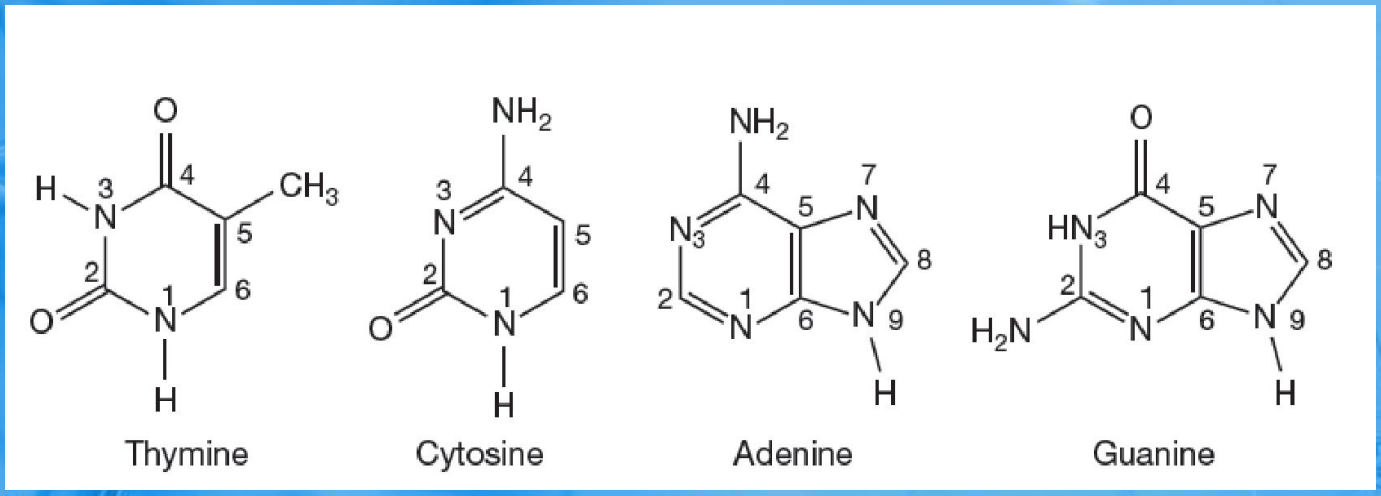
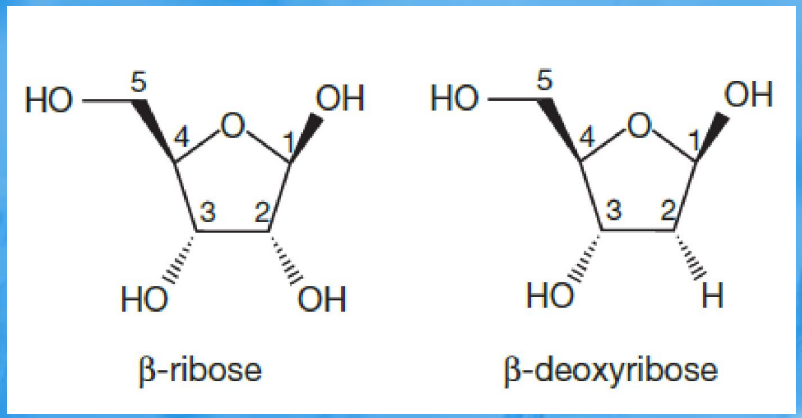
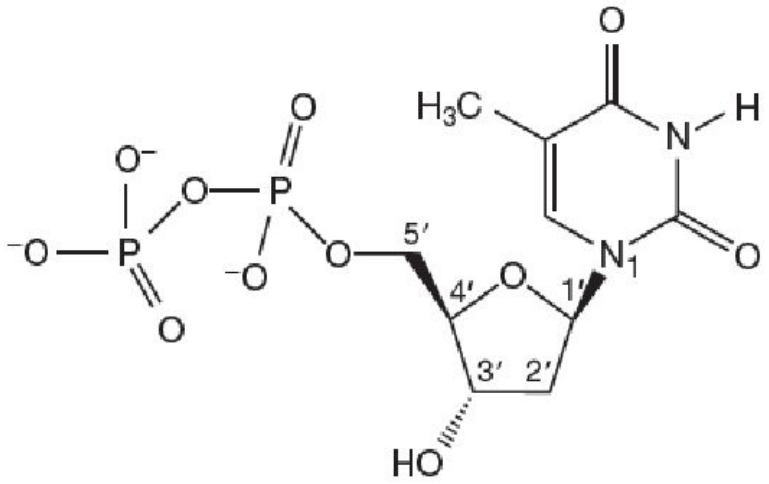
ФАРМАЦЕВТИЧЕСКАЯ ХИМИЯ
ЛЕКЦИЯ

Молекулярные мишени. Нуклеиновые кислоты

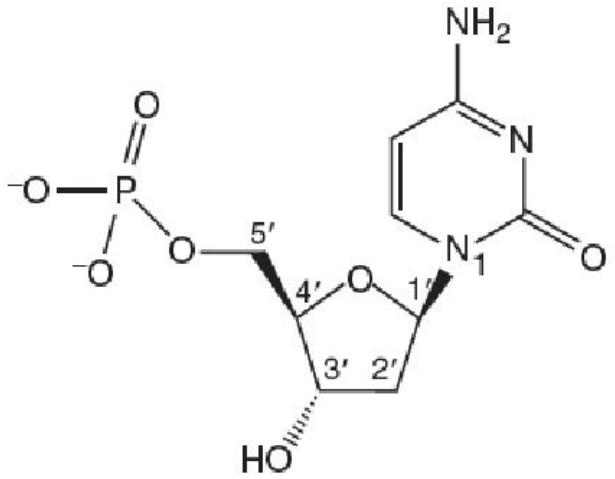




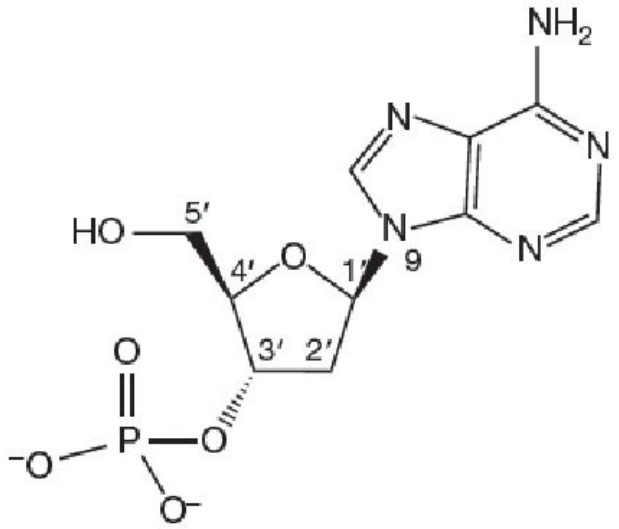
Изобразите структуру α-гликозида дезокситимидина



