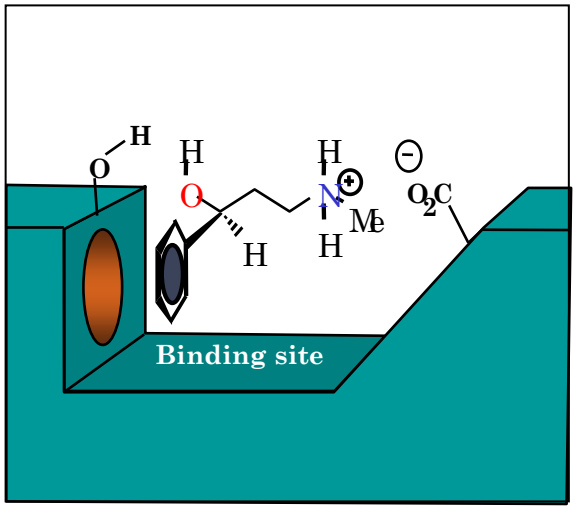
Drug Receptor Interactions

Course: Drug Design
Course code: 0510412



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Learning Outcomes

At the end of this lesson students will be able to

- Define and describe the drug targets and drug binding.
- Explain various drug-receptor interactions such as
  - Covalent bonding
  - Ionic (electrostatic) interaction
  - Dipole-dipole interaction
  - H-bonding
  - Hydrophobic interaction
  - Van der Waals forces.
- Define and describe agonists and antagonists for receptors.

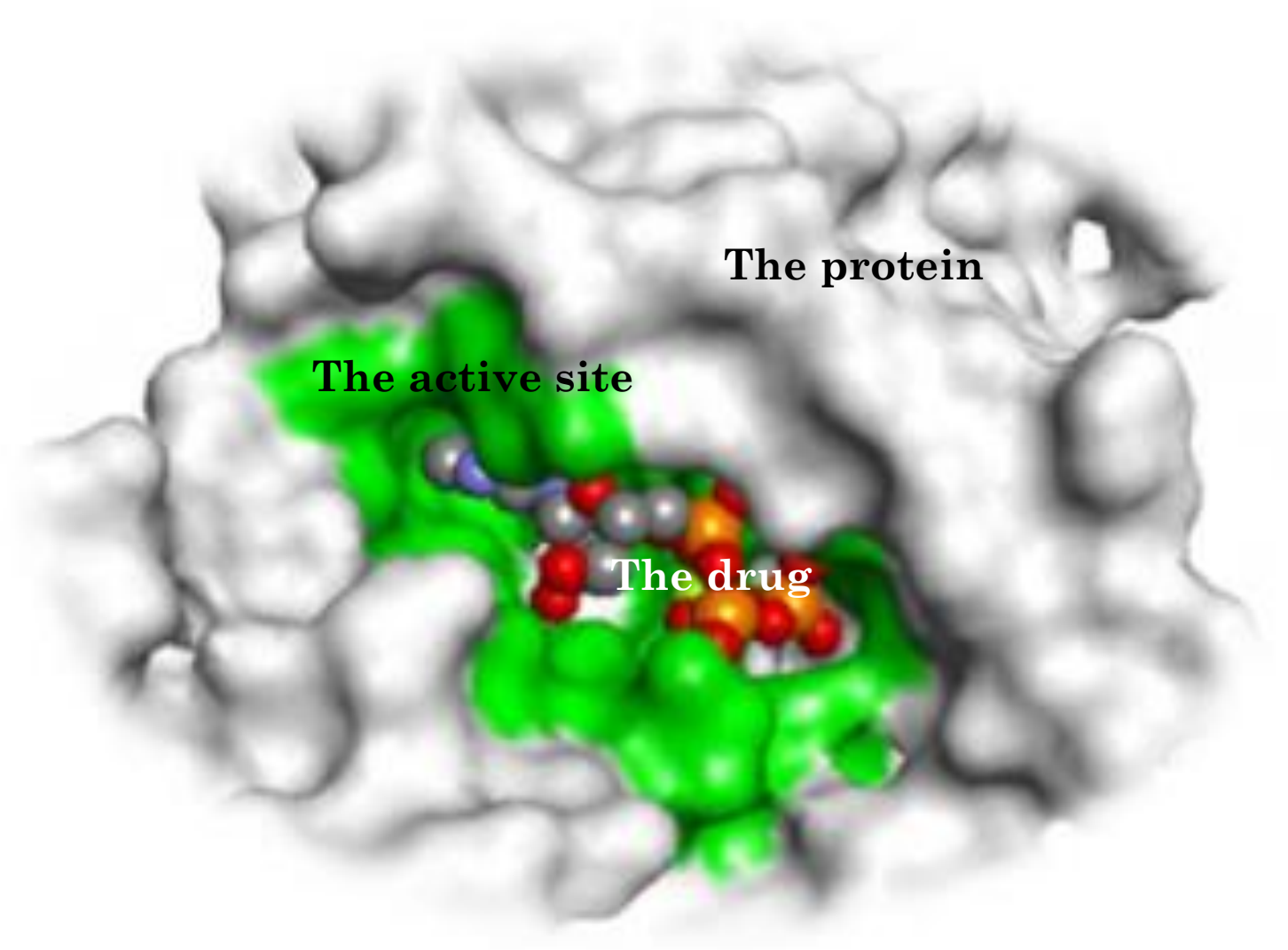
Drug Targets

- **Macromolecules** such as: **1. Proteins (mainly enzymes, receptors and transport proteins) 2. Lipids 3. Carbohydrates 4. Nucleic acids (DNA and RNA)** are the main molecular targets for drugs.

- For a drug to have an action, it should **interact [bind]** with one of these molecules.

- The area of the macromolecule where the interaction takes place is called the ***binding site;*** *which is a pocket or canyon at the surface of the macromolecule.*

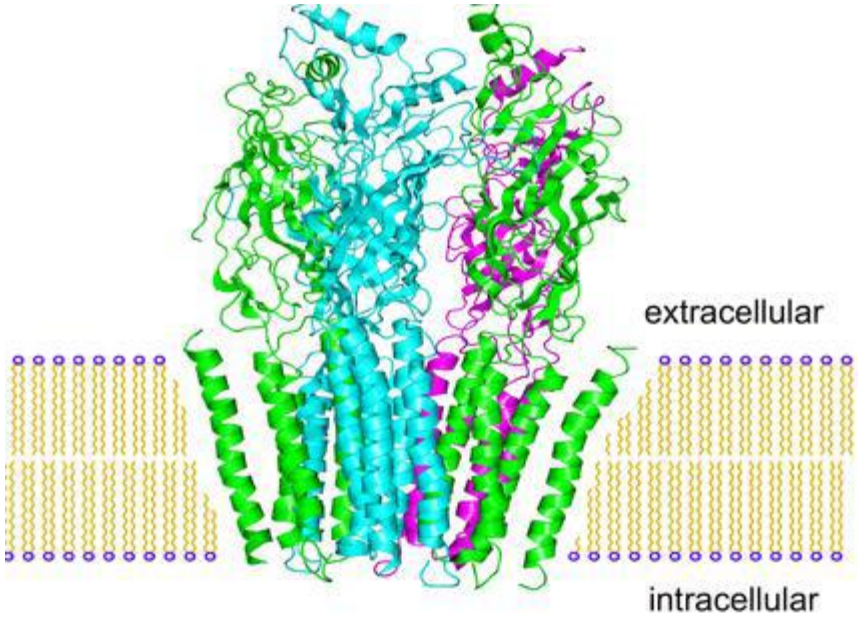
Example



Receptors

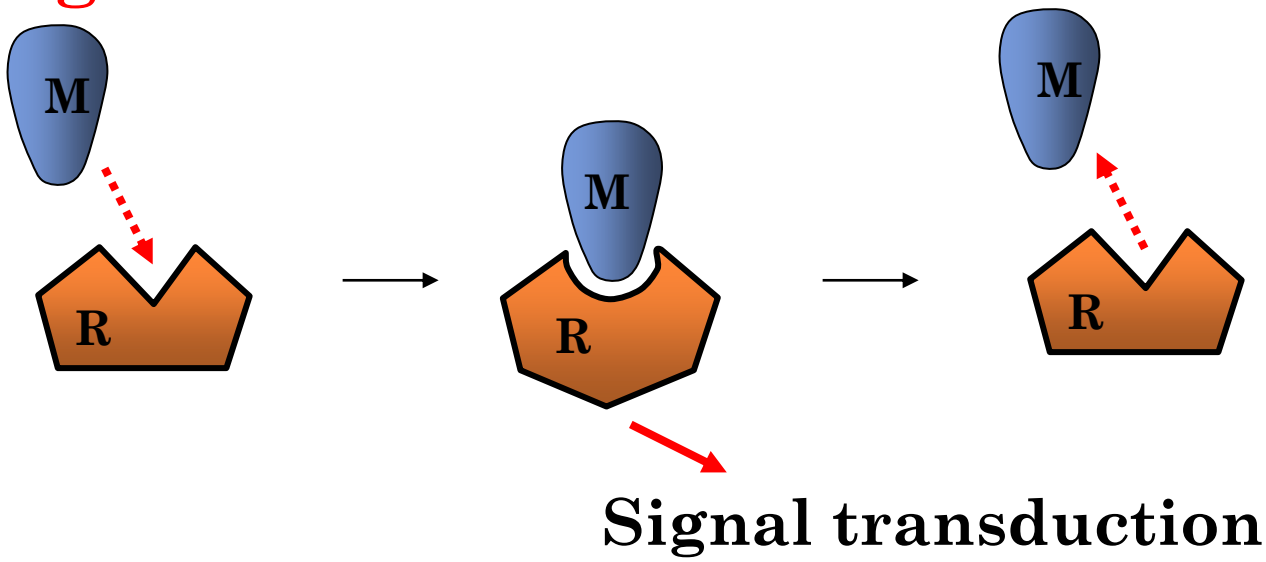
- Receptors are mostly membrane-bound proteins that selectively bind small molecules called ligands which results in physiological response.

- They are difficult to isolate because they exist in tiny amount and if isolated it will be difficult to purify.



