rings in order to maximize binding interactions or to increase selectivity for one target over another.

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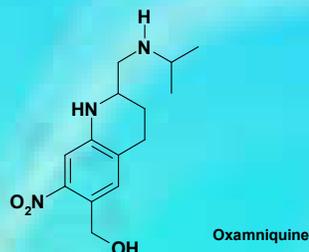
- **5-Classical and non-classical isosteres (bioisosteres)** are frequently used in drug optimization.
- **6-Simplification** involves removing functional groups from the lead compound that are not part of the pharmacophore. Unnecessary parts of the carbon skeleton or asymmetric centers can also be removed in order to design drugs that are easier and cheaper to synthesize. **Oversimplification** can result in molecules that are too flexible, resulting in decreased activity and selectivity.
- **7-Rigidification** is used on flexible lead compounds. The aim is to reduce the number of conformations available while retaining the active conformation. Locking Rotatable rings into ring structure or introducing rigid functional groups are common methods of rigidification.

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- **8-Conformational blockers** are groups which are introduced into a lead compound to reduce the number of conformations that the molecule can adopt through steric interactions.
- Structure-based drug design makes use of X-ray crystallography and computer-based molecular modeling to study how a lead compound and its analogues bind to a target binding site.
- NMR studies can be used to determine protein structure and to design novel drugs.
- Serendipity plays a role in drug design optimization.

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- **Oxamniquine** (schistosomicides) is an example of a drug designed by classical methods.



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## Drug Design: II-optimizing access to the target

- The compound with the best binding interaction is not necessarily the best drug to use in medicine.
- The drug needs to pass through many barriers to reach its target in the body.
- There are many ways to make the drug to reach its target such as linking the drug to polymers or antibodies or encapsulating it within a polymeric carrier.
- Thus, the aim is to design drugs that will be absorbed into the blood supply (absorption) and will reach their target efficiently (distribution) and be stable enough to survive the journey (metabolism) and will be eliminated in a reasonable period of time (elimination).
- In other words, designing a drug with optimum pharmacokinetics can be achieved by different strategies.

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## 1-Improvement of absorption:

- Drug absorption is determined by its **hydrophilic/hydrophobic properties**, which they depends upon polarity and ionization.
- Drugs which are **too polar** or strongly ionized do not easily cross the cell membranes of the gut wall. Therefore, they are **given by injection**, but the disadvantage that they are quickly excreted.
- **Non-polar** drugs, on the other hand, are poorly soluble in aqueous solution and are poorly absorbed. If they are given by injection, they are taken up by fat tissue.
- **In general, the polarity and ionization of compounds can be altered by changing their substituents, and these changes are known as quantitative structure-activity relationships (QSAR).**

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## Strategies to improve absorption

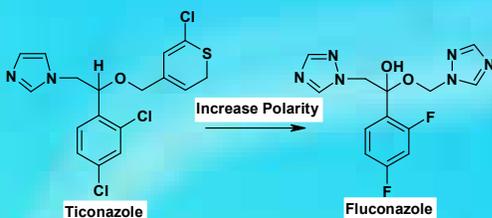
- 1)- Variation of alkyl or acyl substituents to vary polarity:
  - A- Molecules can be made less polar by masking a polar functional group with an alkyl or acyl group.
  - For example: an alcohol or phenols can be converted to ester or amide. Primary and secondary amines can be converted to amides or secondary or tertiary amines.
  - B- Polarity is decreased not only by masking the polar groups, but by addition of an extra hydrophobic alkyl group (large alkyl groups having a greater hydrophobic effect).
  - We have to be very careful in masking polar groups important in binding the drug to its target, as masking them may prevent binding.
  - Extra alkyl groups can be added to carbon skeleton directly or may involve more synthesis.
  - If the molecule is not sufficiently polar then the opposite strategy can be used i.e. replacing large alkyl groups with smaller alkyl groups or removing them entirely.