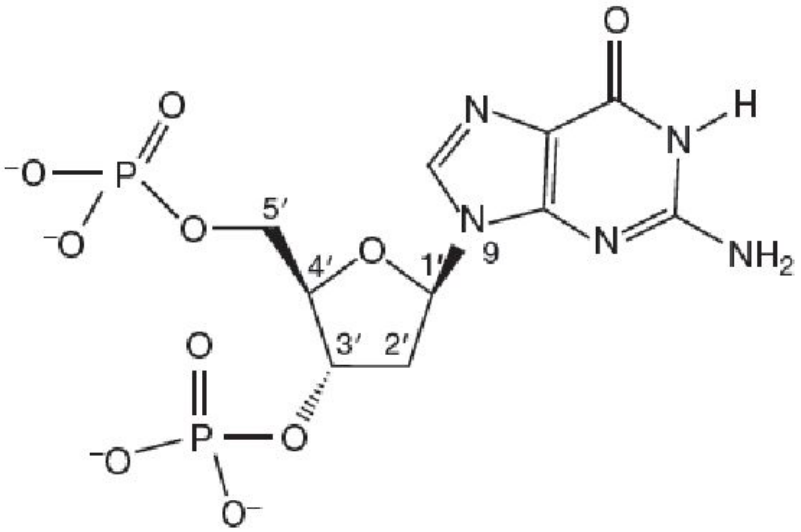
Deoxythymidine-5′-diphosphate



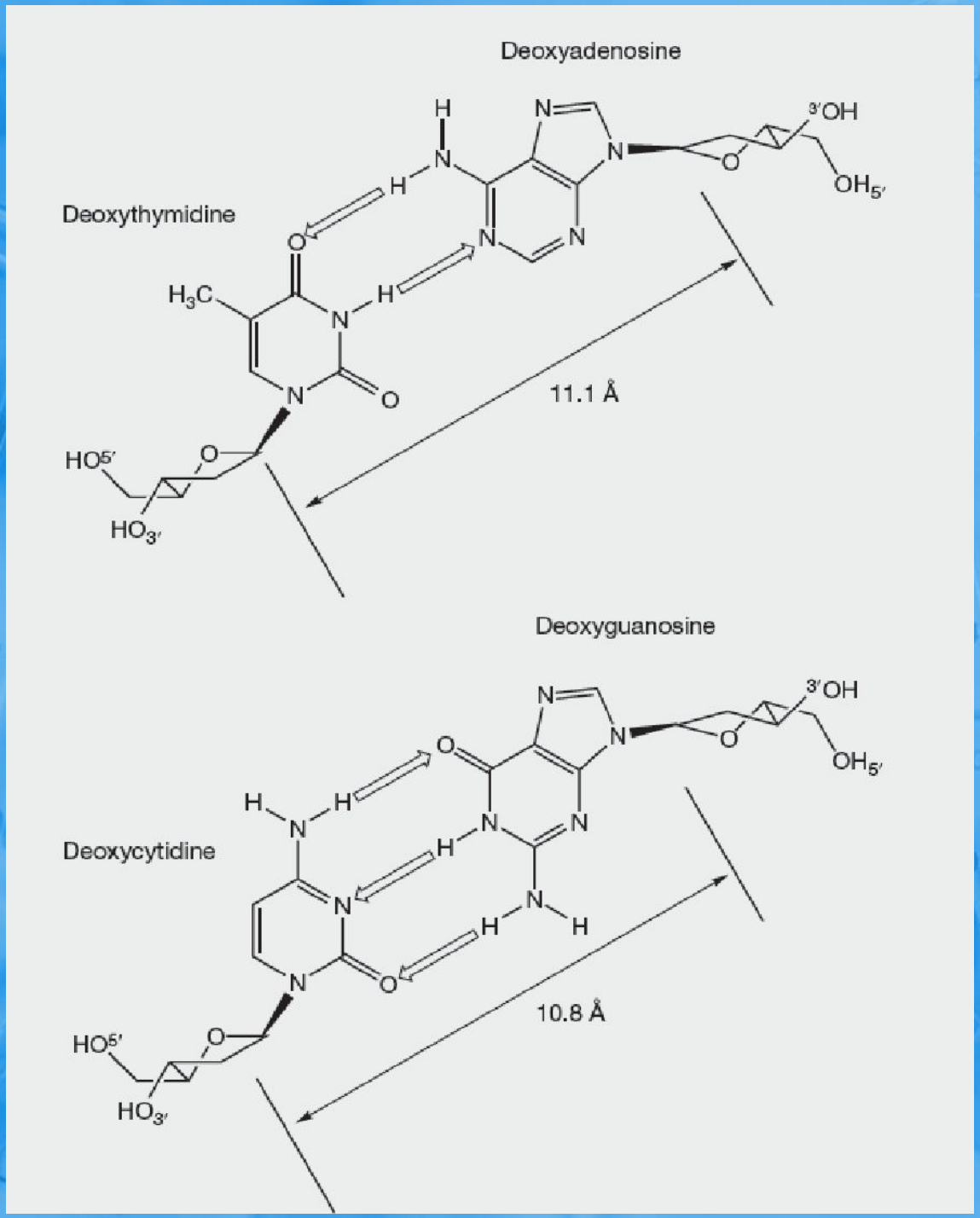
Deoxycytidine-5′-monophosphate



Deoxyadenosine-3′-monophosphate



Deoxyguanosine-3′,5′-biphosphate


Deoxyadenosine
Deoxythymidine
11.1 Å
Deoxyguanosine
Deoxycytidine
10.8 Å

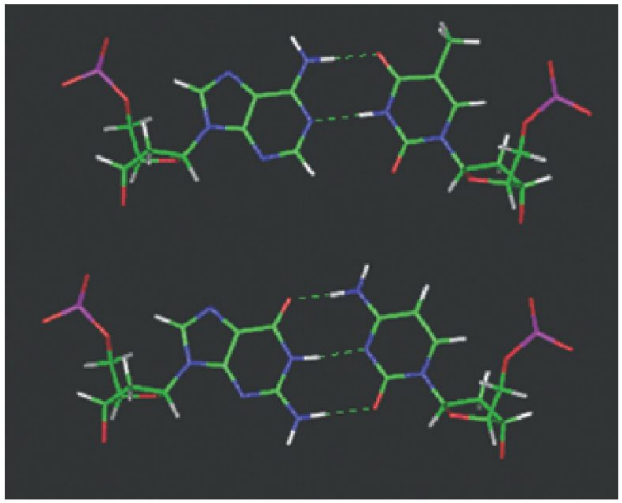


Figure 7.6 Molecular models of the DNA base pairs illustrating 'Watson–Crick' hydrogen bonding complementarity.

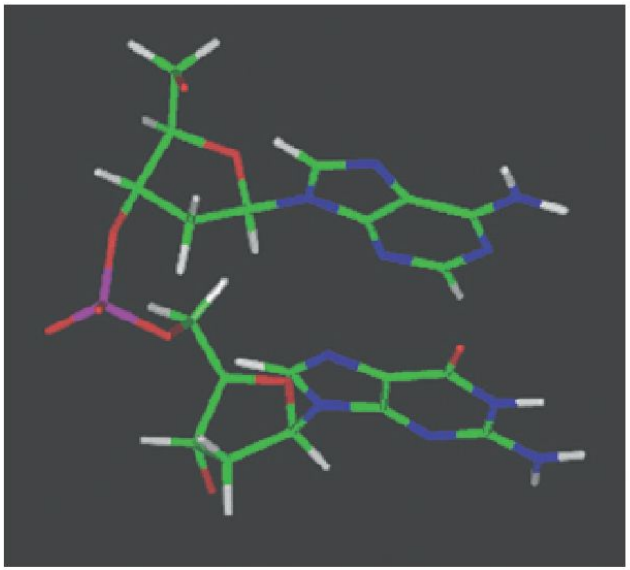


Figure 7.10 Molecular model of a dAdG dinucleotide linked via flexible P–O bonds.

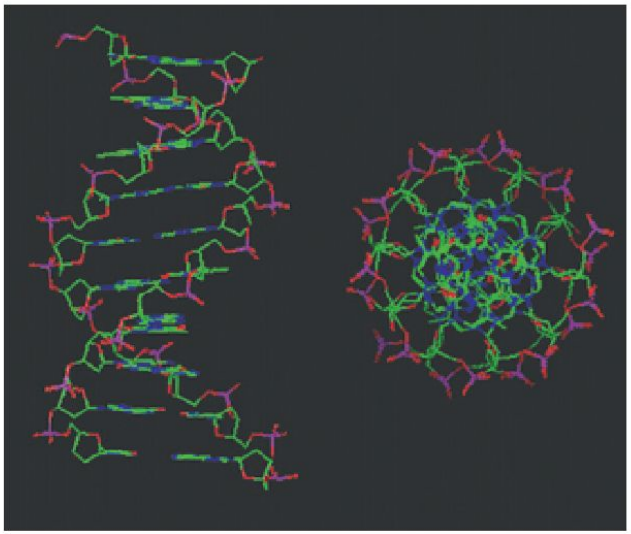


Figure 7.11 Molecular model of double-stranded DNA illustrating base pair stacking from the side and above the helix.