- **The protein surface contains an area which has the correct shape to accept the incoming messenger. This area is known as the binding site and is analogous to the active site of an enzyme. But unlike enzymes, chemical messenger does not undergo a chemical reaction. It fits into the binding site of the receptor protein, passes on its message and then leaves unchanged. Ligand receptor interaction involves the same bonding types that are for drug-enzyme interaction.**

Overall Process of Receptor/ Messenger Interaction



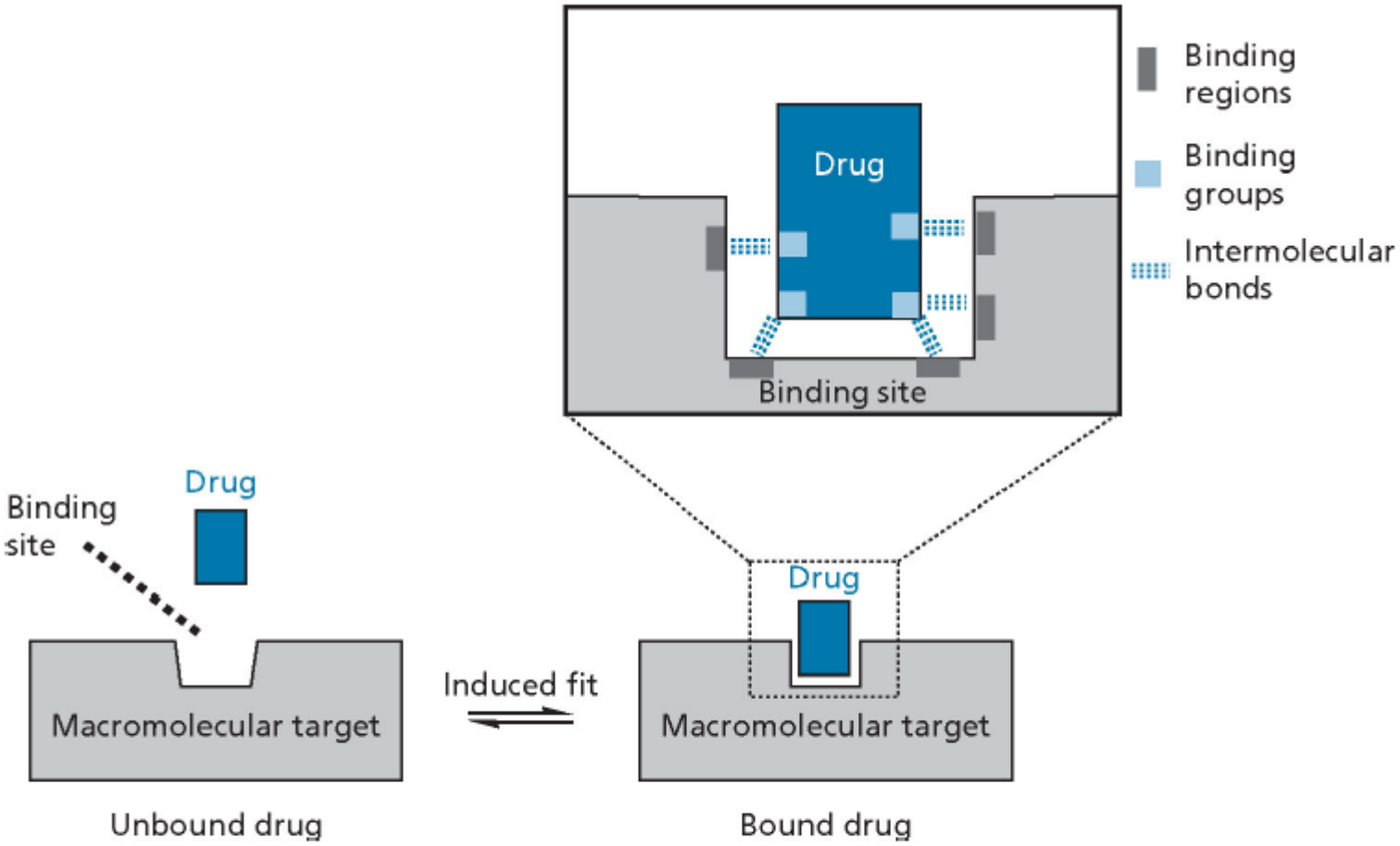
- ✓ **Binding interactions must be strong enough to hold the messenger sufficiently long for signal transduction to take place.**
- ✓ **Interactions must be weak enough to allow the messenger to depart.**
- ✓ **Implies a fine balance.**

RECEPTOR-DRUG INTERACTION

- **The driving force for drug-receptor interaction is the low energy state of the drug-receptor complex.**
- **The biological activity is related to the drug affinity for the receptor, i.e the stability of the complex.**
- **Dissociation constant of the drug-receptor complex gives an idea a bout how potent is the drug.**

How Binding Takes Place

- **Binding occur through points of attachment, for a chemical compound they are the functional groups.**
- **Functional groups use their electronic & shape characters in the binding process.**
- **If we talk about reversible binding, binding of drug to receptor should be in equilibrium state.**



Schematic representation of drug binding, and the equilibrium established between the bound and unbound forms.

$$\text{drug} + \text{receptor} \underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftharpoons}} \text{drug-receptor complex}$$

Receptor-Drug interactions

Drug-target interactions can be grouped into two types:

1- Permanent (Irreversible) - covalent bonding
(strength of 200-400KJ/mol).

2- Reversible – by different types of interactions.

Covalent bonding **Irreversible bond**

Ionic (electrostatic) interaction

Dipole-dipole interaction

H-bonding **Reversible bonds**

Charge-transfer interactions

Hydrophobic interaction

Van der Waals forces

COVALENT BONDS

- A covalent bond is produced between two species by mutual sharing of electrons.
- Strong, irreversible bonds (-40 to -110 Kcal/mol stability).
- Rarely seen in drug-receptor interaction.
- More prevalent in drug-enzyme and drug-DNA interaction.

COVALENT BONDS

- For covalent bond formation, there should be two poles; the ***electrophile*** and the ***nucleophile***.

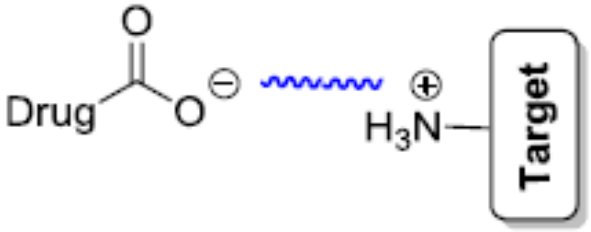
  - **Nucleophiles** in biology have the following functional groups:-
    - Thiol in the amino acid cysteine
    - Hydroxyl in the amino acid serine
    - Amine in the amino acid lysine
    - Carboxylate in the amino acid glutamic acid.

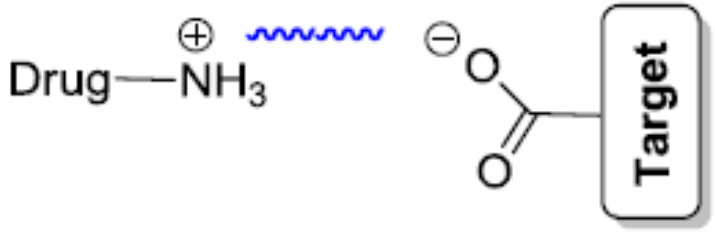
  - **Electrophiles**
    - Epoxide ring
    - Alkyl group attached to halogen
    - Positively charged centre

Ionic or electrostatic interactions

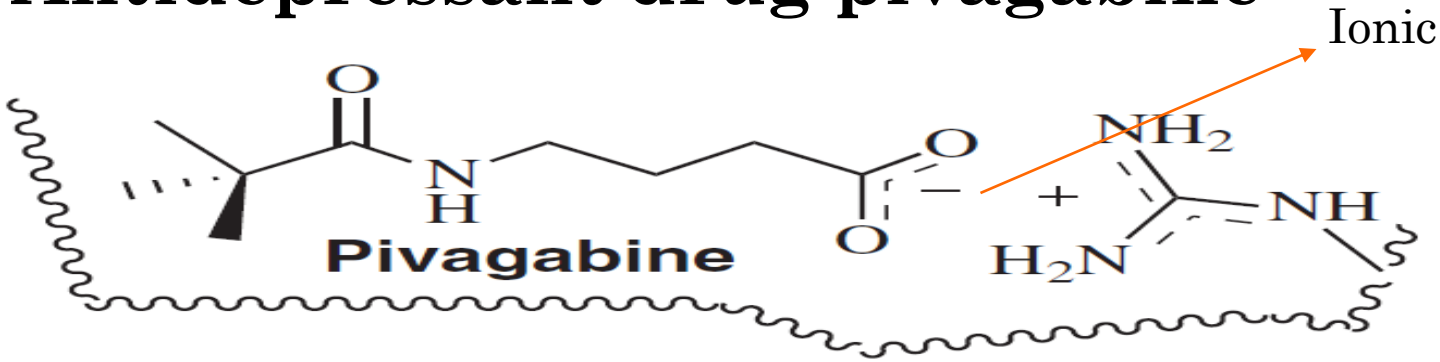
- This type of bond is weaker than covalent bond (-5 Kcal/mol).
- Also known as electrostatic interactions.
- At the same time, it is one of the most prevalent bonds in drug-receptor interaction.
- The drug molecule must have opposite charge compared to the ionized amino acids found in the receptor or enzyme.
  - Extent of ionization affects the occurrence of this bond.
  - The distance between opposite charges has a role as well.

- In biological systems, amino acids having **carboxylate group such as aspartic acid & glutamic acid (acidic amino acids)** deprotonated to give anionic environment.
- Similarly, amino acids such as **Histidine, Lysine and Arginine (basic amino acids**) protonated to give cationic environment.
- Thus, both positive (cationic) and negative (anionic) charges are available in the receptors to take part in an ionic bonding with ionized groups of drugs.



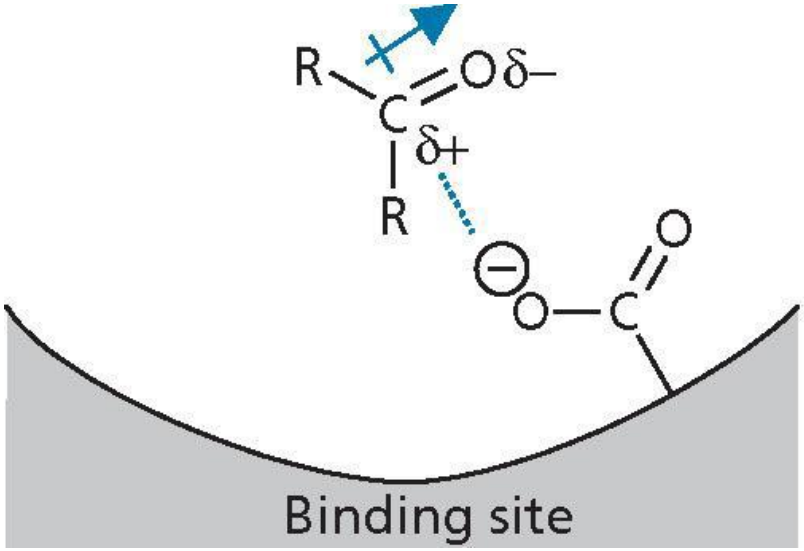


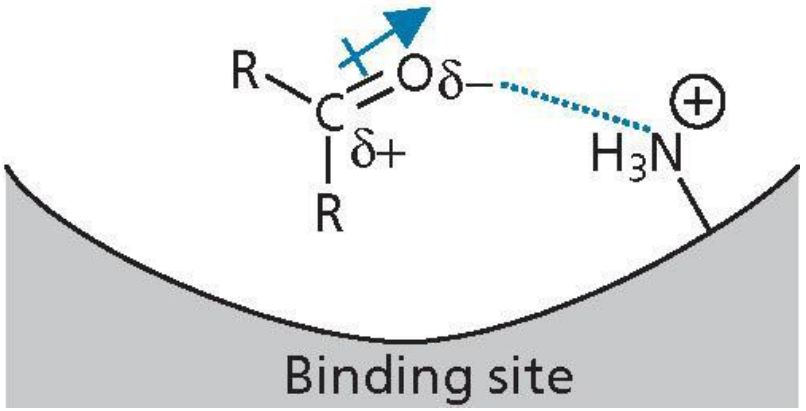
Antidepressant drug pivagabine



Ion-dipole and dipole-dipole interactions

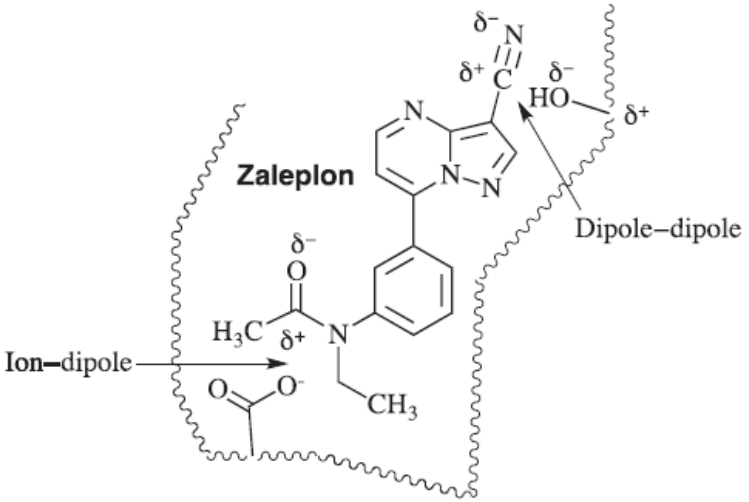
- Electronic dipole is formed when we have polarized bond due to electronegativity of atoms.
- In the polarized bond one of the pole will be partially positive and the other partially negative.
- These partially positive or negative charges might form an electrostatic bond with either partially charged atoms or ionized elements.