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## Strategies to improve absorption

- 2)- Varying polar functional groups to vary polarity
  - A polar functional group could be added to a drug to increase polarity.
  - For example: *Ticonazole* (antifungal) is used only for skin infections because it is non-polar and poorly absorbed in blood by introducing a polar hydroxyl group and more polar heterocyclic ring led to the orally active antifungal agent *Fluconazole*.

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- In contrast, the polarity of an excessively polar drug could be lowered by removing polar functional groups.
- It is important not to remove functional groups which are important to the drug's binding interactions with its target.

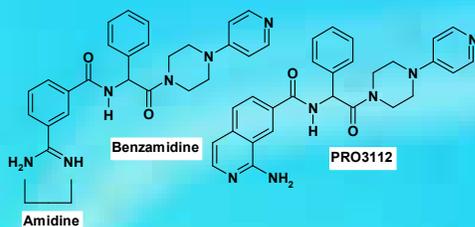
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## Strategies to improve absorption

### 3)- Variation of N-alkyl substituents to vary pka

- Drugs with a pka outside the range 6-9 tend to be too strongly ionized and are poorly absorbed through cell membrane.
- The pka can often be altered to bring it into the preferred range. For example: the pka of an amine can be altered by varying the alkyl substituents.
- In general, electron donating groups (EDG, e.g. alkyl groups) increase basicity (increase pka). But increasing the size of alkyl groups will increase the steric bulk around the nitrogen (Steric hindrance) leading to a decrease of basicity of amine.

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- For example: *Benzamidine* (antithrombotic), the amidine group ( $H_2NC=NH$ ) is too basic for effective absorption. Incorporating this group into an isoquinoline ring system reduced basicity and increased absorption (see structure).

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## Strategies to improve absorption

### 4)- Variation of aromatic substituents to vary pka

- The pka of aromatic amine or carboxylic acid can be varied by adding EDG or electron withdrawing groups or substituents (EWG) to the ring.
- The position of the substituent is important too if the substituent interacts with the ring through resonance.
- In general, EWG increase acidity as they decrease pka and EDG decrease acidity as they increase pka.

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## Strategies to improve absorption

### 5)- Bioisosteres for polar groups

- Bioisosteres as substitutes for important functional groups are required for target interactions but pose pharmacokinetics problem.
- For example: carboxylic acid is a highly polar group which can be ionized and hinder absorption of any drug containing it.
- To overcome this problem we must mask it as an ester prodrug or to replace it with a bioisostere which has similar physicochemical properties and has advantage over carboxylic acid, such as 5-substituted tetrazoles. This ring contains acidic proton like carboxylic acid and ionized at pH 7.4. Therefore, the advantage that the tetrazole anion is 10 times more lipophilic than carboxylate anion and thus better absorbed and also resists many of metabolic reactions that occur on carboxylic acid.

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## II-Improving metabolism:

### I-Making drugs more resistant to chemical and enzymatic degradation

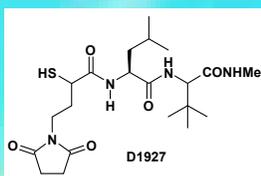
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- There are various strategies that can be used to make drug more resistant to hydrolysis and drug metabolism and thus prolonged their activity (more duration of action) such as:

- 1)- Steric shields
- Some functional groups are more susceptible to chemical and enzymatic degradation than other.
- For example: esters and amides are prone to hydrolysis. A common strategy that is used to protect these groups is to add steric shields.

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- steric shields, designed to hinder the approach of a nucleophile or an enzyme to the susceptible group. These usually involve the addition of a bulky alkyl group close to the functional group. For example: t-butyl group in the antirheumatic agent (D1927) serves as a steric shield and blocks hydrolysis of terminal peptide bond.



Steric shields have also been used to protect penicillins from lactams and to prevent drug interacting with cytochrome P450 enzymes.