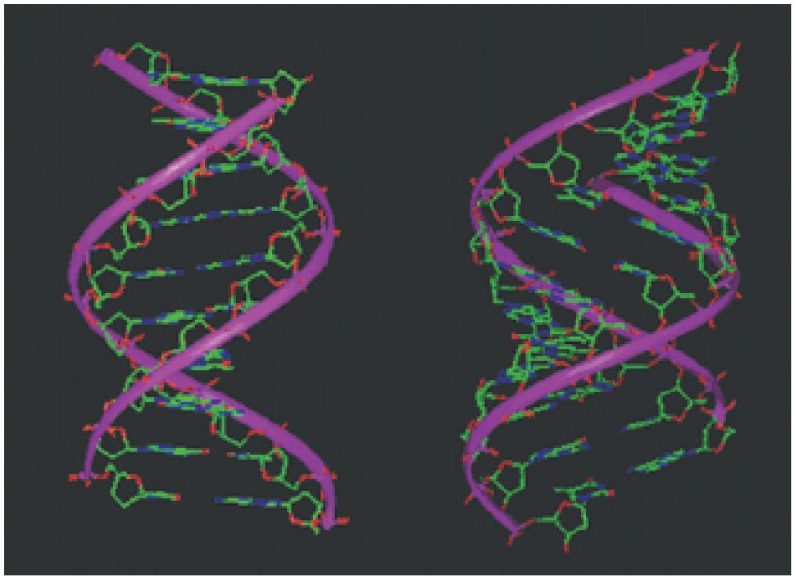
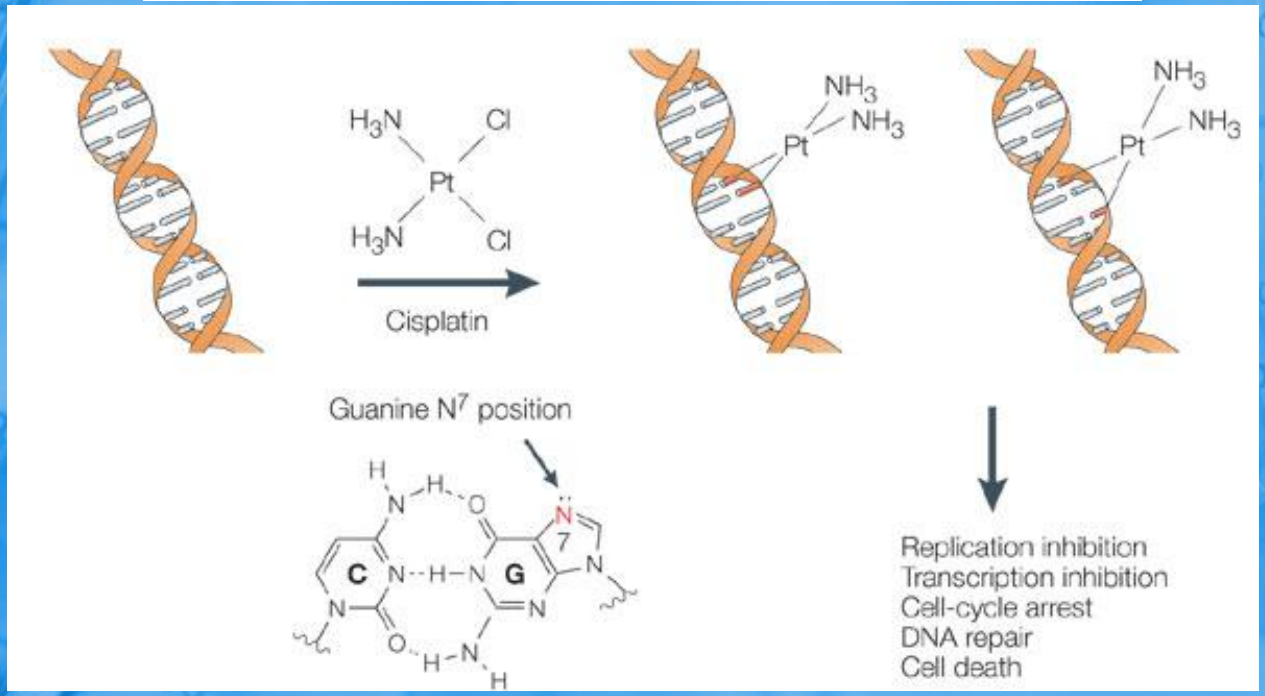


Figure 7.16 One helical turn of B-DNA contains 10 base pairs (left), whilst the equivalent for A-DNA incorporates 11 base pairs.



Агонисты – связывание с рецептором и его активация при низкой концентрации природного лиганда этого рецептора

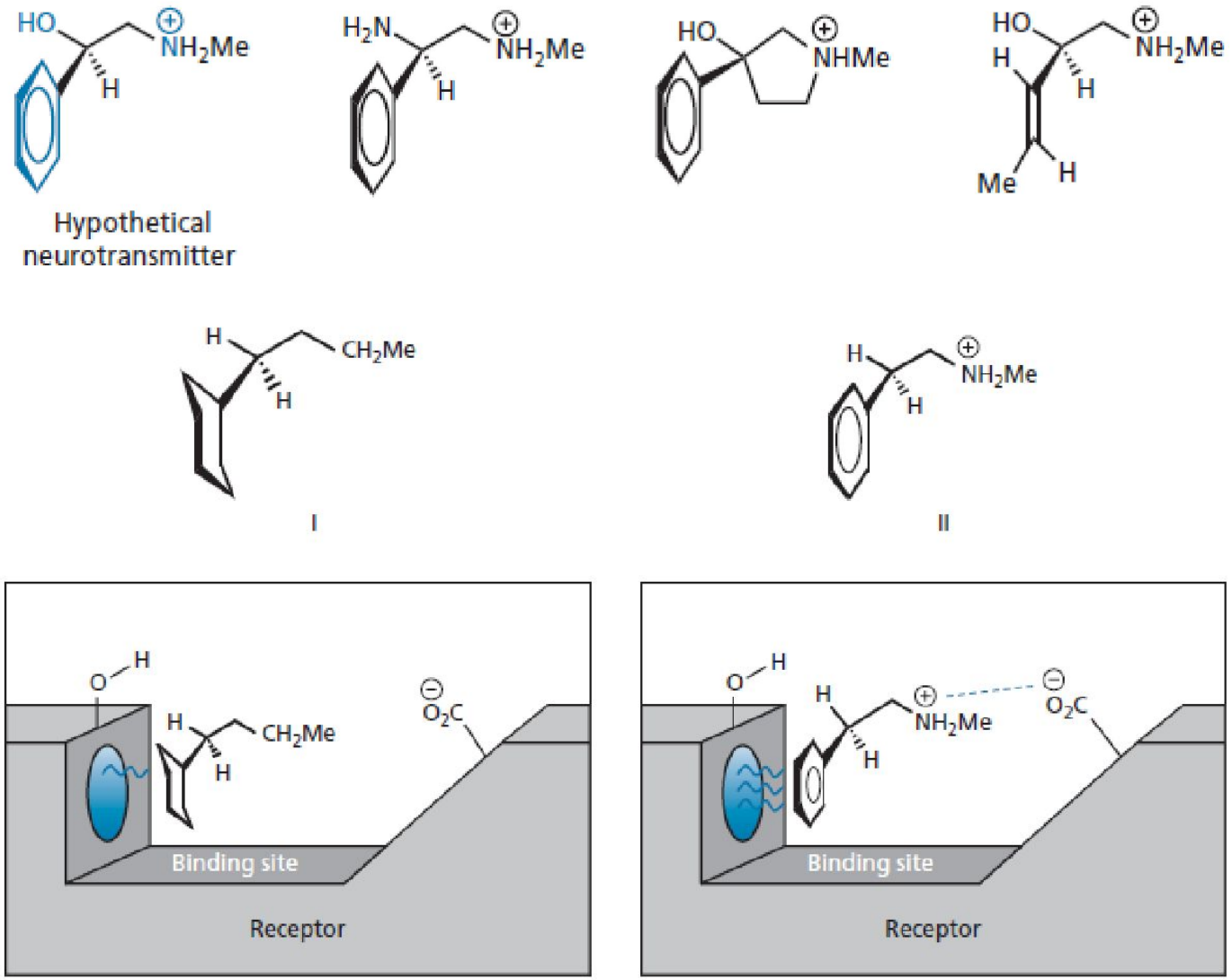


FIGURE 8.3 Weaker binding to the hypothetical receptor by structures that possess fewer than the required binding groups.

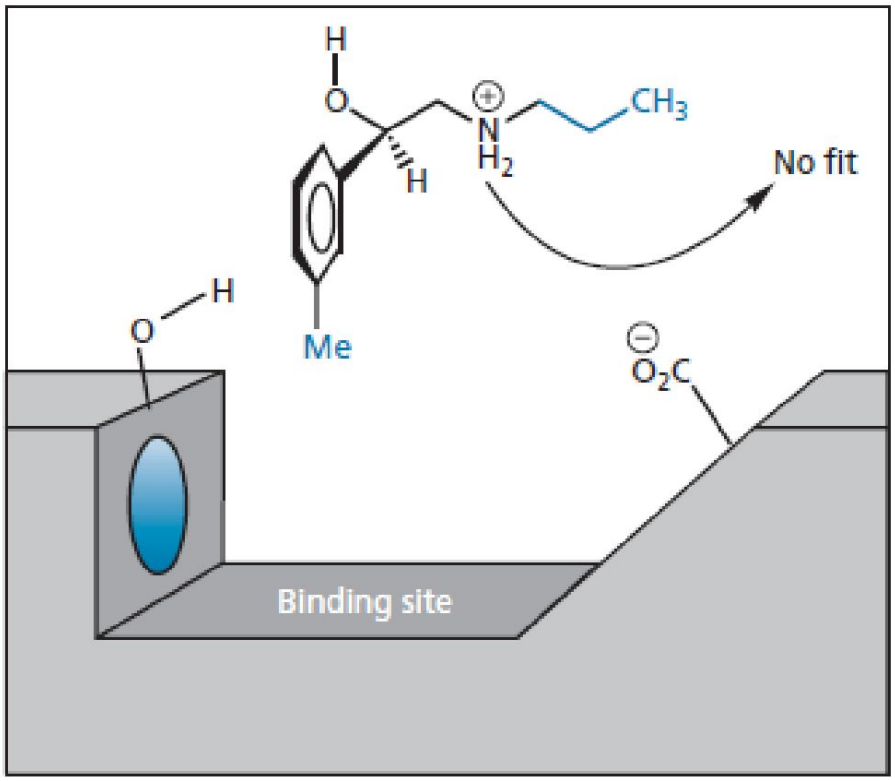


FIGURE 8.6 Failed interaction of a structure with a binding site because of steric factors.