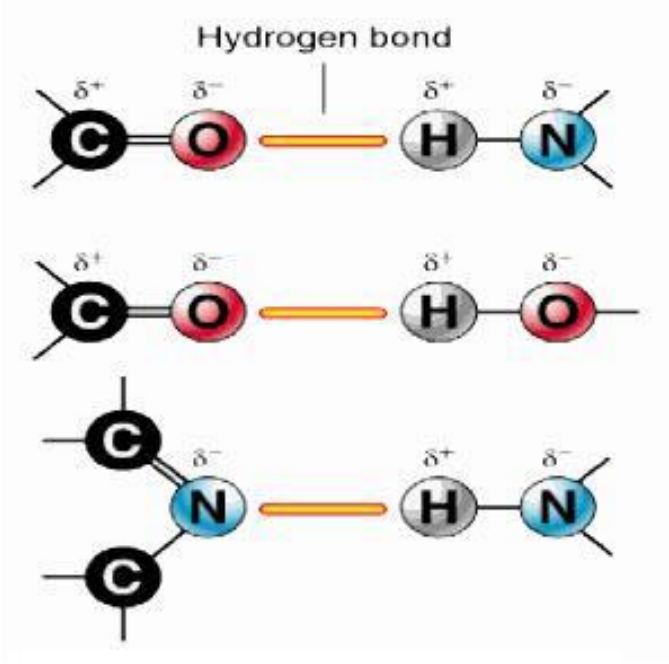
Ion-dipole occur when an ionic group on one molecule interacts with a permanent dipole on a second molecule. It is stronger than dipole-dipole interactions (decreases relative to the square of separation). This type of interaction has the energy -1 to -7 Kcal/mol).

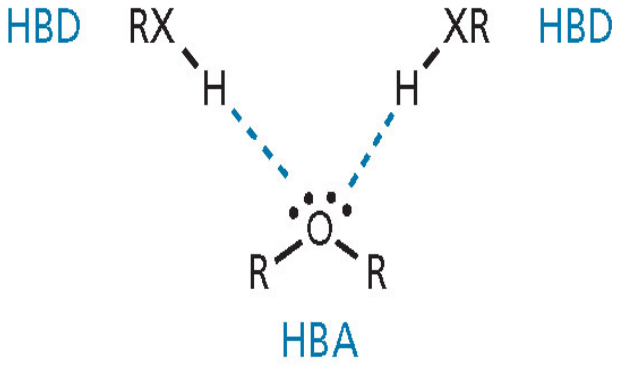
Example of Drug:
Zaleplon (treat insomnia).

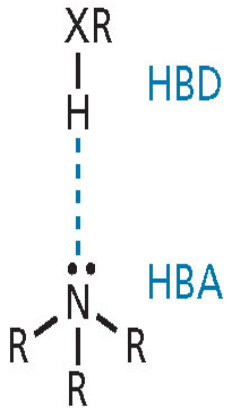


H-BONDING

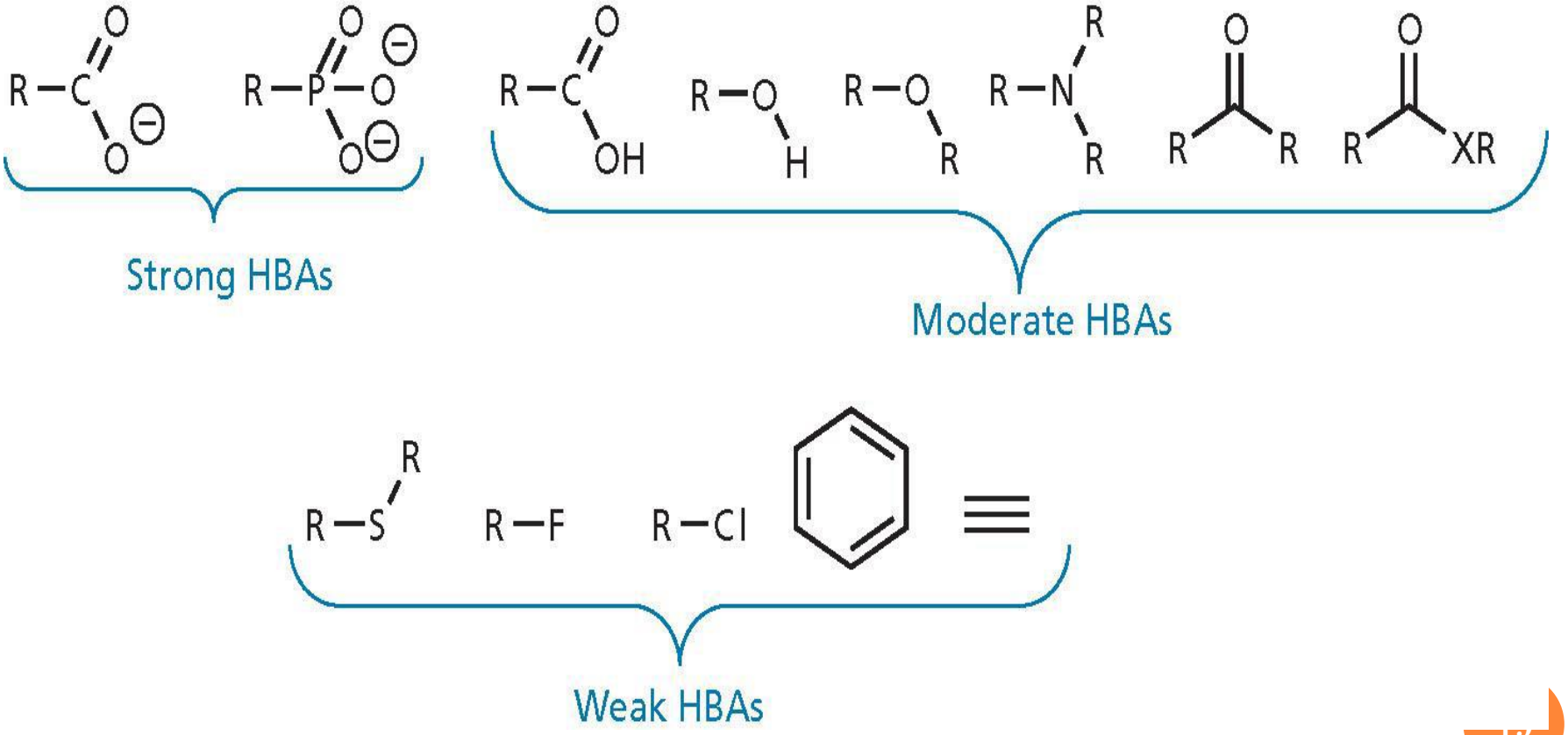
- Should have H-Bond acceptor (the electron rich atom, slightly negative) and H-Bond donor (electron-deficient hydrogen, slightly positive).
- Stability of this bond is -1 to -7 kcal/mol
- H-bonds are between 1.5-2.2 Å.



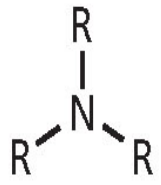




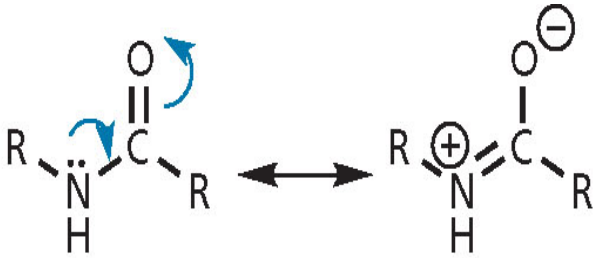
- **Increase electron density, better H-Bond acceptor, so anions are better than uncharged compounds e.g. carboxylate anion.**



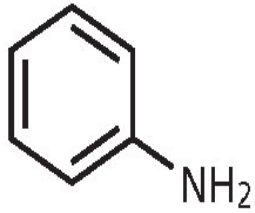
If the lone pair on nitrogen atom are delocalized, this will weaken the HBD capacity.



Tertiary amine—good HBA

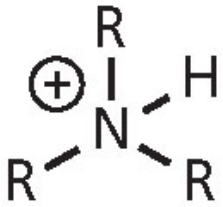


Amide—N acts as poor HBA

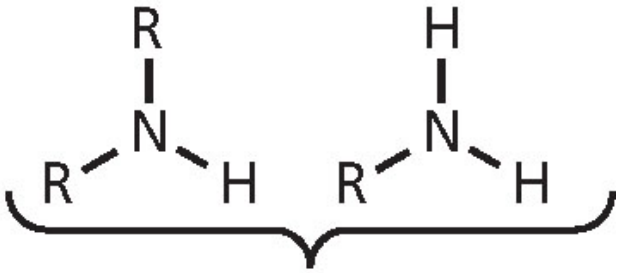


Aniline—N acts as poor HBA

H-Bond donors are better if the H is more electron deficient by attachment to more electron deficient atom such as quaternary ammonium compounds.



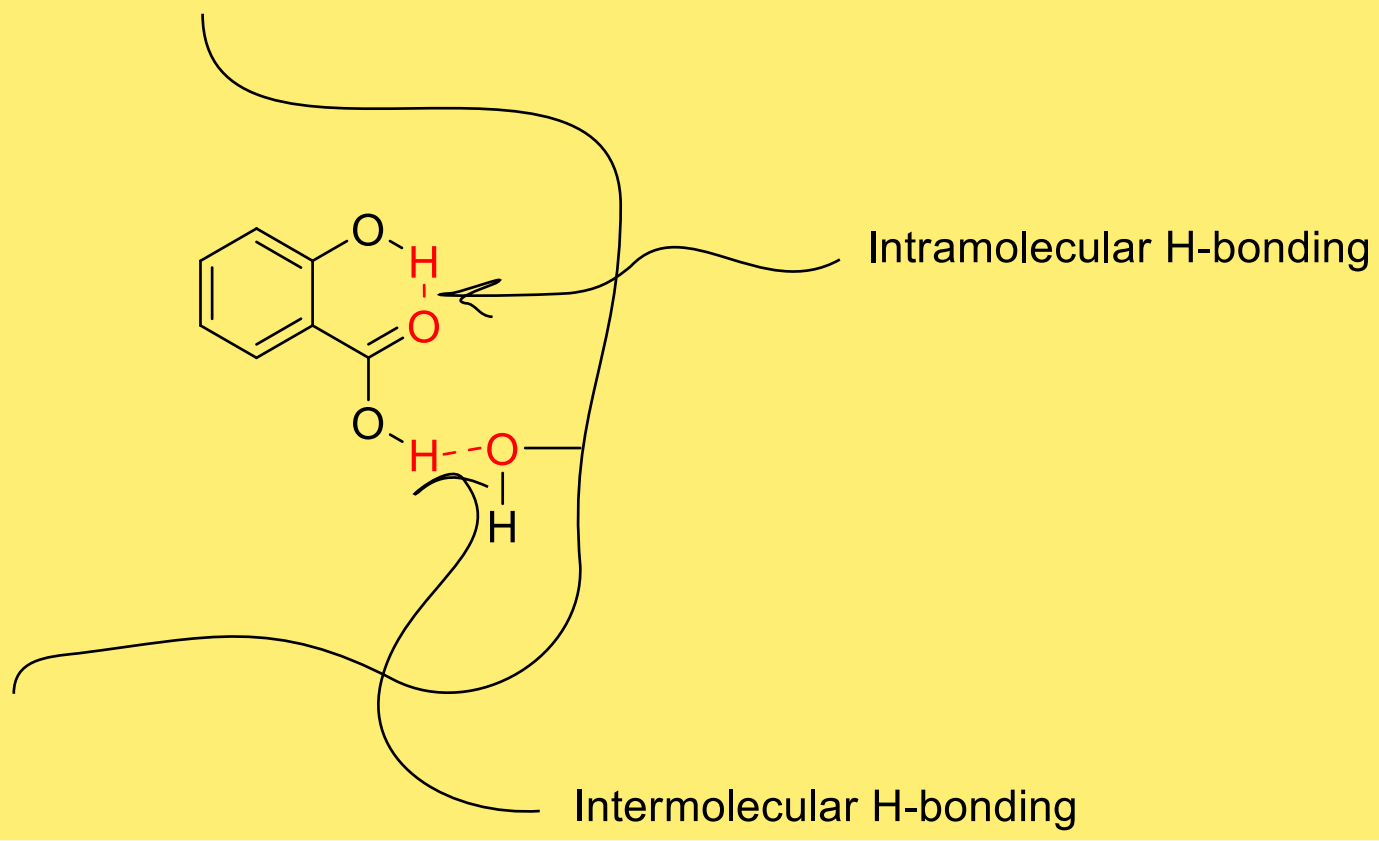
Alkylammonium ion (stronger HBD)



