Inhibición Enzimática

Ejemplos

Aspirina (prostaglandin sintasa)

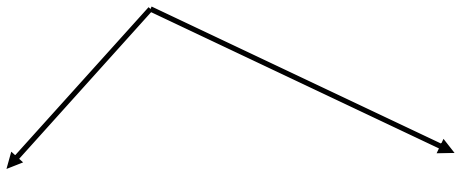
Penicilina (glicopeptido transpeptidasa)

AZT (HIV reverse transcriptasa)

Viagra (cGMP fosfodiesterase)

Metanol (alcohol deshidrogenasa)

Inhibición Enzimática



Reversible

- Equilibrio
- Efectividad = Ki
- Independiente del tiempo

Irreversible

- Progresiva con el tiempo
- Efectividad = Vi

Inhibición Reversible (IR)

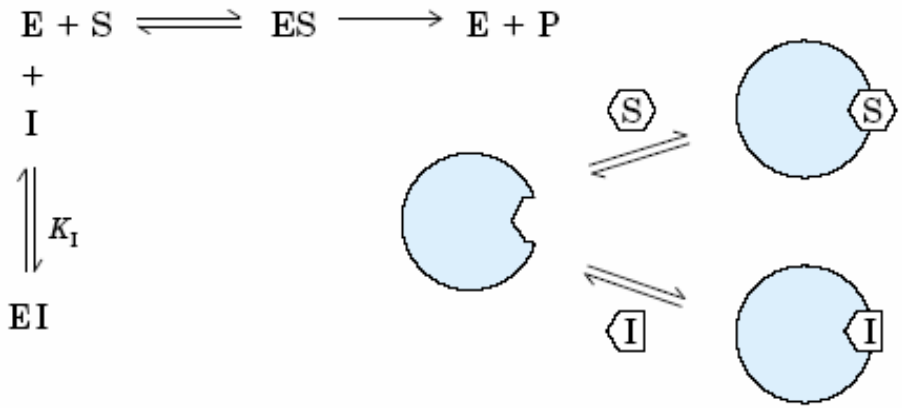
La IR puede afectar a **Vmax** o **Km** o a ambas a la vez