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### 2)- Electronic effects of bioisosteres

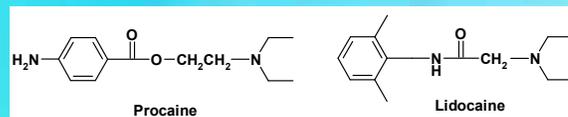
- Another tactic used to protect a labile functional group is to stabilize the group electronically using bioisostere.
- For example: replacing the methyl group of an ethanolate ester with NH<sub>2</sub> gives a urethane functional group which is more stable than the original esters. (H<sub>3</sub>C-COOR → H<sub>2</sub>NCOOR)
- The NH<sub>2</sub> group has same size and valency as the CH<sub>3</sub> group. Therefore, has no steric effect, but it has totally different electronic properties, since it can feed electrons into the carbonyl group and stabilize it from hydrolysis.
- The Carbachol (cholinergic agonist) and Cefoxitin (cephalosporin) are stabilized in this way.

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### 3)- Stereoelectronic modification:

- Steric hindrance and electronic stabilization have used together to stabilize labile groups. E.g. procaine (an ester) is quickly hydrolyzed, but changing the ester to the less reactive amide group reduces hydrolysis (procamide) or to lidocaine.
- The presence of two ortho-methyl groups on the aromatic ring in lidocaine helps to shield the carbonyl group from attack by nucleophiles or enzymes. This results in the longer-acting local anaesthetic. Here both steric and electronic influences are both involved; these modifications are defined as stereoelectronic.

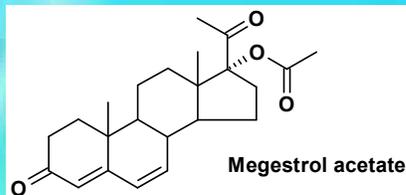
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### 4)- Metabolic Blockers

- Some drugs are metabolized by introducing of polar functional groups at particular positions in their skeleton.
- For example: Megestrol acetate (oral contraceptive) is oxidized at position 6 to give OH group at this position. Bu introducing a methyl group at position 6, metabolism is blocked and the activity of the drug is prolonged.



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### 5)- Removal of susceptible metabolic groups

- Certain chemical groups are particularly susceptible to metabolic enzymes. E.g. methyl groups on aromatic rings are often oxidized to carboxylic acids which then quickly eliminated from the body.
- Other common metabolic reactions include aliphatic and aromatic C-hydroxylation, N- & S-oxidations, O & S-dealkylations and deamination.
- Susceptible group can sometimes be removed replaced by groups that are stable to oxidation, in order to prolong the lifetime of the drug.
- e.g. The methyl group of Tolbutamide (anti diabetic) was replaced by a chlorine atom to give chlorpropamide which is much longer lasting. Replacement of a susceptible ester in cephalosporins (cephaloridine & Cefalexin).

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### 6)- Group Shifts

- Removing or replacing a metabolically vulnerable group is feasible if the group concerned is not involved in important binding interactions with the binding site.
- If the group is important, then we have to use a different strategy such as: either mask the vulnerable group by using a prodrug or shifting the vulnerable group within the molecular skeleton.
- By this tactic Salbutamol was developed in 1969 from its analogue neurotransmitter noradrenaline (catechol structure).
- Noradrenaline is metabolized by methylation of one of phenolic groups with catechol O-methyl transferase. The other phenolic group is important for receptor binding interaction.

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- Removing the OH or replacing it with a methyl group prevents metabolism but also prevent H-bonding interaction with the binding site. While moving the vulnerable OH group out from the ring by one carbon unit as in *Salbutamol* make this compound unrecognizable by the metabolic enzyme, but not to the receptor binding site (prolonged action).
- Shifting is a useful important tool to overcome the problem but no guarantee that this tactic will be always successful and may make the molecule unrecognizable both to its target and to the metabolic enzyme.