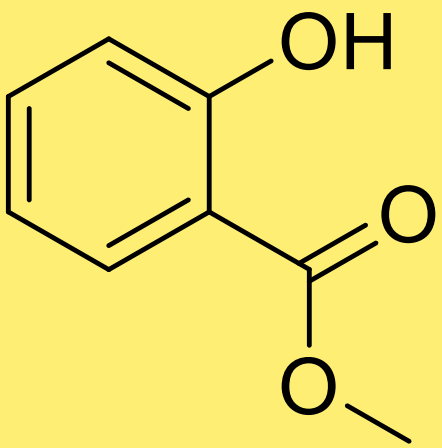
Secondary and primary amines

Two types of H-bonding:-

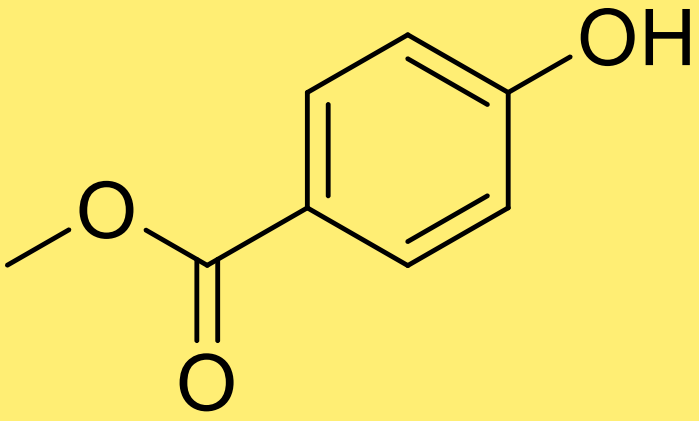
- Intramolecular H-bonding: which occur within the same molecule.
- Intermolecular H-bonding: occurs between two nearby molecules



- The occurrence of intramolecular H-bonding could affect the pharmacological action of a drug:



Methyl salicylate



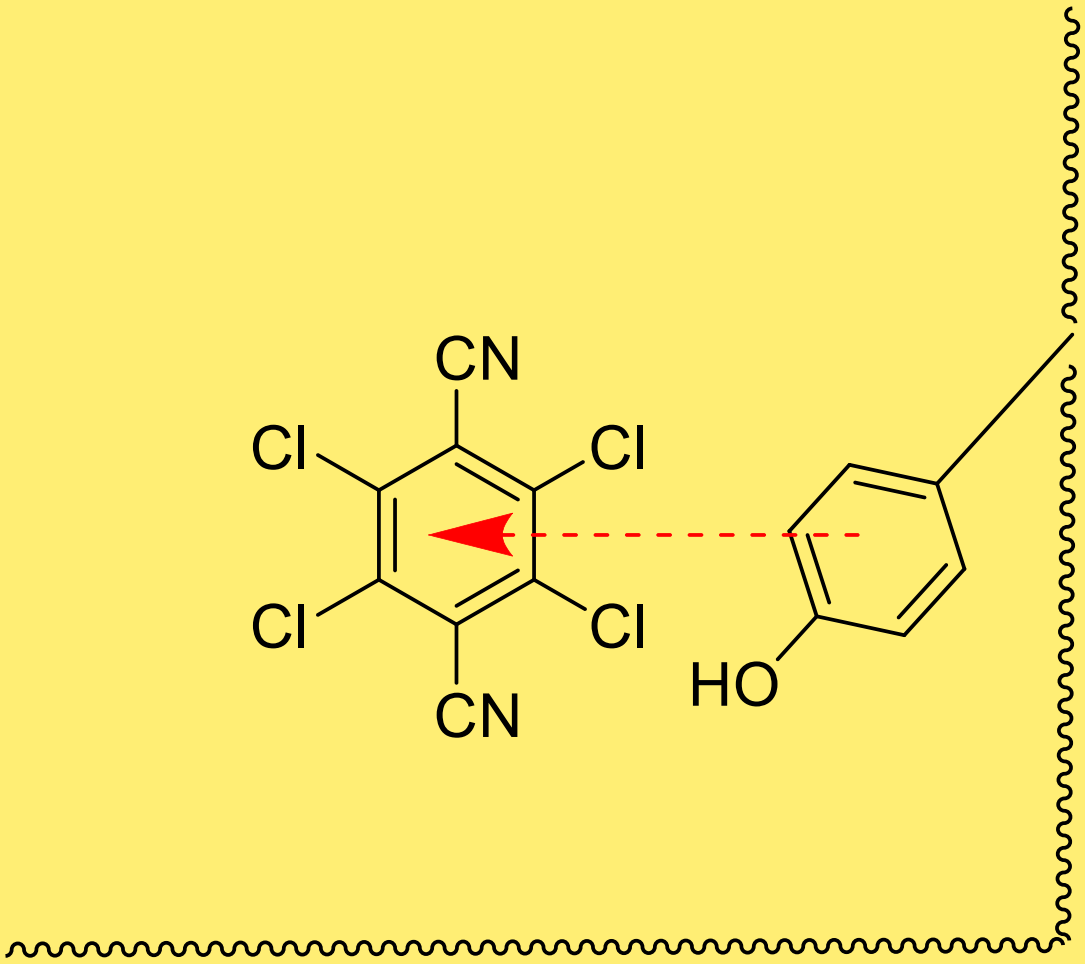
P-hydroxybenzoate

- *P*-hydroxybenzoate has more potent antibacterial action compared to methyl salicylate, it is normally used as food additive as preservative.

CHARGE-TRANSFER INTERACTIONS

- Occurs between an electron donor group in one molecule and an electron acceptor in another molecule.
  - Electron donors such as alkenes, alkynes and aromatic ring bearing an electron donating group, and atoms having pairs of non-bonded electrons such as O, N and S
  - Electron acceptors such as aromatic ring bearing an electron withdrawing group,
  - These groups might exist in the receptor binding sites:
    - Electron donor such as aromatic ring of tyrosine and carboxylate group of aspartate.
    - Electron acceptor: cysteine
    - Having both: Histidine, tryptophan and Asparagine.

Charge-Transfer bonds



the antifungal Chlorthalinol bound to tyrosine residue

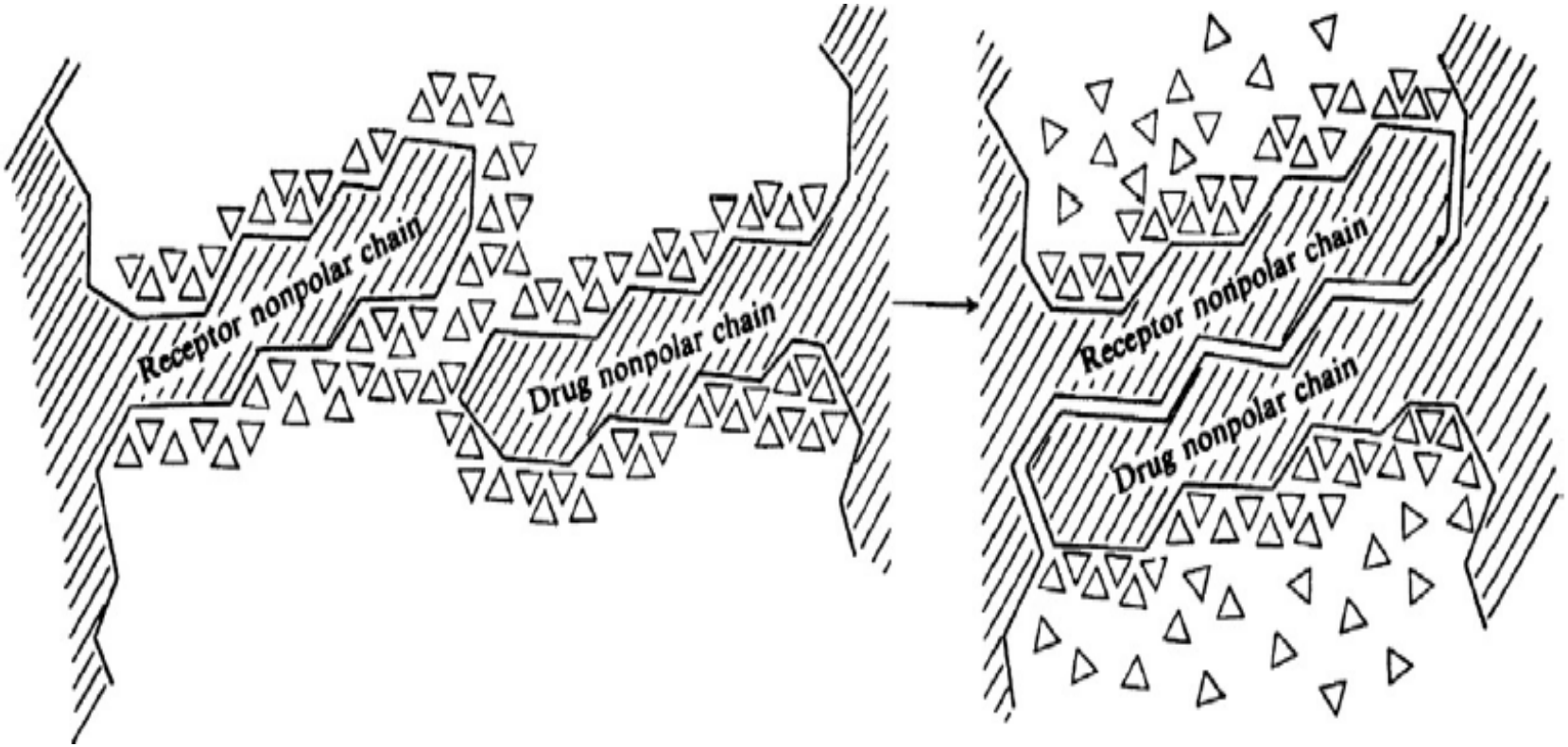
HYDROPHOBIC INTERACTIONS

- When two nonpolar groups (lipophilic group on a drug and a nonpolar receptor group), each surrounded by ordered water molecules which become disordered in an attempt to associate with each other.

- This increases entropy, therefore, results in a decrease in the free energy ($\Delta G = \Delta H - T\Delta S$), which stabilizes the drug–receptor complex.