Si sólo afecta **Km** ⇒ **IR Competitiva**

Si sólo afecta **Vmax** ⇒ **IR No-Competitiva**

Si afecta tanto a **Km** y a **Vmax** ⇒ **IR Acompetitiva**, **IR Mixta**

Inhibición Revesible Competitiva

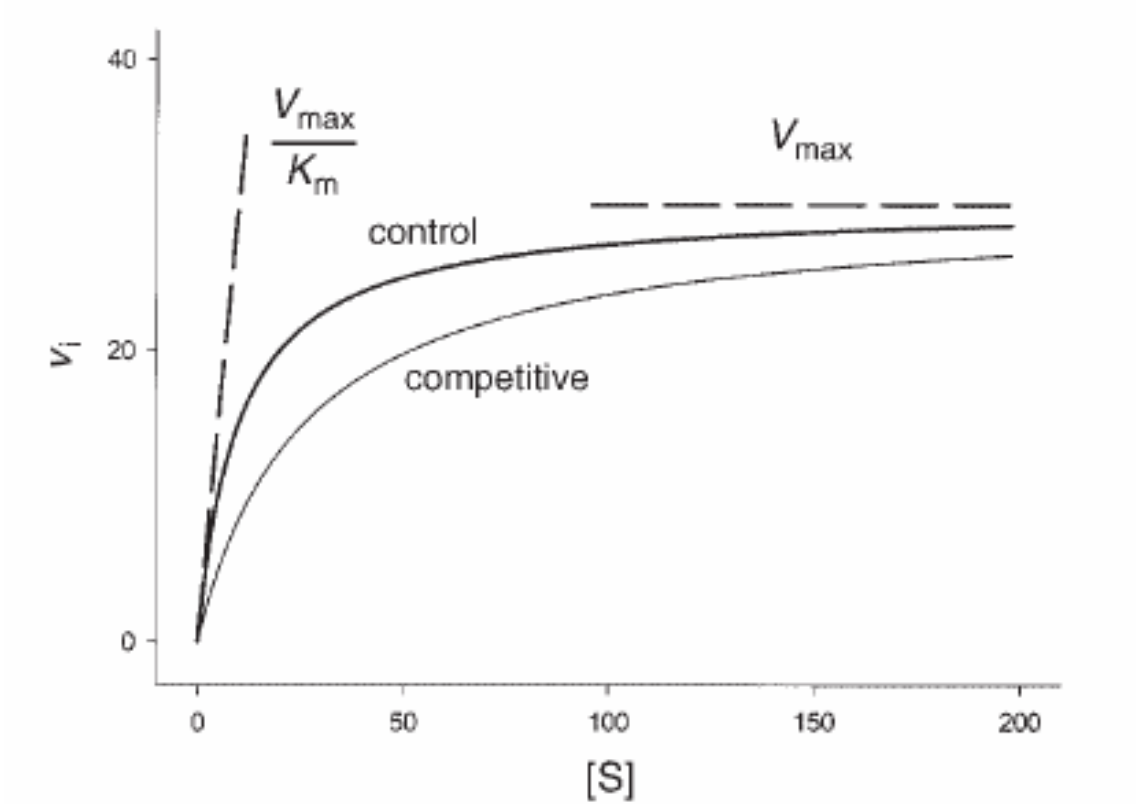


(a) Competitive inhibition

$$V_0 = \frac{V_{max}[S]}{\alpha K_m + [S]}$$

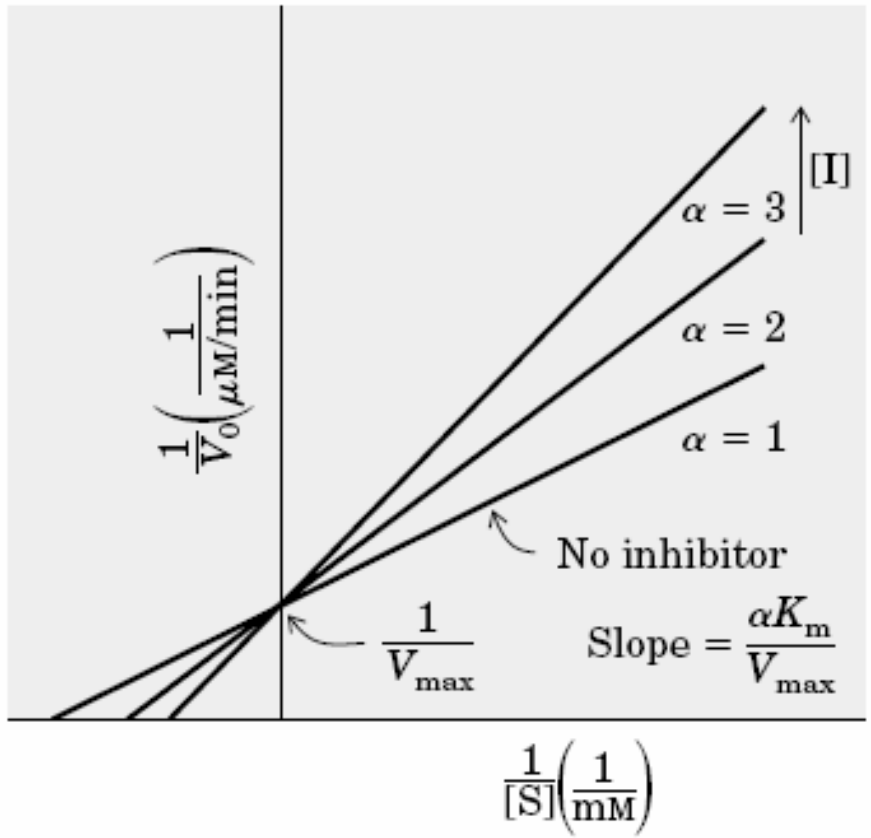
$$\alpha = 1 + \frac{[I]}{K_I}$$

$$K_I = \frac{[E][I]}{[EI]}$$

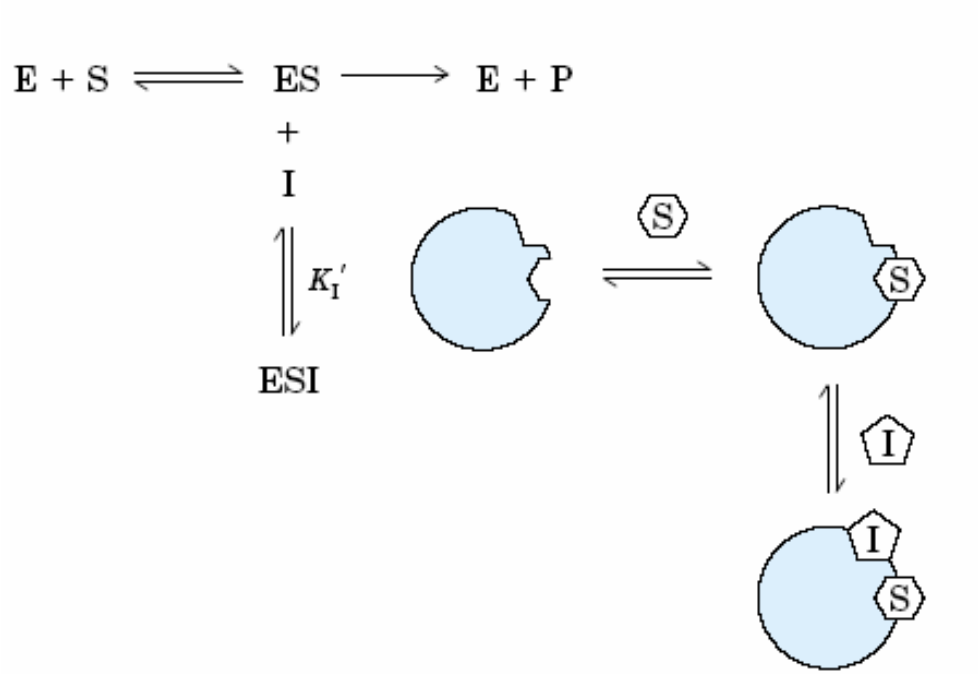

40
20
0
v_i
$\frac{V_{max}}{K_m}$
V_{max}
control
competitive
0
50
100
150
200
[S]