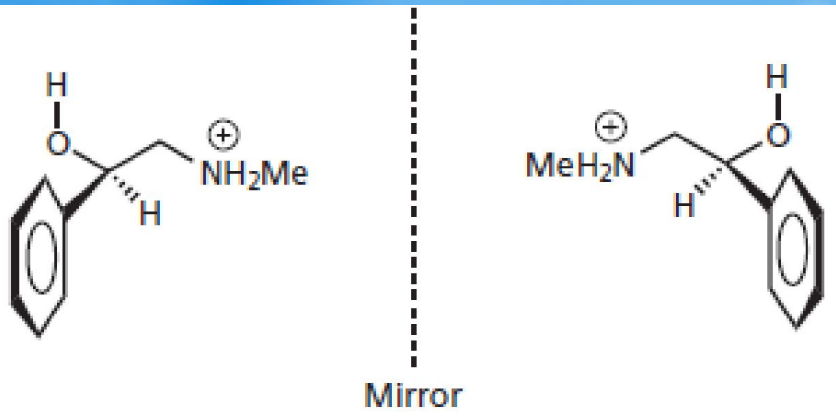


FIGURE 8.5 Mirror image of a hypothetical neurotransmitter.

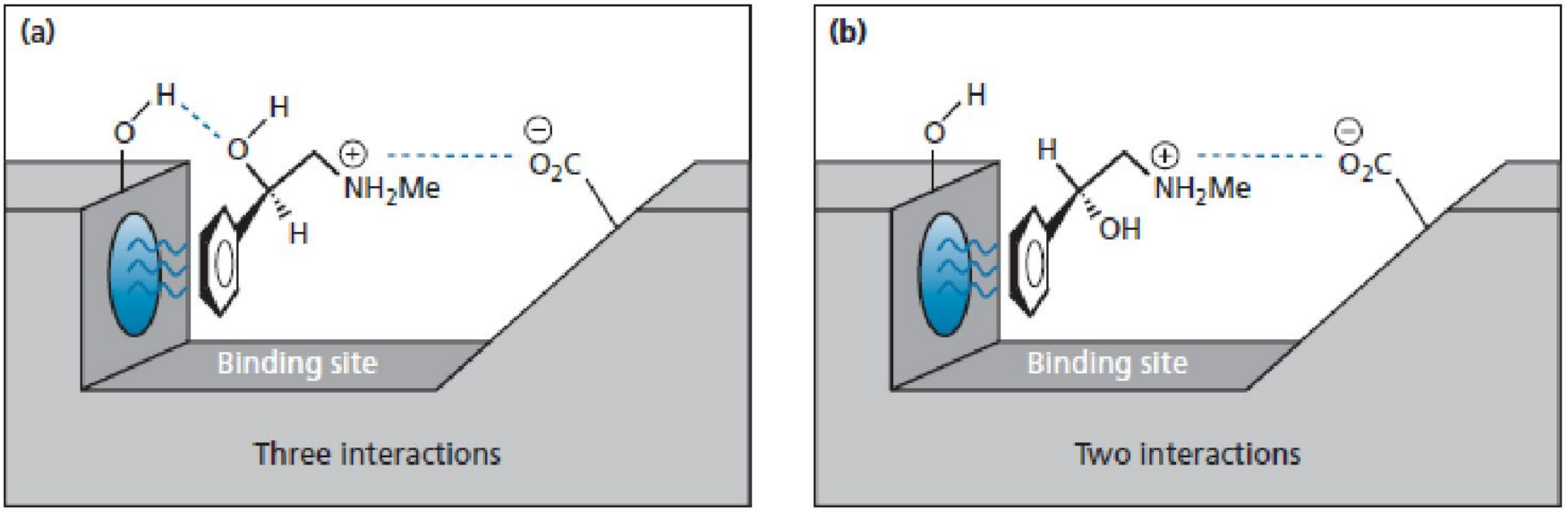


FIGURE 8.2 A comparison of interactions involving (a) the hypothetical neurotransmitter and (b) its mirror image with a hypothetical binding site.

Антагонисты – связывание с рецептором без его активации

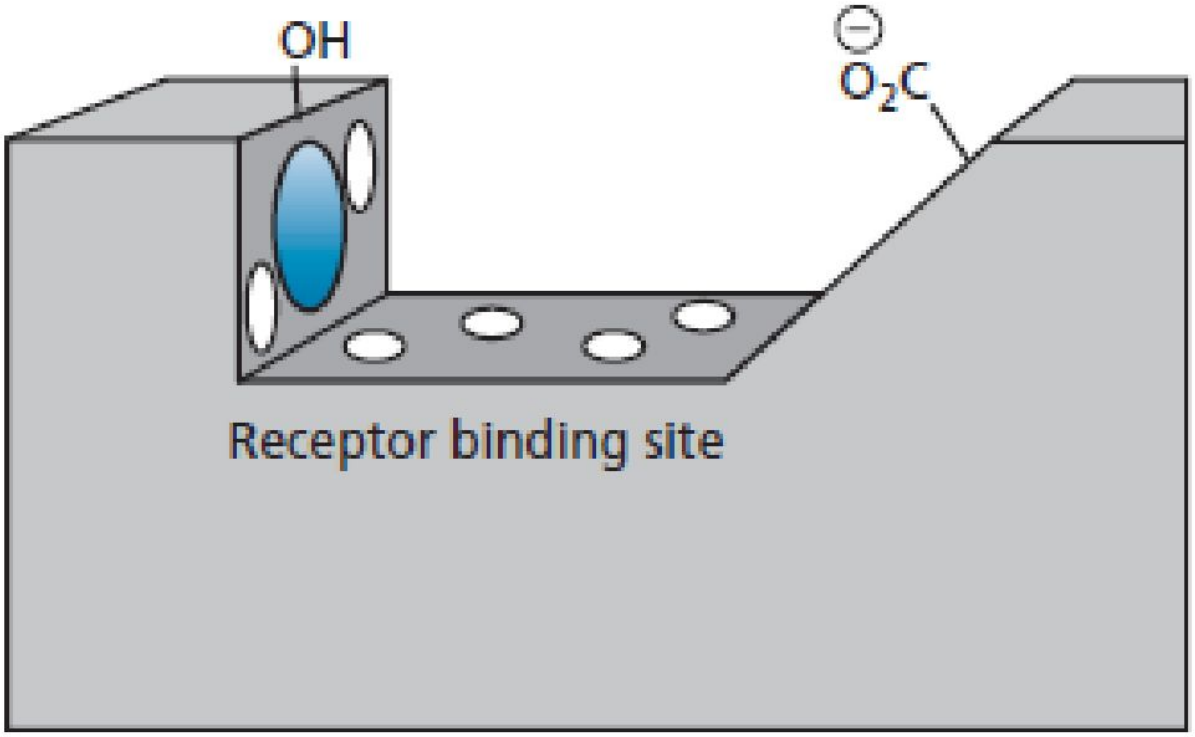


FIGURE 8.7 The hypothetical binding site showing extra binding regions (in white) that are not used by the natural chemical messenger.