- This stabilization is known as a *hydrophobic interaction*.

Example of hydrophobic interactions



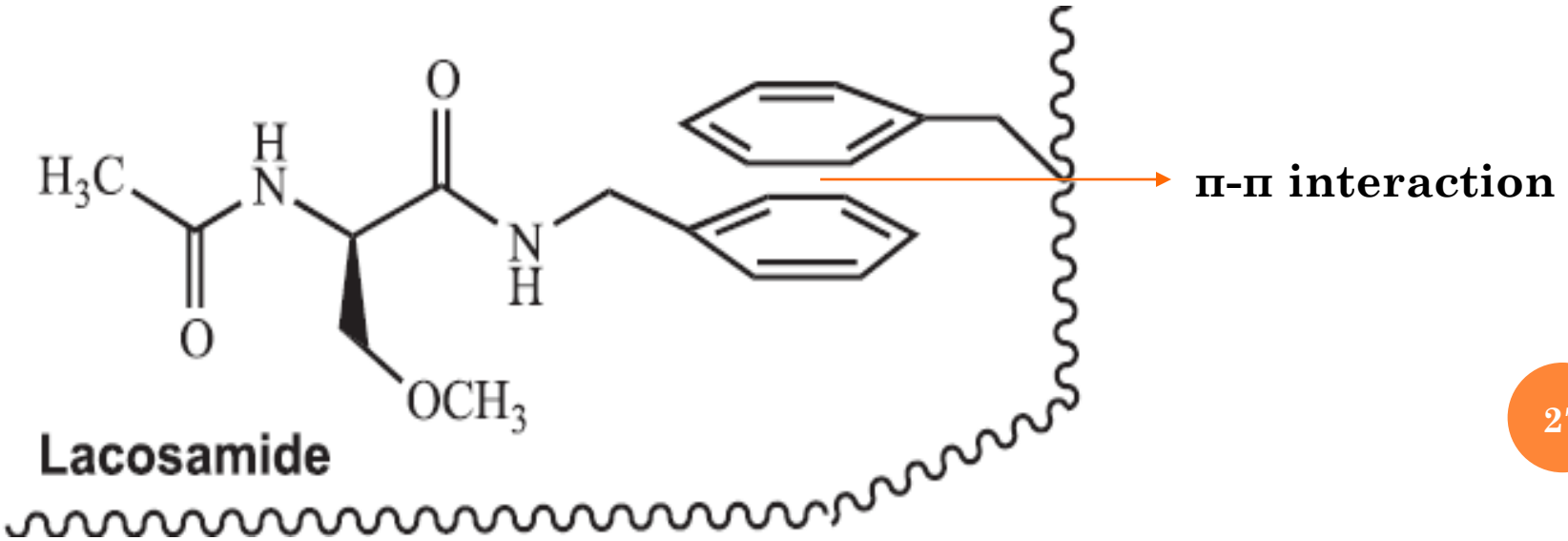
Hydrophobic interactions are responsible for non-covalent intermolecular interactions in aqueous solution.

- Another type of hydrophobic interactions is called as π-π interaction.
- This involve a parallel arrangement of aromatic rings in which the π-electrons interact in a face-to-face arrangement.

Example: Anticonvulsant drug **Lacosamide.**

It has *phenyl ring (π electrons)*

The receptor has amino acid phenyl alanine that contains the *phenyl ring (π electrons)*

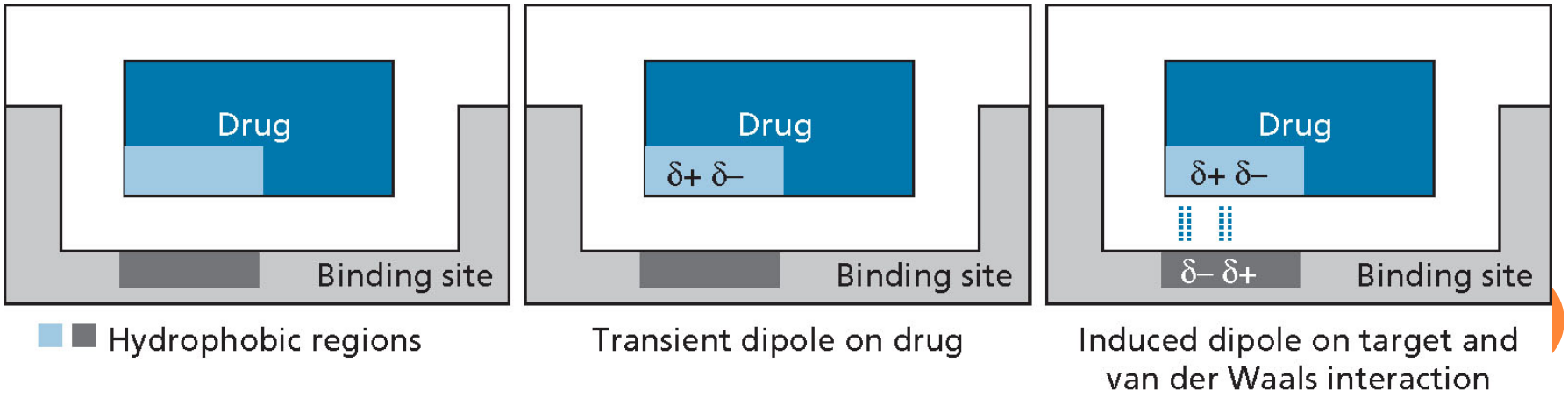


Lacosamide

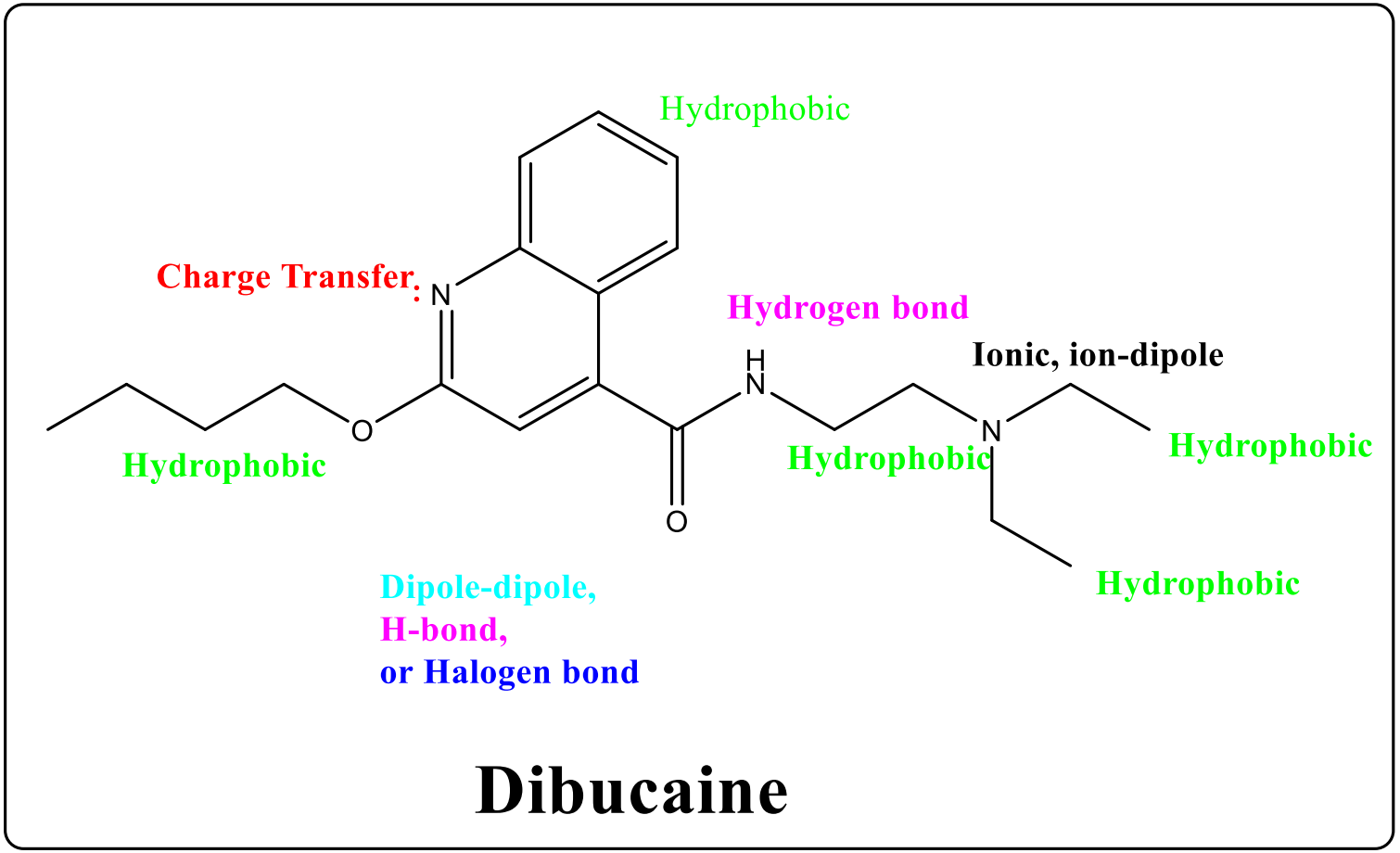
Van der Waals forces

- The formation of temporary non-symmetrical distribution of electron density in molecule to produce temporary dipole that will interact with nearby dipole.

- Stability accounts for only -0.5 kcal/mole. So this type of bonds are much weaker than other bonds.



Example of potential multiple drug–receptor interactions



Dibucaine, the local anaesthetic drug exhibits variety of *interactions*.

AFFINITY, EFFICACY, AND POTENCY

- **Affinity: how strongly the drug binds to the receptor; depends on the molecular complementarily of drug and receptor.**
- **Efficacy: the maximum biological effect the drug can produce. A compound with high affinity does not necessarily have high efficacy (e.g. antagonists).**
- **Potency: the amount of drug needed to achieve a defined biological effect. The smaller the dose required, the more potent the drug. It is possible to have potent drugs with low efficacy. Potency depends in part on the affinity of the receptor for binding the drug, and in part on the efficiency with which the drug-receptor interactions is coupled to response.**