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### 7)- Ring Variation

- Certain ring systems are often found to be susceptible to metabolism and so varying the ring can often improve metabolic stability.
- e.g. replacement of imidazole ring (susceptible to metabolism) in Tioconazole with 1,2,4-triazole ring gives Fluconazole with improved stability as shown previously.

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### II-Making drug less resistance to drug metabolism

- Drug that is extremely stable to metabolism and is very slowly excreted can cause problems as that is susceptible to metabolism. Such as cause toxicity and side effects.
- Therefore, designing drugs with decreased chemical and metabolic stability can sometimes be useful.

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### Strategies of designing such drugs:

- 1)- Introducing metabolically susceptible groups
- Introducing groups that are susceptible to metabolism is a good way of shorting the lifetime of a drug.
- For example: methyl group was introduced to some drug to shorten its lifetime because methyl can be metabolically oxidized to polar alcohol as well as to a carboxylic acid.

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### 2)- Self-destruct drugs

- A self-destruct drug is one which is chemically stable under one set of conditions but becomes unstable and spontaneously degrades under another set of conditions.
- The advantage of a self-destruct drug is that inactivation does not depend on the activity of metabolic enzyme, which could vary from patient to patient.
- e.g. *Atracurium* (neuromuscular blocking agent) stable at acid pH but self-destructs when it meets the slightly alkaline conditions of the blood. i.e. the drug has a short duration of action, allowing anesthetists to control its blood levels during surgery by providing it as a continuous intravenous drip.

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### Summary

- The polarity or pka of a lead compound can be altered by varying alkyl substituents or functional groups, allowing the drug to be absorbed more easily.
- Drugs can be made more resistant to metabolism by introducing steric shields to protect susceptible functional groups. It may also be possible to modify the functional group itself to make it more stable. When both tactics are used together, this is termed as a stereoelectronic modification.
- Metabolically stable groups can be added to block metabolism at certain positions.

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- Groups which are susceptible to metabolism may be modified or removed to prolong activity, as long as the group is not required for drug-target interactions.
- Metabolically susceptible groups which are necessary for drug-target interactions can be shifted in order to make them unrecognizable by metabolic enzymes, as long as they are still recognizable to the target.
- Varying a heterocyclic ring in the lead compound can sometimes improve metabolic stability.
- Drugs which are slowly metabolized may linger too long in the body and cause side effects.
- Groups which are susceptible to metabolic or chemical change can be incorporated to reduce a drug's lifetime.

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## Targeting Drugs

### Targeting Drugs

- One of the major goals in drug design is to find way of targeting drugs to the exact location in the body where they are most needed.
- The principle of targeting drugs can be traced back to Paul Ehrlich who developed antimicrobial drugs that were selectively toxic for microbial cells over human cells.

### Tactics and strategies used to target drugs

#### Targeting tumor cells-search and destroy drugs:

- A major goal in cancer chemotherapy is to target drugs efficiently against tumor cells rather than normal cells.
- One method to achieving this is to design drugs which make use of specific molecular transport systems.
- The idea is to attach the active drug to an important building block molecule that is needed in large amounts by the rapidly divided tumor cells.
- This could be an amino acid or a nucleic acid base (e.g. uracil mustard).

### 2-Targeting gastrointestinal tract (GIT) infections

- If the drug is to be target against infection of GIT it must be prevented from being absorbed into the blood supply.
- This can easily be done by using a fully ionized drug which is incapable of crossing cell membranes.
- e.g. highly ionized sulfonamides are used against GIT infections because they are incapable of crossing the gut wall.

### 3-Targeting peripheral regions rather than the central nervous system (CNS)

- It is often possible to target drugs such that they act peripherally and not in CNS.
- By increasing the polarity of drugs, they are less likely to cross the blood-brain barrier and this means they are less likely to have CNS side effects.
- Achieving selectivity for CNS over peripheral regions of the body is not so straightforward.

## Reducing toxicity

## Reducing toxicity

- It is often found that a drug fails clinical trials because of its toxic side effects.
- This may be due to toxic metabolites, in which case the drug should be made more resistant to metabolism as described previously.