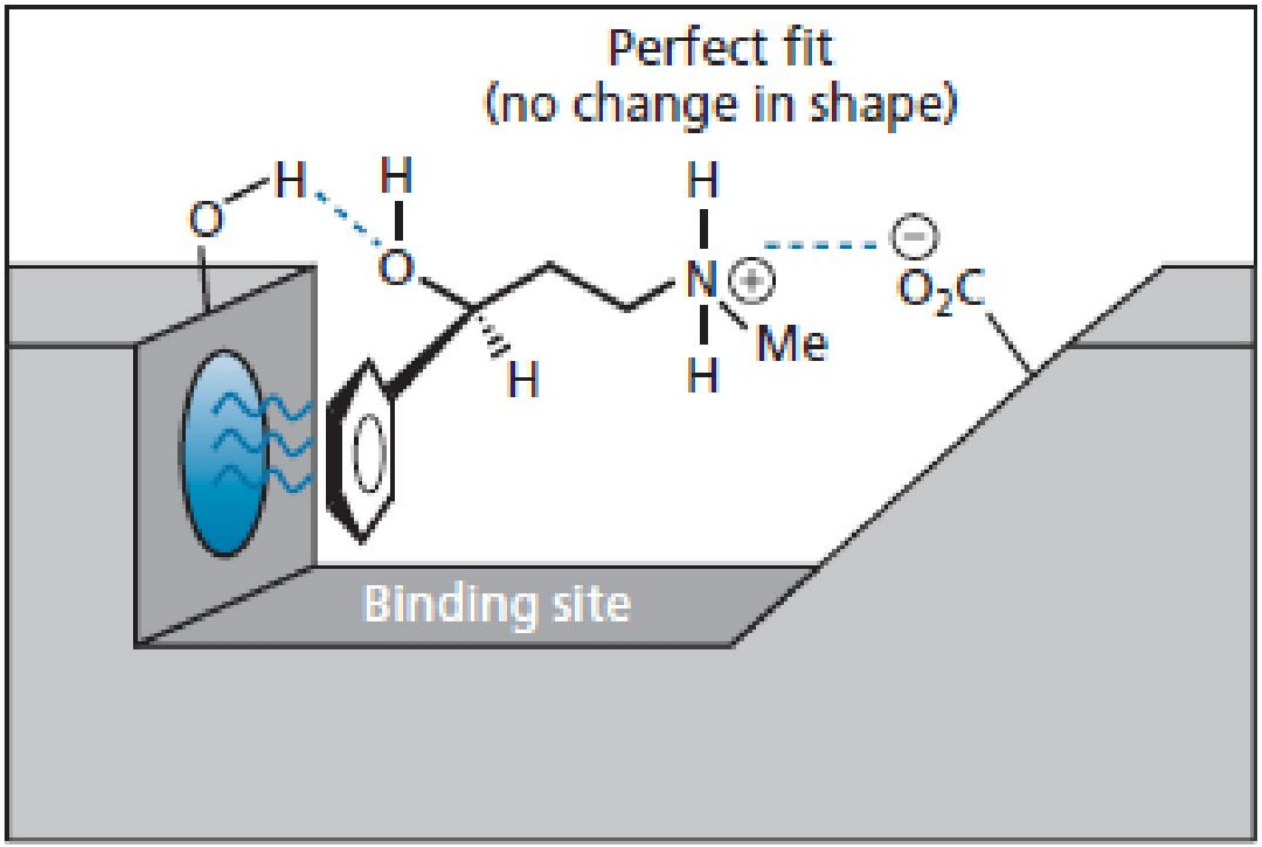


FIGURE 8.9 Compound acting as an antagonist at the binding site.

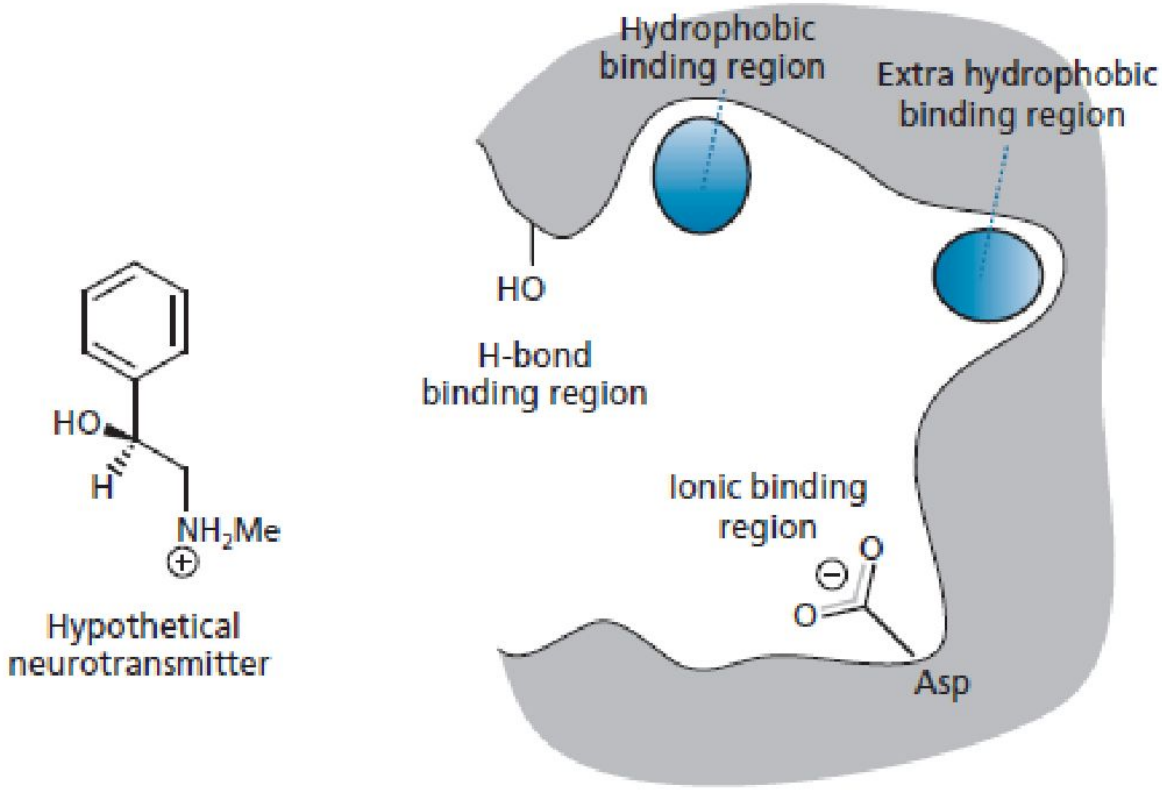


FIGURE 8.10 'Map' of the hypothetical binding site.

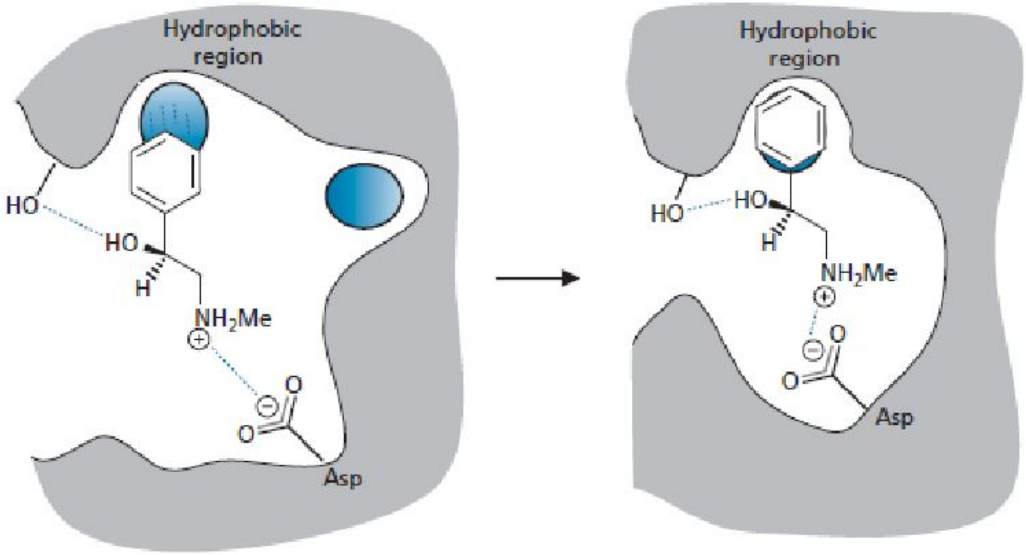


FIGURE 8.11 Binding of the natural chemical messenger resulting in an induced fit that activates the receptor.

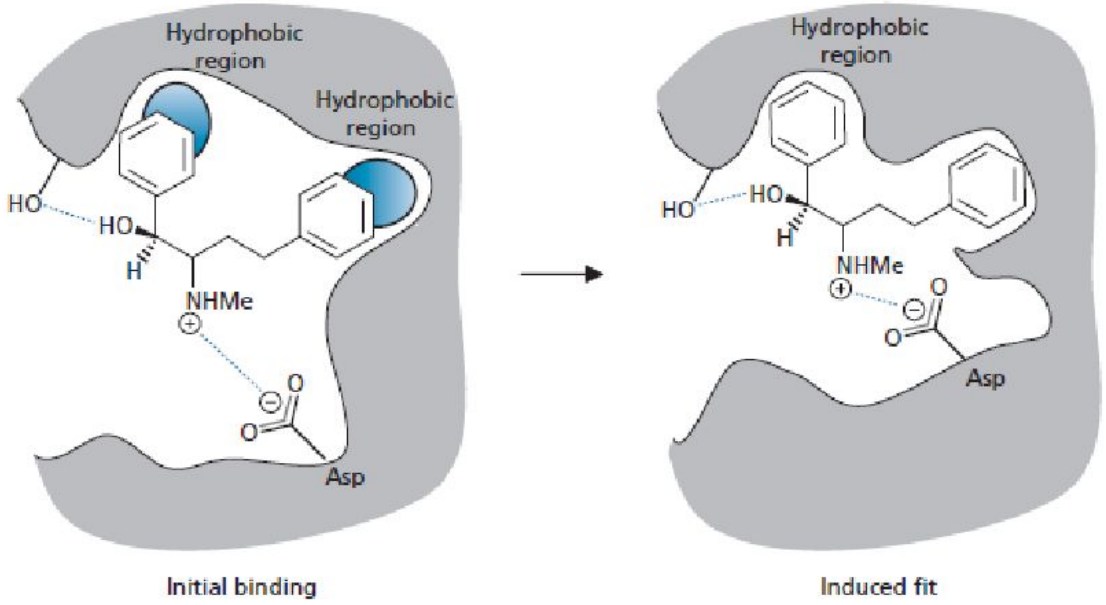


FIGURE 8.12 Binding of an antagonist leading to a different induced fit.