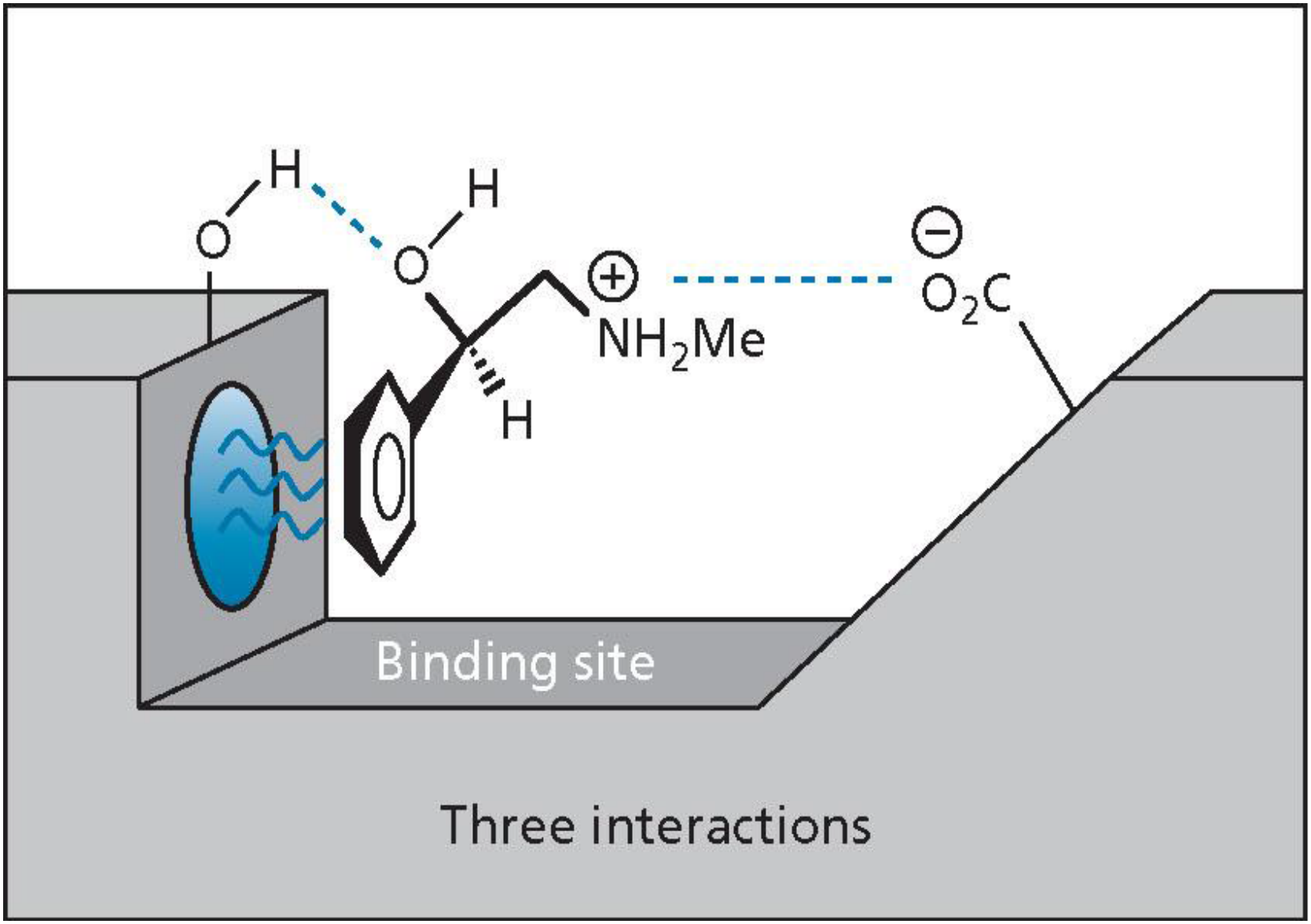
RECEPTOR'S AGONIST

- Agonists ***mimic the natural messenger of a receptor.***
- Agonists bind ***reversibly to the binding site and produce the same induced fit as the natural messenger - receptor is activated.***
- ***Similar intermolecular bonds formed as with natural messenger.***
- Agonists are often ***similar in structure to the natural messenger.***

Receptor's agonist

- To design an **agonist you have to know:**
  - The geometry and topography of the active site.
  - The chemical structure (preferably the 3D structure) of the normal substrate that act upon.

- ***Requirements for agonist design:***
  - The agonist must have the correct binding groups.
  - The binding groups must be correctly positioned to interact with complementary binding regions.
  - The drug must have the correct shape and size to fit the binding site.



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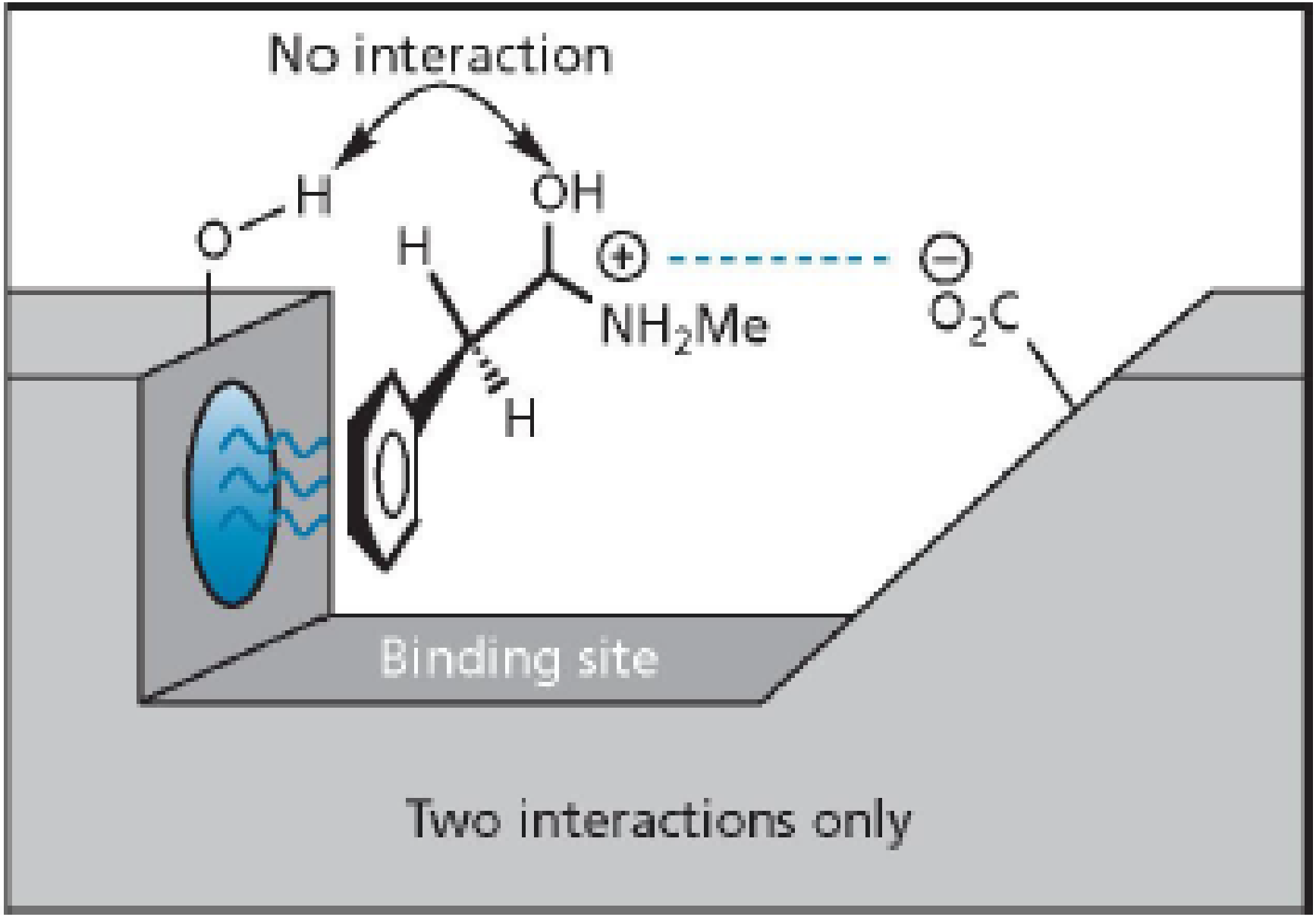