$$\frac{1}{V_0} = \left(\frac{\alpha K_m}{V_{max}}\right)\frac{1}{[S]} + \frac{1}{V_{max}}$$

$$\alpha = 1 + \frac{[I]}{K_I}$$

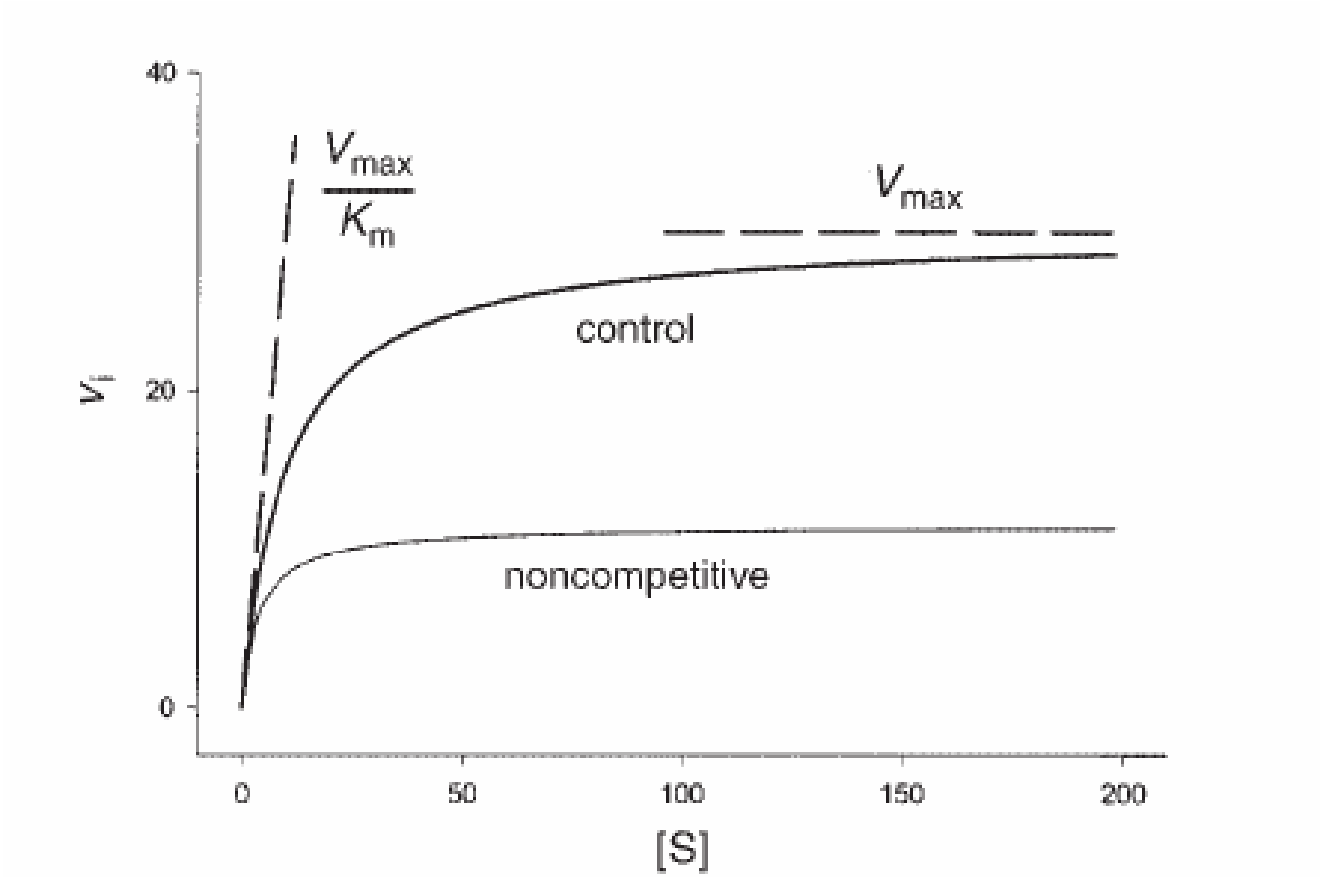


Inhibición Revesible Acompetitiva



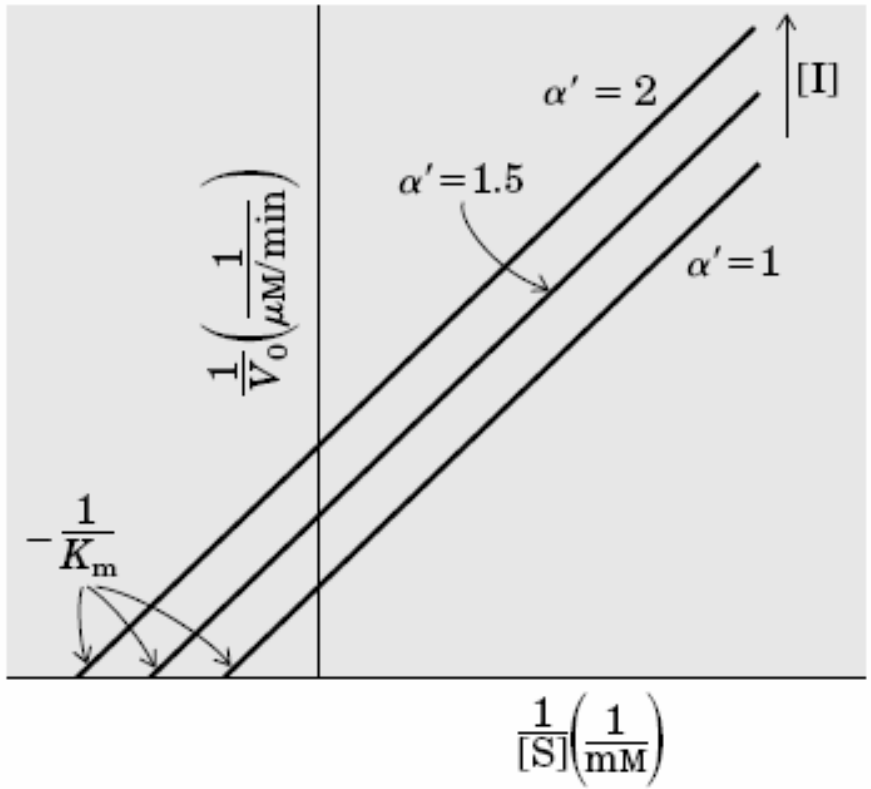
(b) Uncompetitive inhibition