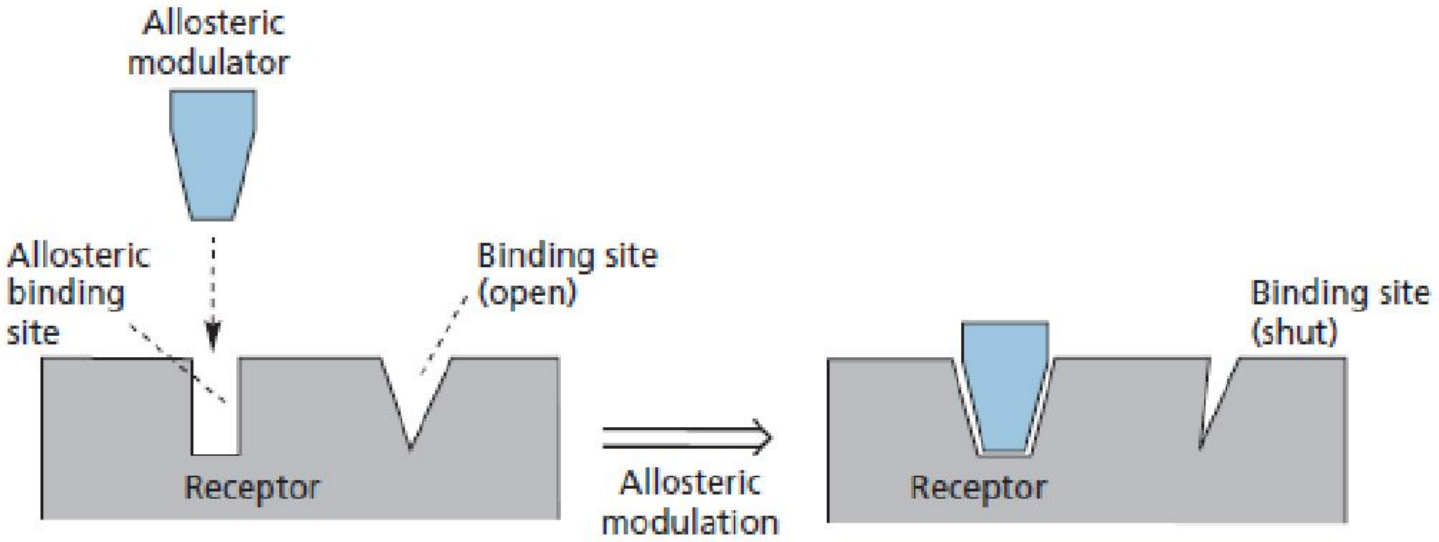


FIGURE 8.13 Principle by which an allosteric antagonist distorts a binding site.

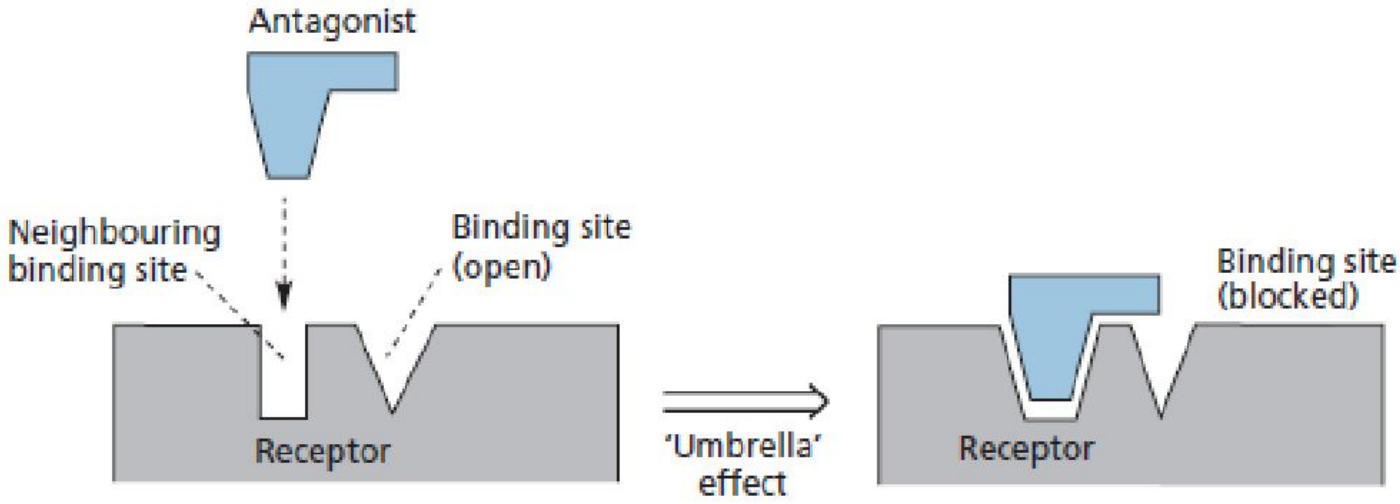


FIGURE 8.14 Antagonism by the 'umbrella effect'.

$$L + R \rightleftharpoons \underset{\text{Receptor–ligand complex}}{LR} \qquad K_d = \frac{[L] \times [R]}{[LR]}$$

$$[R_{tot}] = [R] + [LR]$$

This means that the number of receptors unoccupied by a ligand is

$$[R] = [R_{tot}] - [LR]$$

Substituting this into the first equation and rearranging leads to the **Scatchard equation**, where both [LR] and [L] are measurable:

$$\frac{[\text{Bound ligand}]}{[\text{Free ligand}]} = \frac{[LR]}{[L]} = \frac{R_{tot} - [LR]}{K_d}$$

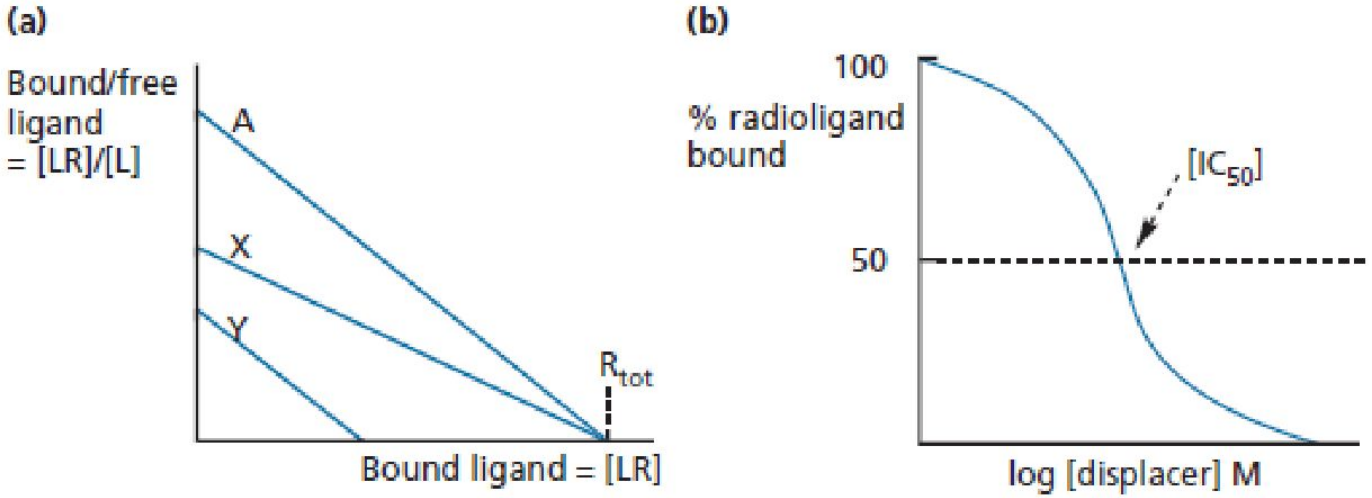


FIGURE 8.20 (a) Scatchard plot (A = radioligand only, X = radioligand + competitive ligand, Y = radioligand + non-competitive ligand). (b) The displacement or inhibition curve.

KEY POINTS

- Affinity is a measure of how strongly a drug binds to a receptor. Efficacy is a measure of the effect of that binding on the cell. Potency relates to how effective a drug is in producing a cellular effect.
- Affinity can be measured from Scatchard plots derived from radioligand displacement experiments.
- Efficacy is determined by the EC_{50} value—the concentration of agent required to produce 50% of the maximum possible effect resulting from receptor activation.
- A Schild analysis is used to determine the dissociation constant of competitive antagonists.