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## Reducing toxicity

- It is known that functional groups such as aromatic nitro groups, aromatic amines, bromoarenes, hydrazines, hydroxylamines, or polyhalogenated groups are often metabolized to toxic products.
- Side effects might be reduced or eliminated by varying apparently harmless substituents (E.g. addition of halogen (Fluro) to UK 47265 (antifungal agent) gives less toxic Fluconazole) or varying the position of the substituents (e.g. replacing the cyano group at a different position prevented the inhibition of cytochrome P450 enzymes by different compounds which have this side effect)

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## Summary

- Strategies designed to target drugs to particular cells or tissues are likely to lead to safer drugs with fewer side effects.
- Drugs can be linked to amino acids or nucleic acid bases to target them against fast-growing and rapidly divided cells.
- Drugs can be targeted to the GIT by making them ionized or highly polar such that they can not cross the gut wall.
- The CNS side effects of peripherally acting drugs can be eliminated by making the drugs more polar so that they do not cross the blood-brain barrier.
- Drugs with toxic side effects can sometimes be made less toxic by varying the nature or position of substituents, or by preventing their metabolism to a toxic metabolite.

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## Prodrugs

## Prodrugs

- Prodrugs are compounds which are inactive in vitro and converted in the body to active drug.
- They have been useful in talking problems such as:
  1. Acid sensitivity
  2. Poor membrane permeability
  3. Drug toxicity & side effects
  4. Bad taste
  5. Short duration of action
  6. Solubility
  7. Stability

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- A metabolic enzyme is usually involved in converting the prodrugs to the active forms.
- Good knowledge of drug metabolism and enzymes allows the medicinal chemist to design a suitable prodrug.
- Not all prodrugs are activated by metabolic enzymes. *E.g. photodynamic therapy involves the use of an external light source to activate prodrugs.*
- When designing a prodrug, it is important to ensure that the prodrug is effectively converted to the active drug once it has been absorbed in blood supply.
- It is also important to ensure that any groups that are cleaved from the molecule are non-toxic.

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## Summary

- Prodrugs are inactive compounds which are converted to active drugs in the body-usually by drug metabolism.
- Esters are commonly used as prodrugs to make a drug less polar, allowing, it to cross cell membranes more easily. The nature of the ester can be altered to vary the rate of hydrolysis.
- Introducing a metabolically susceptible N-methyl group can sometimes be advantageous in reducing polarity.
- Prodrugs with a similarity to important biosynthesis building blocks may be capable of cross cell membranes with the aid of carrier proteins.

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## Summary

- The activity of a drug can be prolonged by using a prodrug which is converted slowly to the active drug.
- The toxic nature of a drug can be reduced by using a prodrug which is slowly converted to the active compound, preferably at the site of action.
- Prodrugs which contain metabolically susceptible polar groups are useful in improving water solubility. They are particularly useful for drugs which have to be injected, or for drugs which are too hydrophobic for effective absorption from the gut.

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## Drug alliances

## Drug alliances

- A sentry drug is a drug which is administered alongside another drug to enhance the latter's activity.
- 1-Many sentry drugs protect their partner drug by inhibiting an enzyme which acts on the latter (e.g. *carbidopa* and *levodopa*).
- 2-Sentry drugs have also been used to localize the site of action of local anaesthetics and to increase the absorption of drugs from the GIT (e.g. adrenaline & procaine), adrenaline constricts the blood vessels in the vicinity of the injection and so prevents procaine being rapidly removed from the area by the blood supply.