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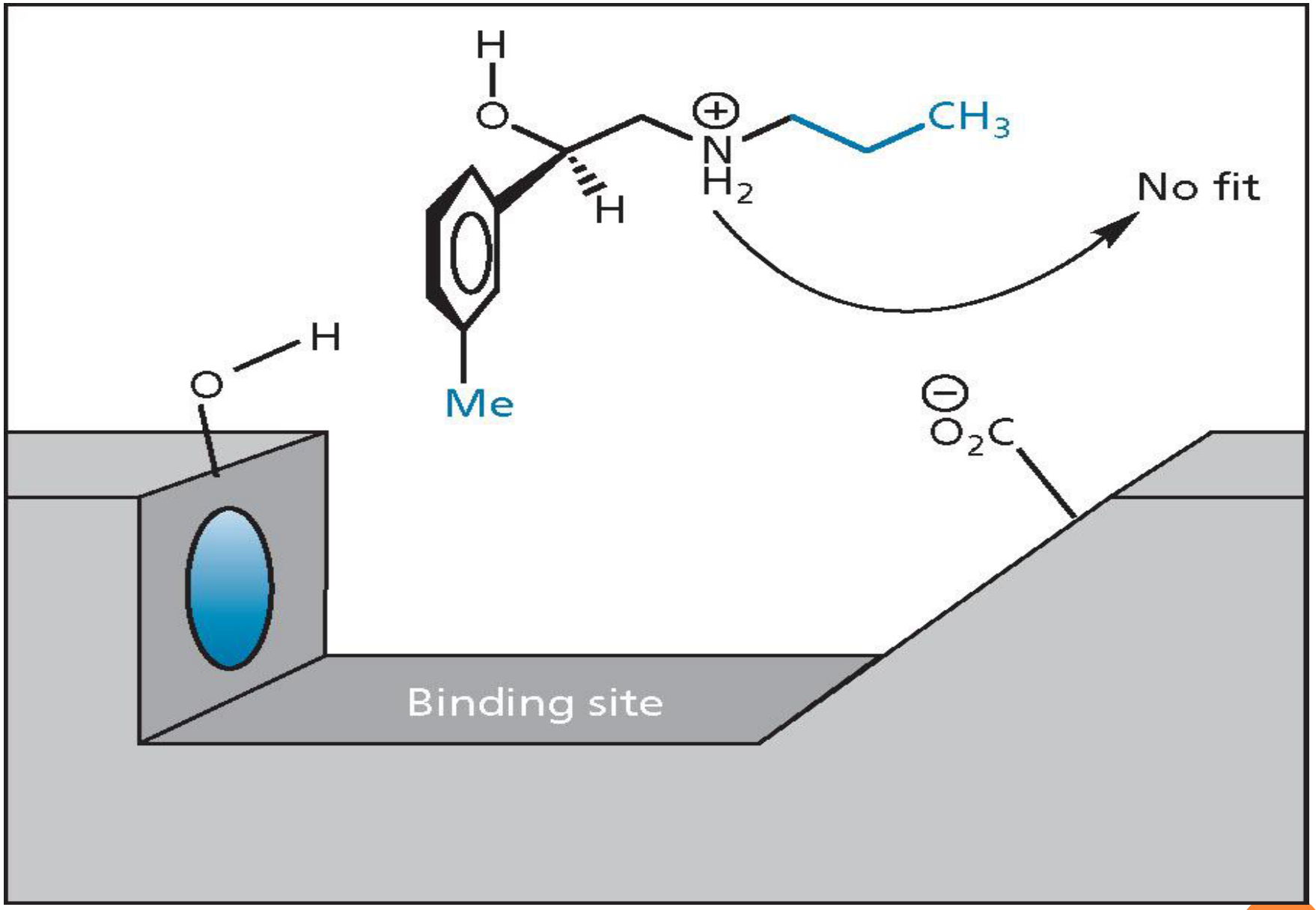
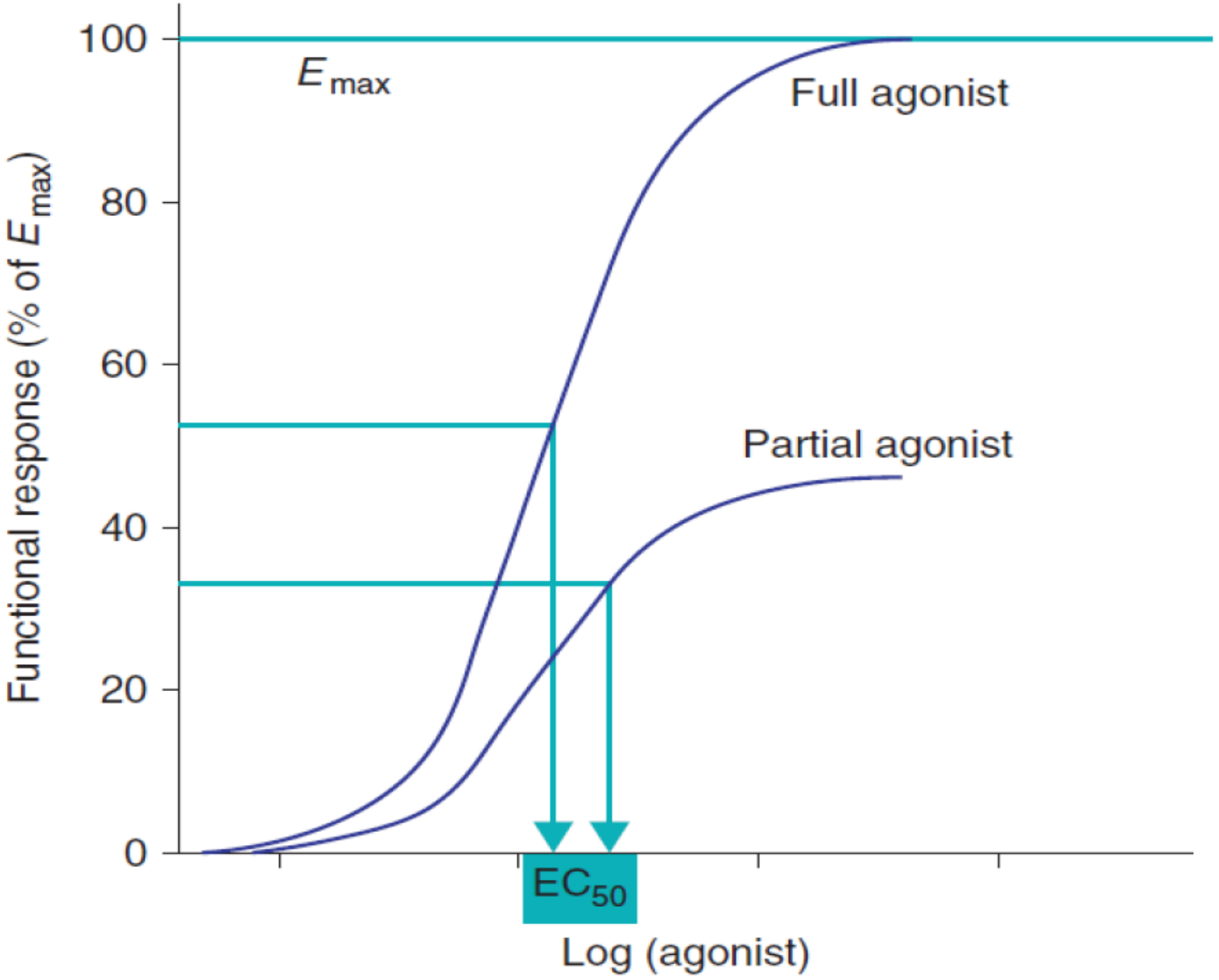
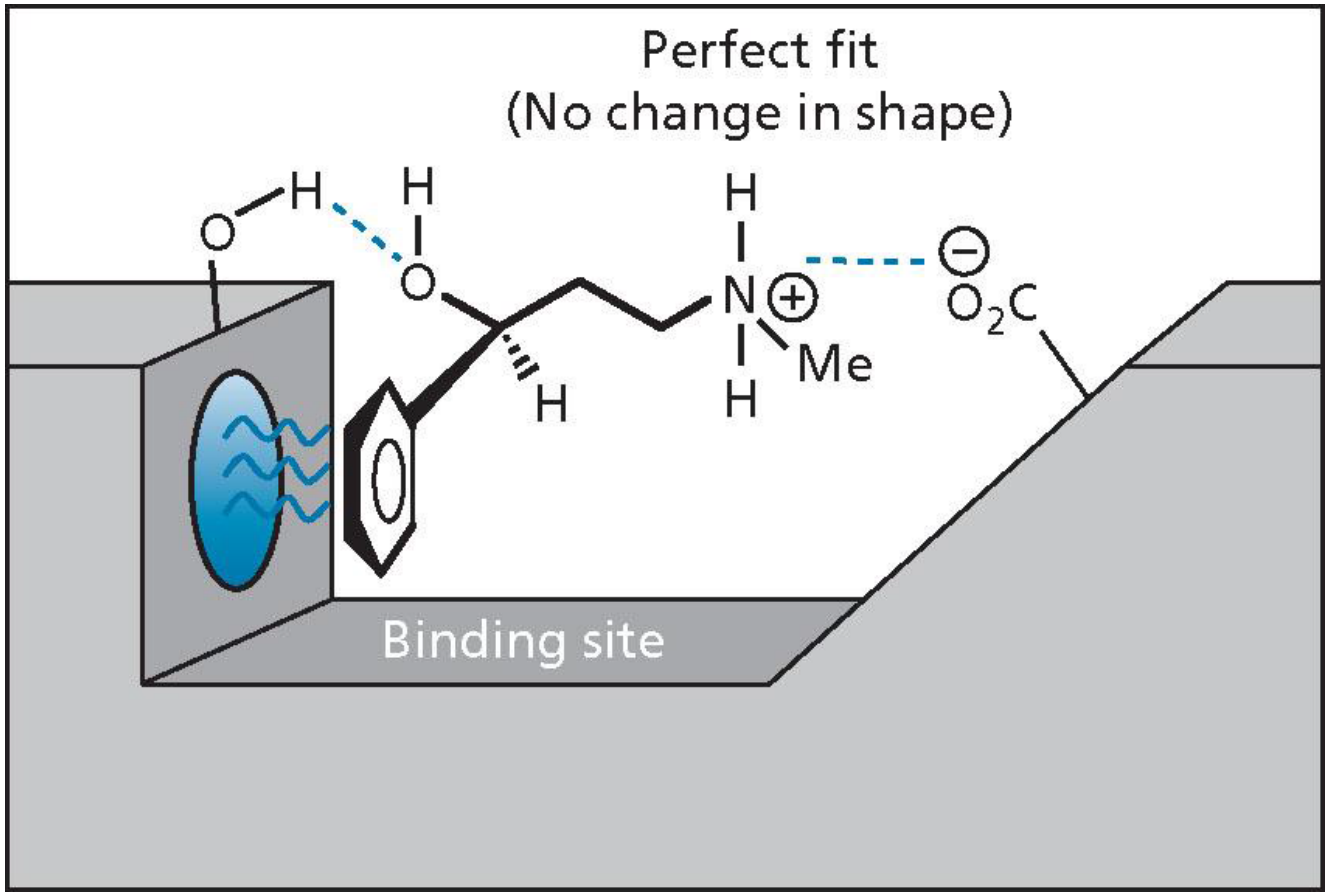


The drug must have the correct shape and size to fit the binding site


100
80
60
40
20
0
E_{max}
Full agonist
Partial agonist
Functional response (% of E_{max})
EC_{50}
Log (agonist)

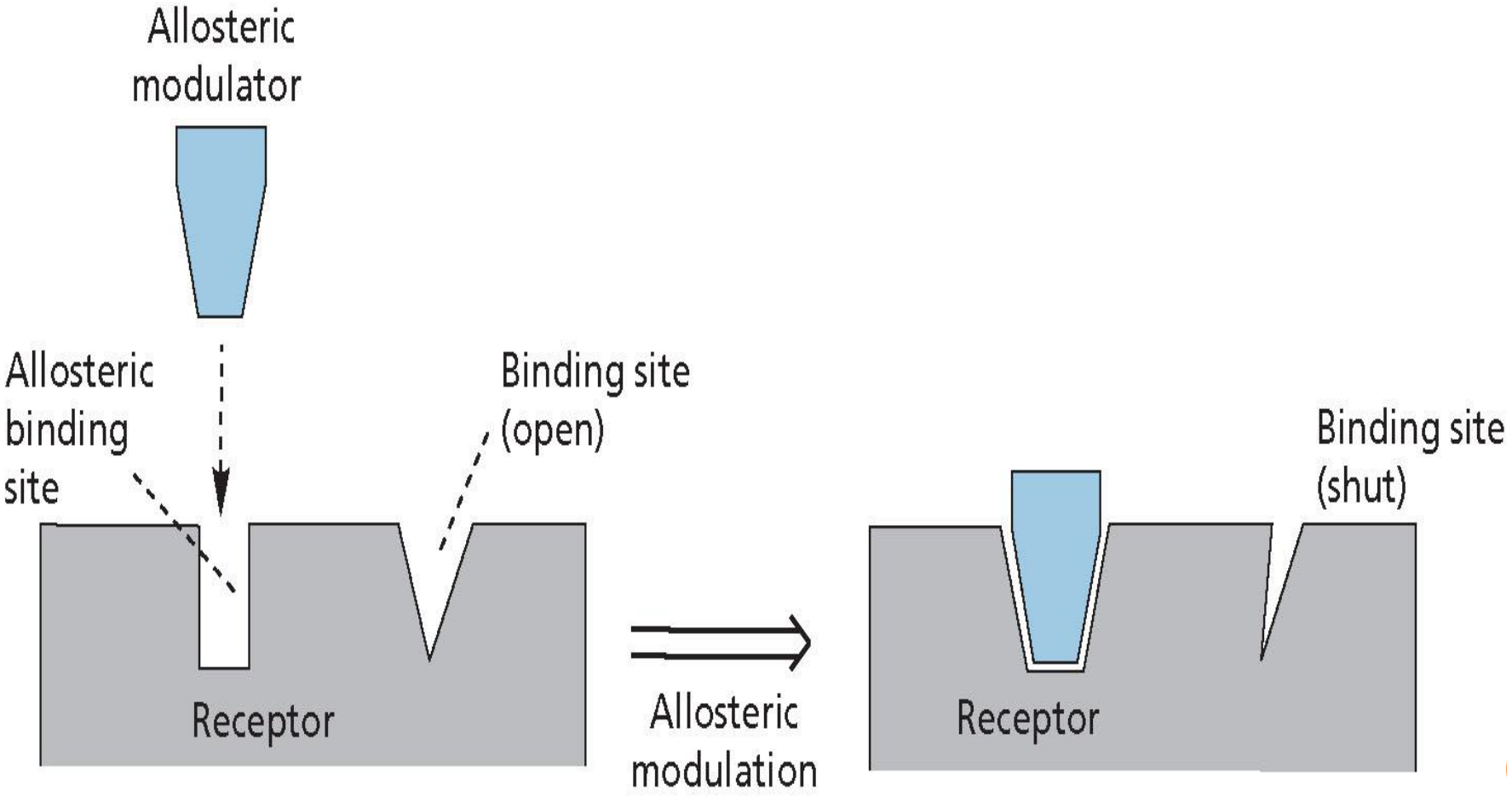
RECEPTOR'S ANTAGONIST

- Strategies to design an antagonists:
  - It is to design a drug that has the right shape to bind to the receptor site, but which would ***fail to change the shape*** *of the receptor*.