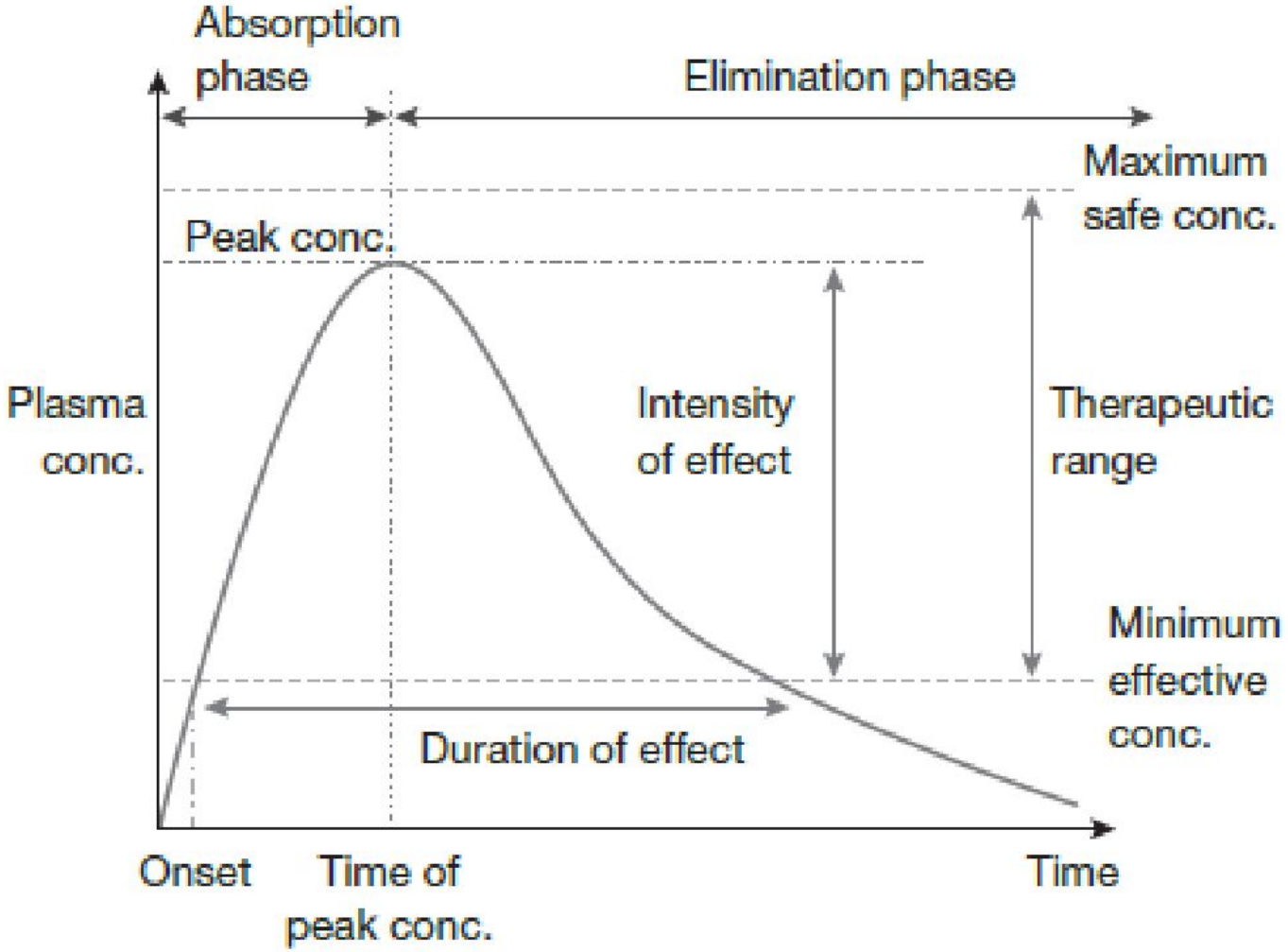
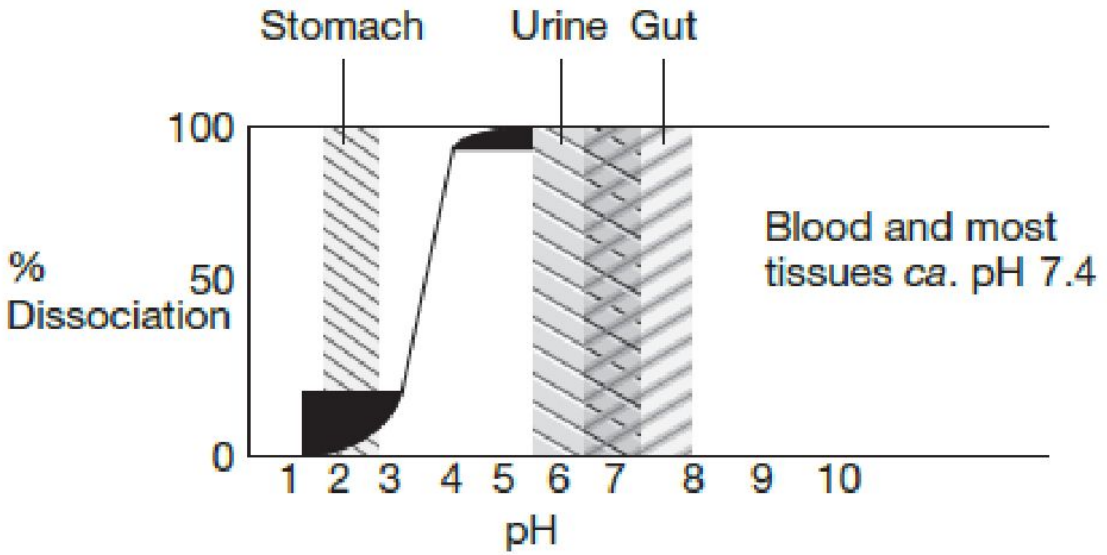
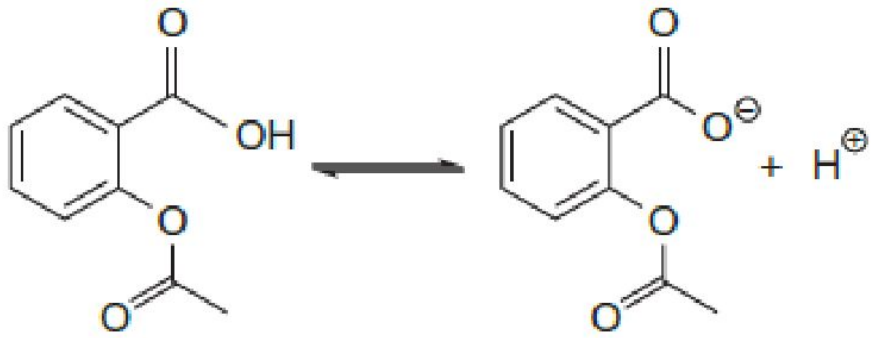


Figure 8.1 Drug dose response profile for a hypothetical drug, showing the absorption and elimination phases following administration.





Aspirin is undissociated in the stomach

Aspirin is dissociated in the small intestine, plasma

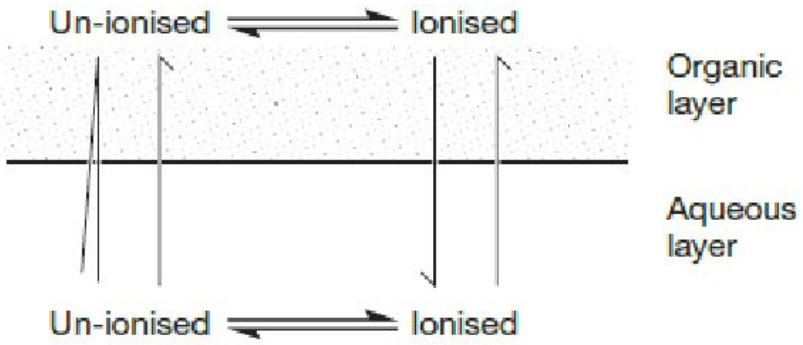


Figure 8.6 Ionised and un-ionised drug in aqueous and organic phases.

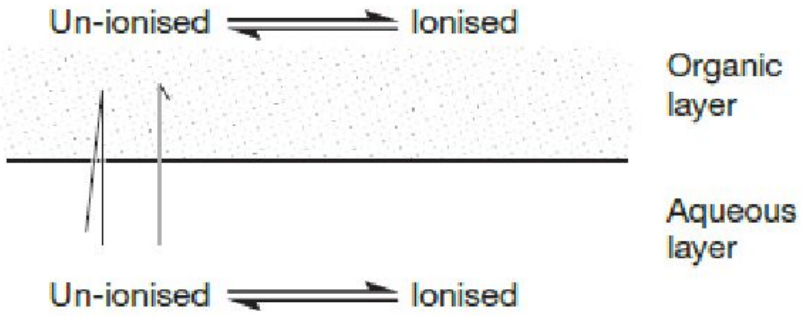


Figure 8.7 Un-ionised drug in an organic layer in equilibrium with un-ionised and ionised drug in an aqueous layer.

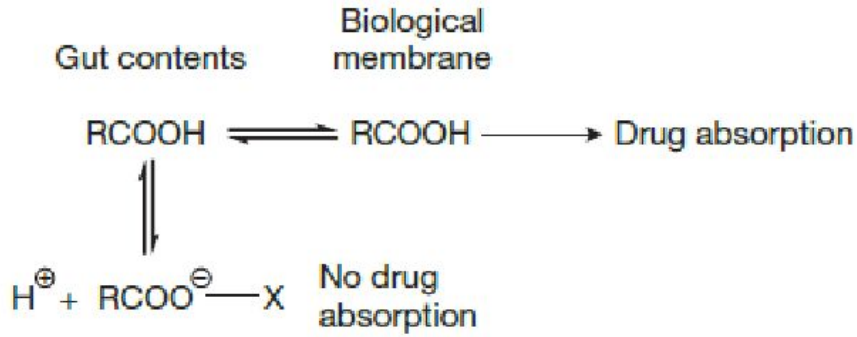


Figure 8.8 The effect of pH on the absorption of an organic acid.