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## Endogenous compounds as drugs

- Endogenous compounds are molecules which occur naturally in the body. Many could be extremely useful in medicines (e.g. hormones, peptides, neurotransmitters, oligonucleotides).
- 1-Neurotransmitters are not effective as drugs as they have a short lifetime in the body, and have poor selectivity for the various types and subtypes of a particular target.
- 2-Hormones are more suitable as drugs, and several are used clinically. Others are susceptible to digestive or metabolic enzymes, and show poor absorption when taken orally. Adverse immune

- Peptides and proteins generally suffer from poor absorption or metabolic susceptibility. Peptidomimetic compounds that are derived from peptide lead compounds, but have been altered to disguise their peptide character and are orally active, more stable (less metabolized and less digested).
- Oligonucleotides are susceptible to metabolic degradation, but can be stabilized by modifying the sugar phosphate backbone so that it is no longer recognized by relevant enzymes.

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## ***Drug Development***

- The drug development phase is significantly more expensive in terms of time and money than either lead discovery or drug design and many drugs will fall during the wayside.
- On average, for every 10000 structures synthesized during drug design, 500 will reach animal testing, 10 will reach phase I clinical trials and only 1 will reach the market place.
- The average overall development cost of a new drug was recently estimated as \$ 800 million or \$ 444 million.

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## **Three main issues are involved in drug development**

1. The drug has to be tested to ensure that it is not only safe and effective, but can be administered in a suitable fashion. This involves preclinical and clinical trials covering toxicity, drug metabolism, stability, formulation, and pharmacological tests.
2. There are the various patenting and legal issues.
3. The drug has to be synthesized in ever-increasing quantities for testing and eventual manufacture (this is known as chemical and process development).

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- Toxicity tests are carried out in vivo on drug candidates to assess acute and chronic toxicity. During animal studies, blood and urine samples are taken for analysis.
- Individual organ are analyzed for tissue damage or abnormalities.
- Toxicity testing is important in defining what the initial dose level should be for phase I clinical trials.
- Drug metabolism studies are carried out on animals and human to identify drug metabolites. The drug candidate is labeled with an isotope in order to aid the detection of metabolites.
- Pharmacology testes are carried out to determine a drug's mechanism of action and to determine whether it acts at targets other than the intended one.
- Formulation studies aim to develop a preparation of the drug which can be administered during clinical trials and beyond.
- The drug must remain stable in the preparation under variety of environmental conditions.

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## **Clinical trials involve four phases.**

- In phase I healthy volunteers are normally used to evaluate the drug's safety, its pharmacokinetics, and the dose levels that can safely be administered.
- Phase II studies are carried out on patients to assess whether the drug is effective, to give further information on the most effective dosing regime and to identify side effects.
- Phase III studies are carried out on larger numbers of patients to ensure that results are statistically sound, and to detect less common side effects.
- Phase IV studies are ongoing and monitor the long-term use of the drug in specific patients, as well as the occurrence rare side effects.

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- Patent are taken out as soon as a useful drug has been identified. They cover a structural class of compounds rather than a single structure.
- A significant period of the patent is lost as a result of the time taken to get a drug to the market place.
- Patents can cover structures, their medicinal uses, and their method of synthesis.
- Regulatory bodies are responsible for approving the start of clinical trials and the licensing of new drugs for the market place.

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- Drugs that show promise in a field which devoid of a current therapy may be fast tracked.
- Special incentives are given to companies to develop orphan drug-drug that are effective in rare diseases.
- Pharmaceutical companies are required to abide by professional codes of practice known as good laboratory practice, good manufacturing practice, and good clinical practice.
- Chemical development involves the development of a synthetic route which is suitable for large scale synthesis of a drug.

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- The priorities in chemical development are to develop a synthetic route which is straightforward, safe, cheap, and efficient, has the minimum number of synthetic steps, and provide a consistency good yield of high-quality product that meets predetermined purity specifications.
- An early priority in chemical development is to define the purity specifications of the drug and to devise a purification procedure which will satisfy these requirements.
- Process development aims to develop a production process which is safe, efficient, economic, environmentally friendly, and produces product of a consistent yield and quality to satisfy purity specification.
- Drugs derived from natural sources are usually produced by harvesting the natural source or through semi-synthetic methods.

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