$$V_0 = \frac{V_{max}[S]}{K_m + \alpha'[S]} \qquad \alpha' = 1 + \frac{[I]}{K_I'} \qquad K_I' = \frac{[ES][I]}{[ESI]}$$

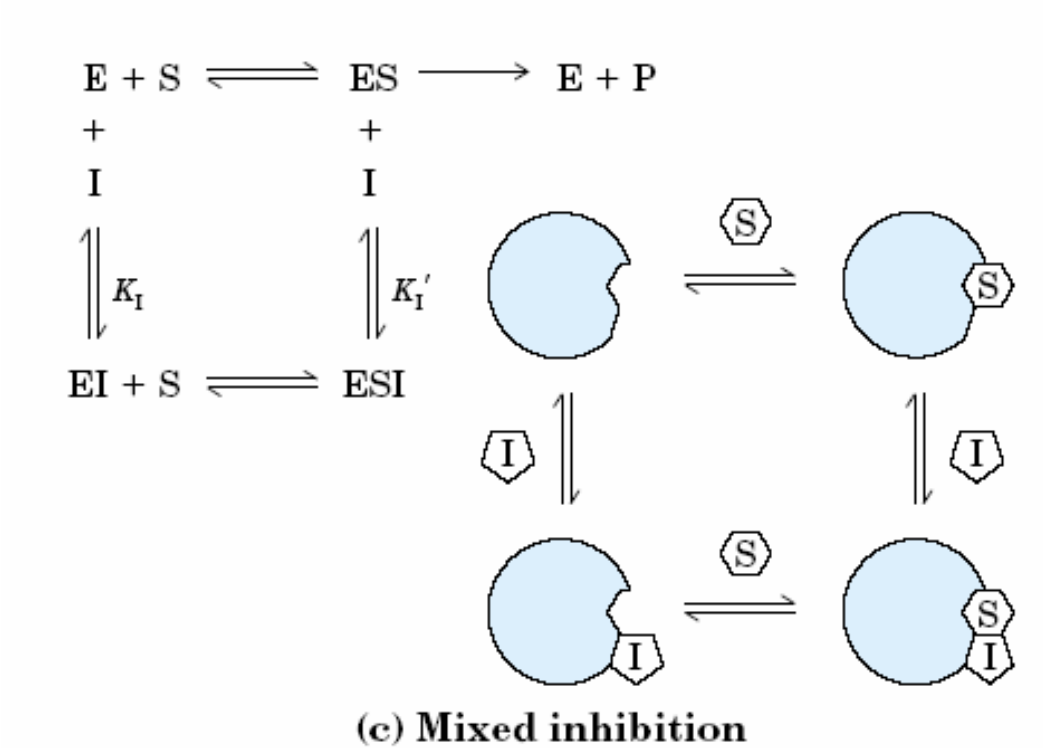

40
20
0
V_i
$\frac{V_{max}}{K_m}$
V_{max}
control
noncompetitive
0
50
100
150
200
[S]

$$\frac{1}{V_0} = \left(\frac{K_m}{V_{max}}\right)\frac{1}{[S]} + \frac{\alpha'}{V_{max}}$$