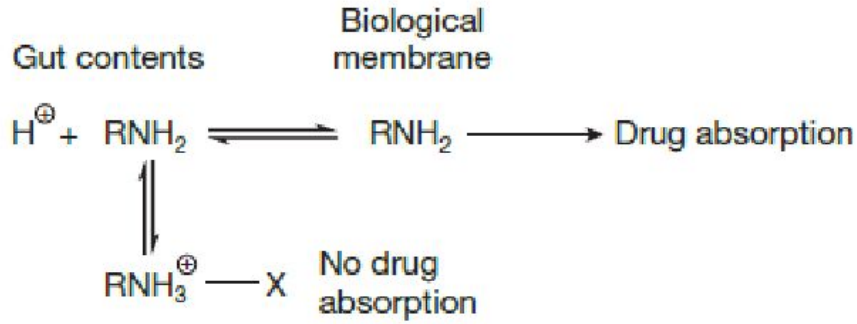
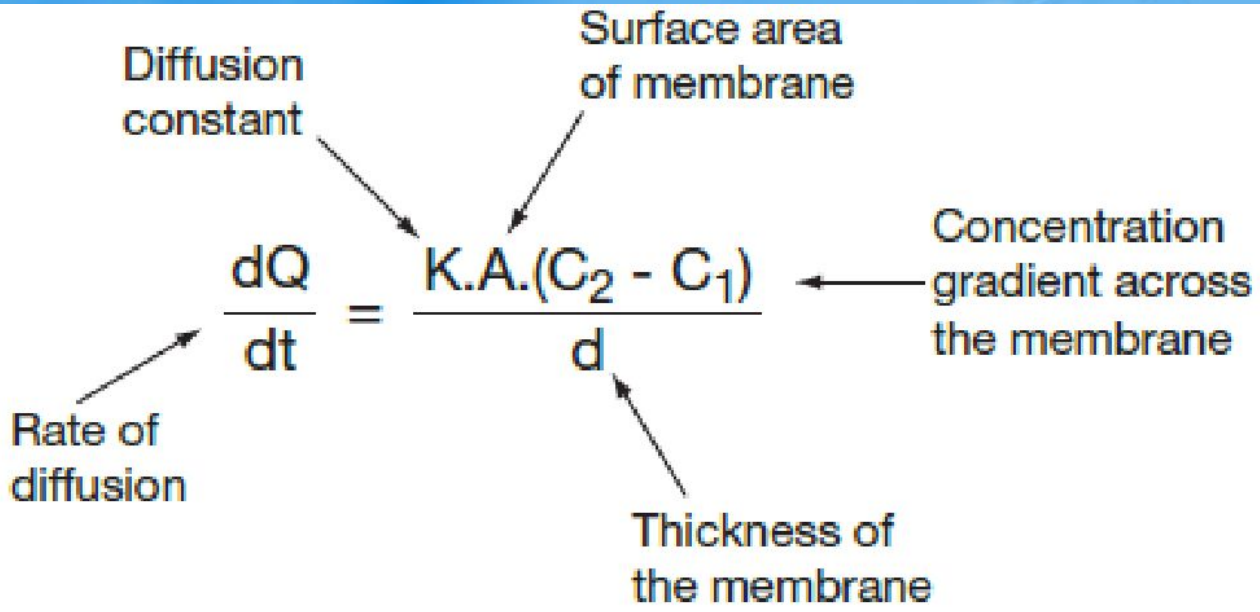


Figure 8.9 The effect of pH on the absorption of an organic base.



The diffusion constant, K, is a function of:

- aqueous solubility of the drug i.e. hydrophilic character
- lipid solubility of the drug i.e. o/w partition coefficient
- molecular size, i.e. RMM
- molecular shape
- p*Ka* of the drug
- pH of the environment.

Рациональный подход к дизайну пролекарства:

1. Идентификация проблем, связанных с доставкой лекарства.

2. Определение физико-химических свойств, необходимых для максимального увеличения эффективности доставки.

3. Подбор подходящего производного, обладающего желаемыми физико-химическими свойствами, которое будет наиболее эффективно расщепляться в нужном биологическом отсеке, высвобождая при этом фармакологически активное вещество.

Several criteria have to be considered in the design of a prodrug, including:

1. the functional group(s) in the parent drug molecule which are amenable to chemical derivatisation
2. the mechanism(s) available in the body for bioactivation of the prodrug
3. ease of synthesis and purification of the prodrug, i.e. economic considerations
4. stability of the prodrug per se and its compatibility with other components of a pharmaceutical formulation
5. the rate and extent of regeneration of the parent drug from the prodrug in vivo, i.e. Biochemical considerations
6. toxicity of the prodrug and also of its transport group.

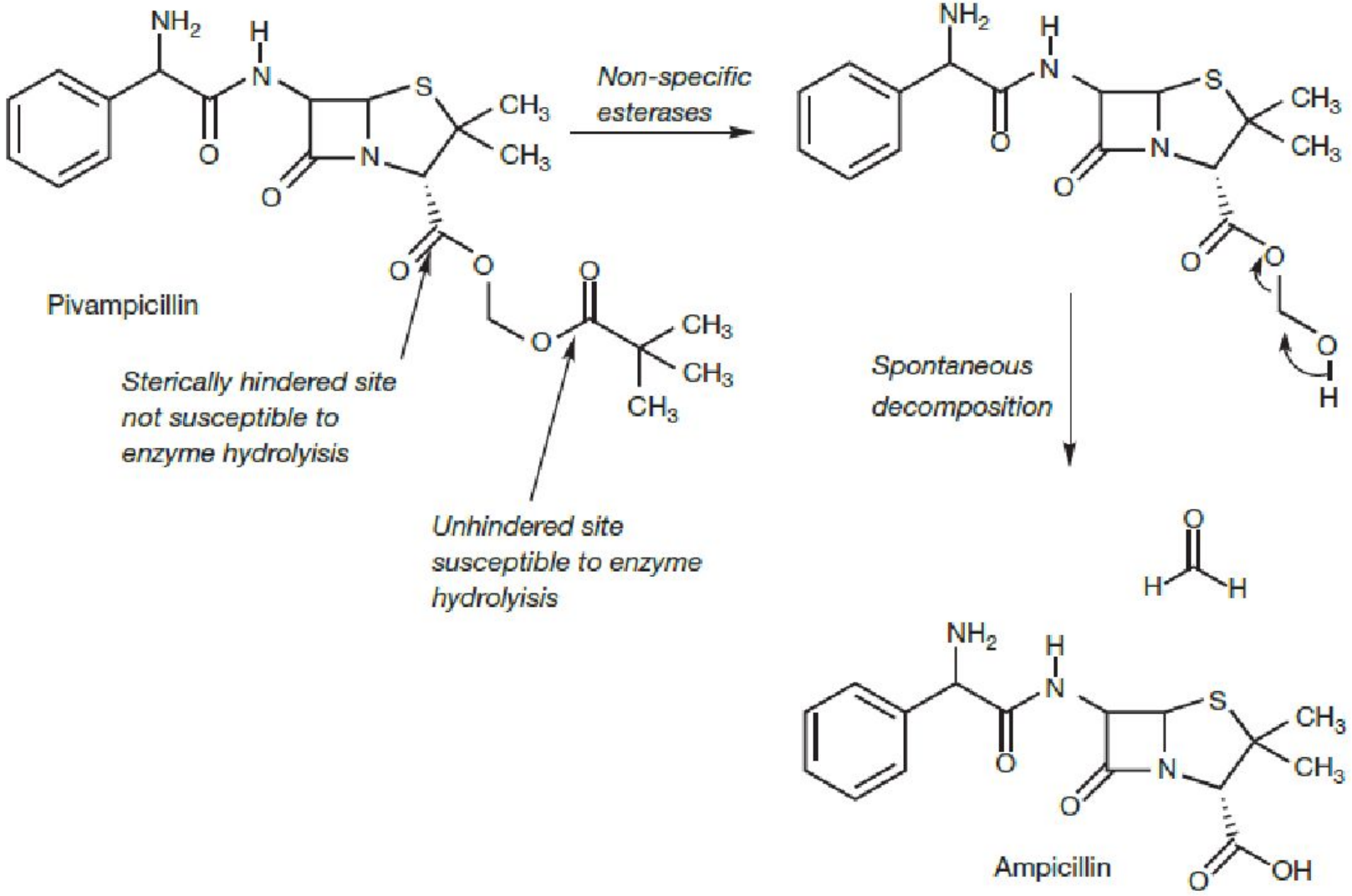


Figure 8.19 Conversion of pivampicillin into ampicillin by esterase activity followed by spontaneous decomposition.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