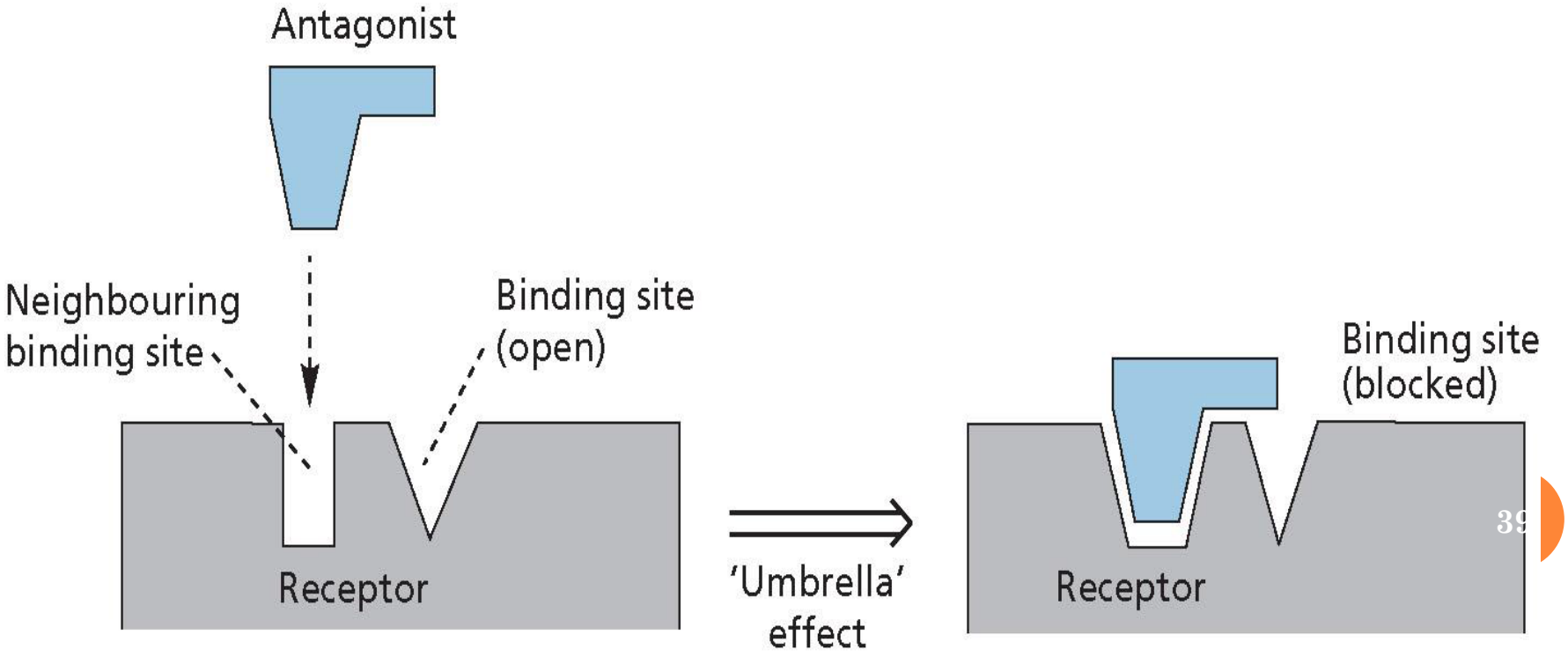
RECEPTOR'S ANTAGONIST

Allosteric antagonists

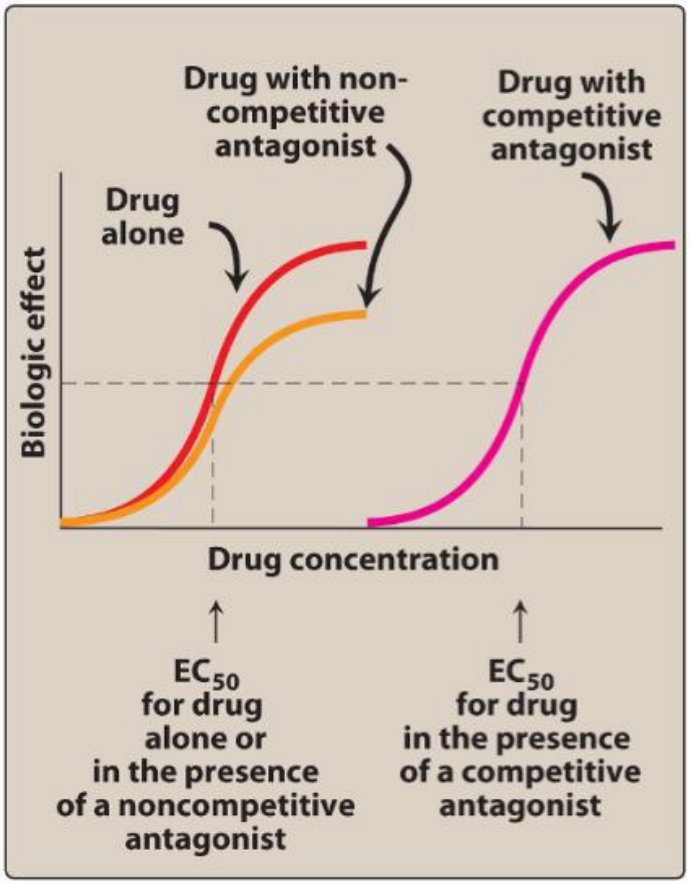


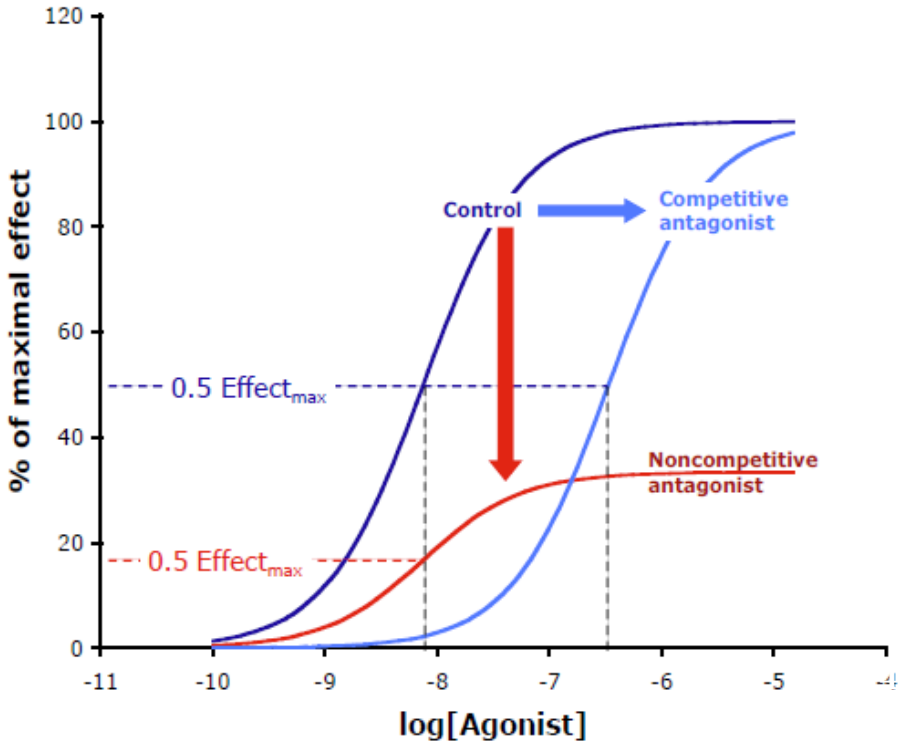
RECEPTOR'S ANTAGONIST

- Antagonism by the 'umbrella' effect: Here the drug will bind to a region close to binding site, once bound, part of its structure (tail) will cover the opening of the binding site….preventing the normal messenger from accessing the binding site.

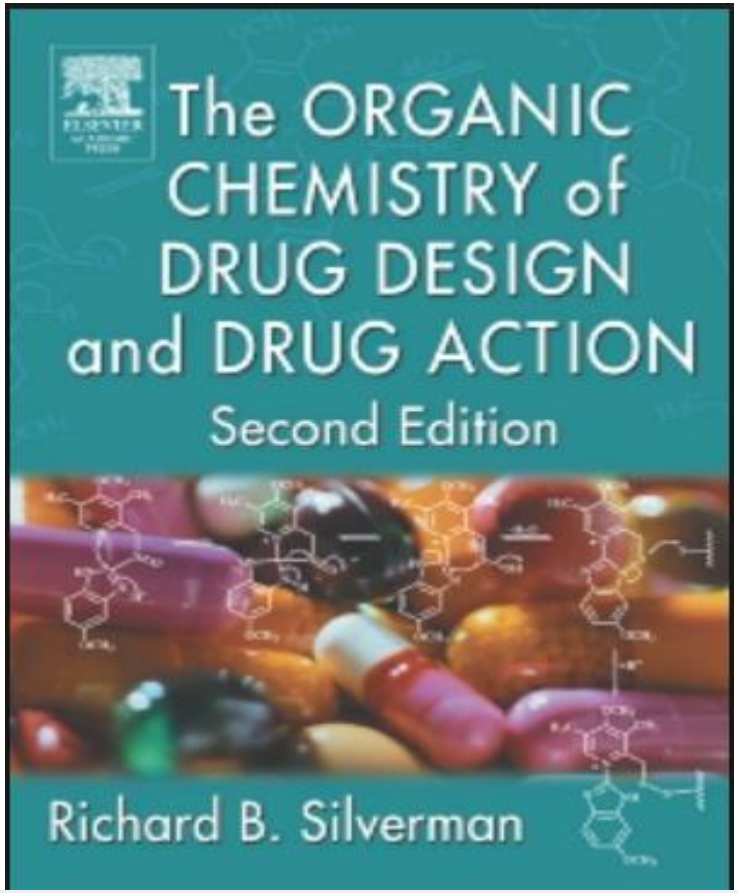


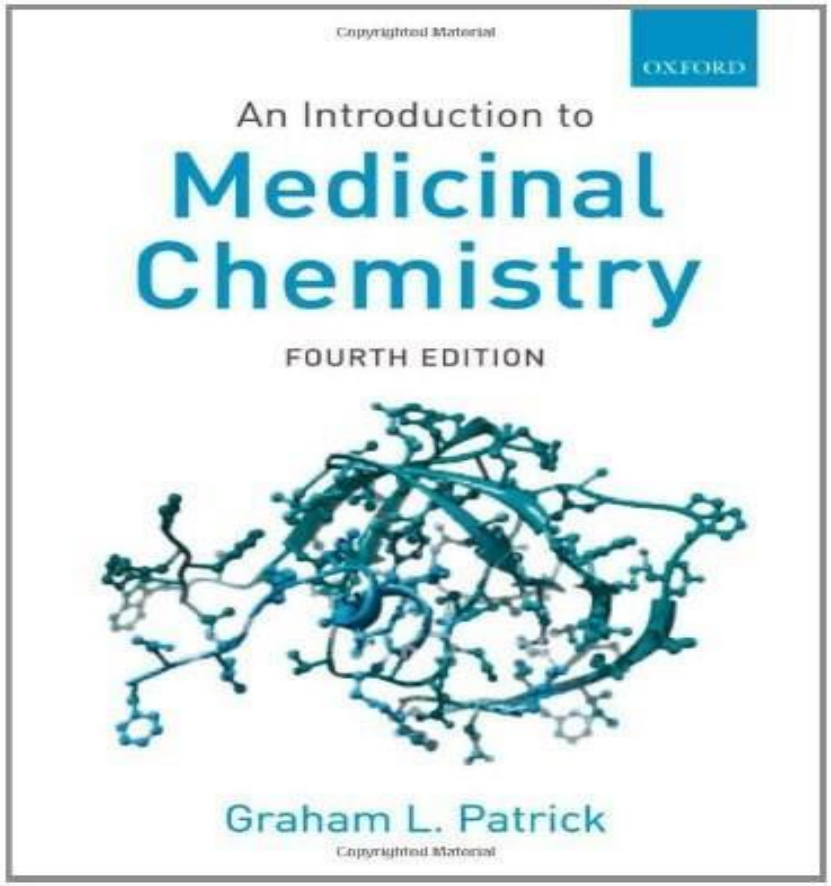
- ***Competitive Antagonists:*** *Compete with agonist for receptor binding => Agonist appears less potent, but can still achieve 100% effect but at higher concentrations.*
- ***Non-competitive Antagonists:*** *Bind to receptor at different site and either prevent agonist binding or the agonist effect => maximal achievable response reduced.*





Recommended Books





1. The organic chemistry of drug design by Richard B. Silverman. Second edition, Elsevier, 2004.

2. An introduction to Medicinal Chemistry by Graham L. Patrick. Fourth edition, Oxford, 2009.


Thank
You