$$\alpha' = 1 + \frac{[I]}{K_I'}$$

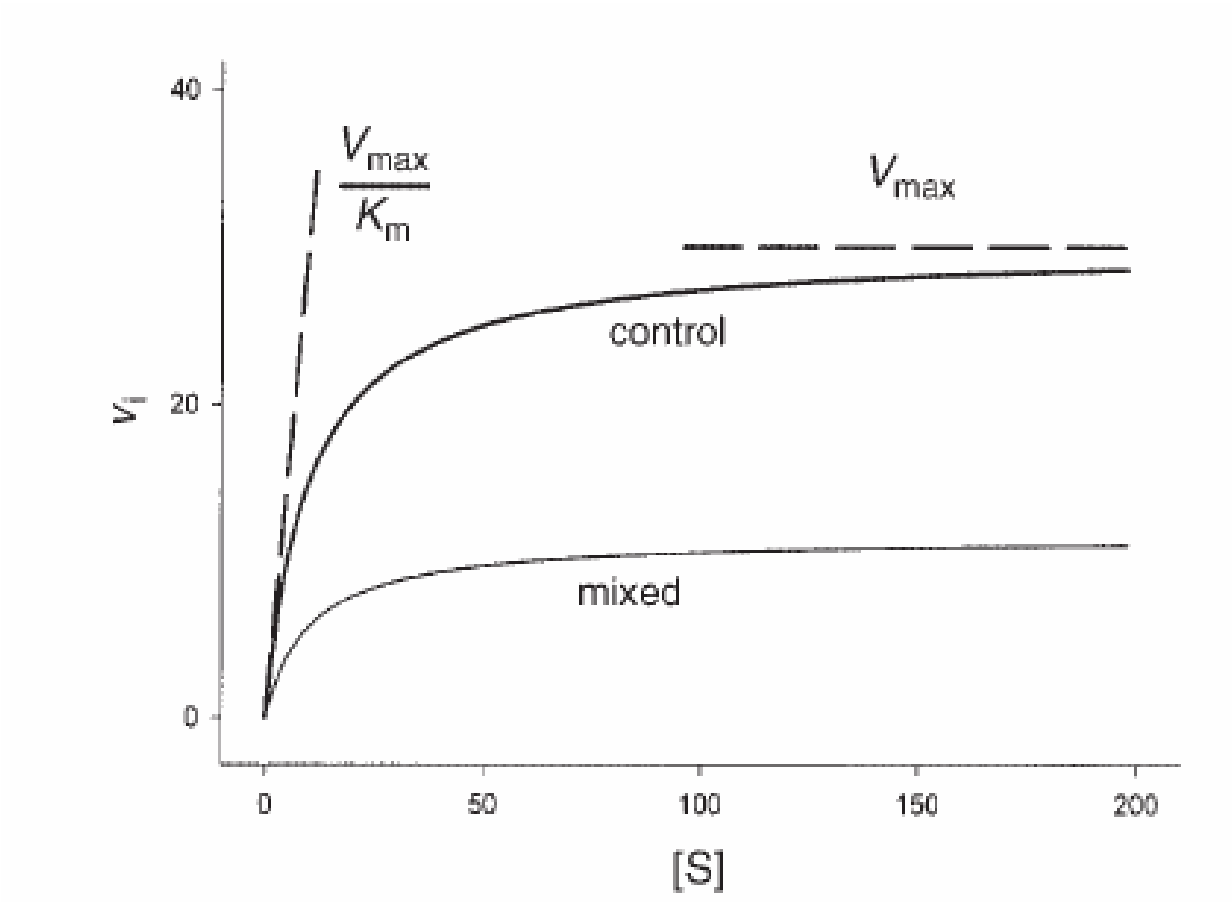


Inhibición Revesible Mixta



(c) Mixed inhibition

$$V_0 = \frac{V_{max}[S]}{\alpha K_m + \alpha'[S]} \qquad \alpha' = 1 + \frac{[I]}{K_I'} \qquad \alpha = 1 + \frac{[I]}{K_I}$$


40
20
0
V_i
$\frac{V_{max}}{K_m}$
V_{max}
control
mixed
0
50
100
150
200
[S]

Si $K_I < K'_I$

$$\frac{1}{V_0} = \left(\frac{\alpha K_m}{V_{max}}\right)\frac{1}{[S]} + \frac{\alpha'}{V_{max}}$$

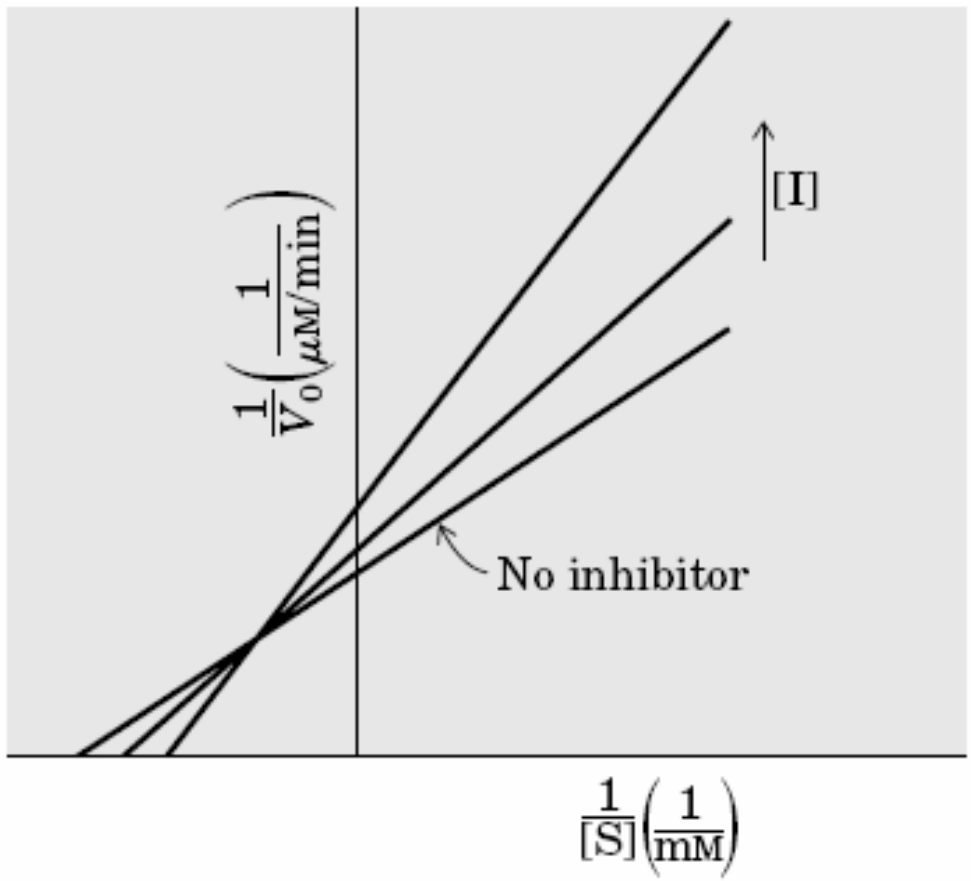
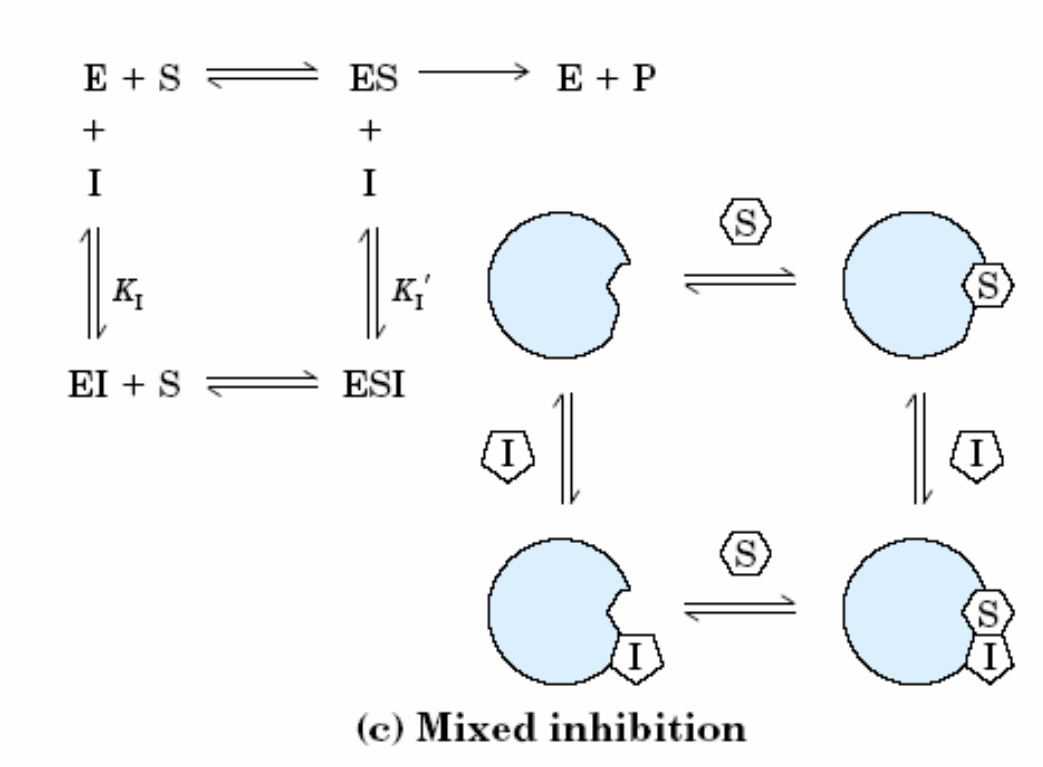


Table 1. Influence of an Enzyme Inhibitor on Kinetic Constant Pairs V_{max}, K_m and V_{max}, V_{max}/K_m

Inhibition Type	Effect of Inhibitor on			
	V_{max}	K_m	V_{max}	V_{max}/K_m
Competitive	—	↑	—	↓
Uncompetitive	↓	↓	↓	—
Mixed	↓	—	↓	↓

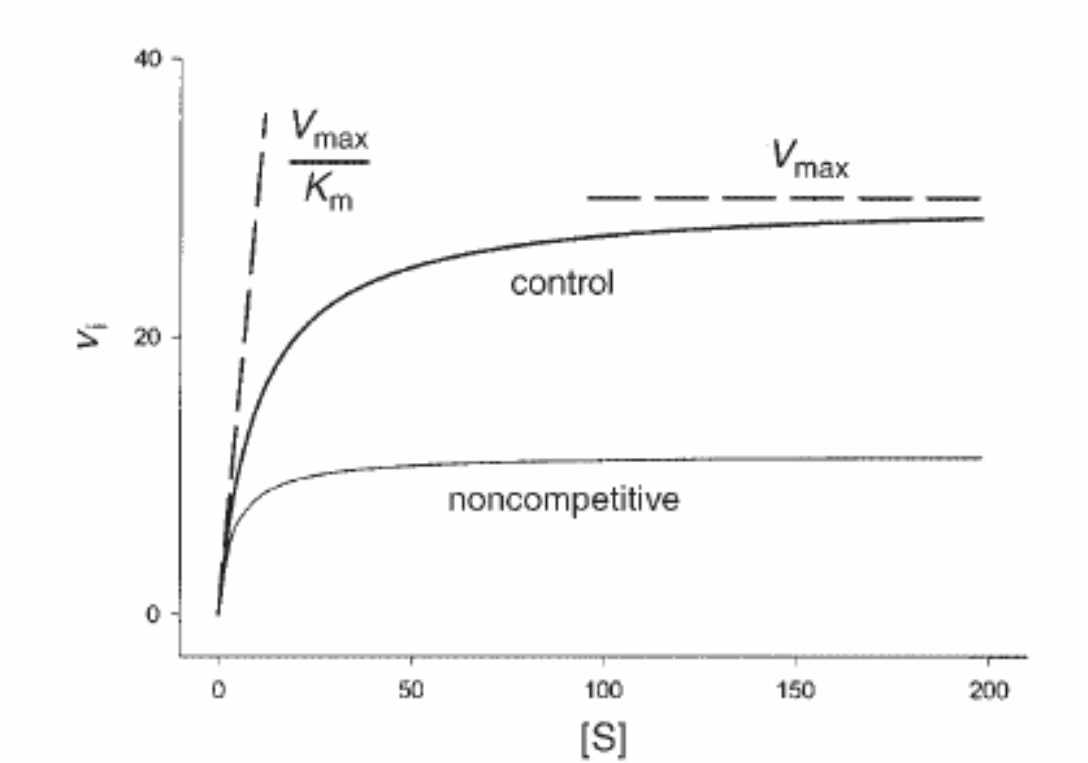
Inhibición No-Competitiva



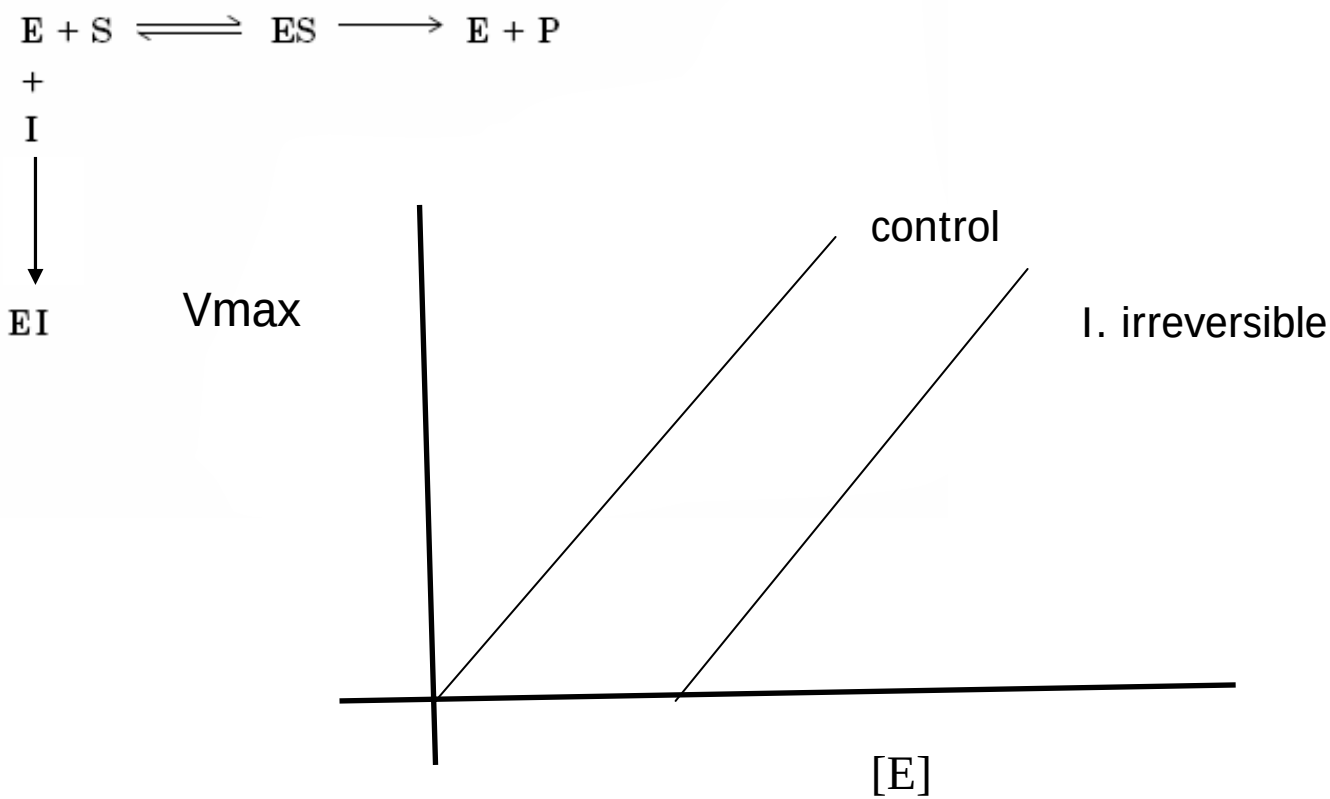
(c) Mixed inhibition

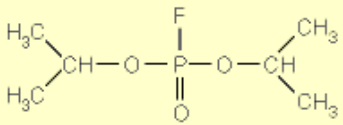
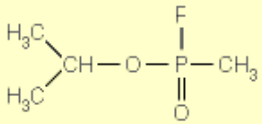
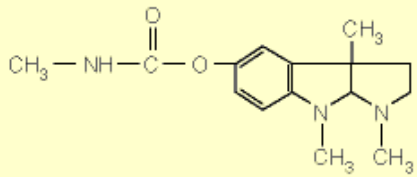
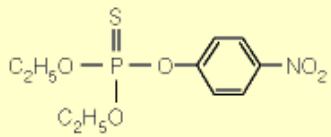
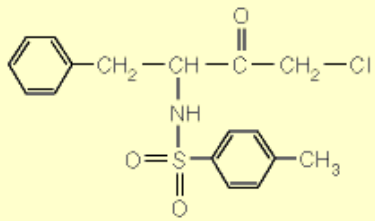
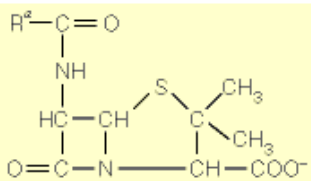
Es no-competitiva si $\alpha = \alpha'$

$$V_0 = \frac{V_{\max}[\mathrm{S}]}{\alpha K_\mathrm{m} + \alpha'[\mathrm{S}]}$$

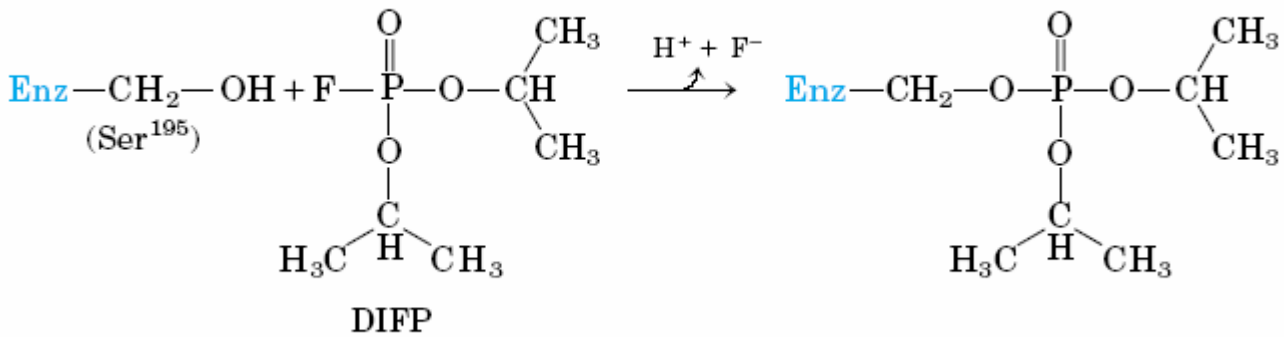


Inhibición Irreversible



Name	Formula[a]	Source	Mode of Action
Cyanide	CN^-	Bitter almonds	Reacts with enzyme metal ions (i.e., Fe, Zn, Cu); respiratory chain enzymes are primary targets (see Chapter 15)
Diisopropyl fluorophosphate (DFP)		Synthetic	Inhibits enzymes with active site serine, including acetylcholinesterase
Sarin		Synthetic (nerve gas)	Like DFP
Physostigmine		Calabar beans	Like DFP
Parathion		Synthetic (insecticide)	Like DFP, but especially inhibitory to insect acetylcholinesterase
N-Tosyl-L-phenyl-alaninechloro-methyl ketone (TPCK)		Synthetic	Reacts with His 57 of chymotrypsin
Penicillin		From *Penicillium* fungus	Inhibits enzymes in bacterial cell wall synthesis (see Chapter 16)

[a]R = variable group; differs on different penicillins.


Enz—CH2—OH + F—P—O—CH
(Ser195)
CH3
CH3
O
O
C
H
H3C
CH3
H+ + F−
Enz—CH2—O—P—O—CH
CH3
CH3
O
O
C
H
H3C
CH3

DIFP