Kerbala University
College of Pharmacy
Dep. of Pharmaceutical Chemistry
Organic Pharmaceutical Chemistry II

By:

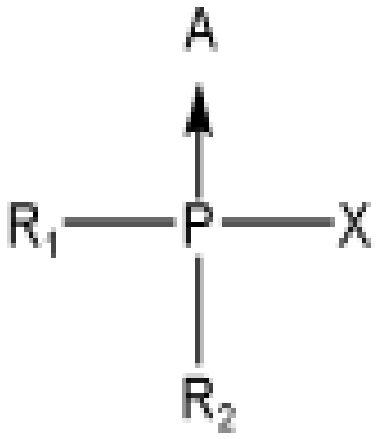
Zaid Al-Obaidi
Assistant Lecturer in Pharmaceutical Chemistry
MSc Pharmaceutical Analysis
Sheffield, UK

Irreversible Cholinesterase Inhibitors:

- Both AChE and BuChE are inhibited irreversibly by a group of phosphate esters that are highly toxic (LD50 for humans is 0.1–0.001 mg/kg).
- These chemicals are nerve poisons and have been used in warfare, in bioterrorism, and as agricultural insecticides.

Organophosphorous esters

- A is usually oxygen or sulfur but may also be selenium. When A is other than oxygen, biological activation is required before the compound becomes effective as an inhibitor of cholinesterases.



where R_1 = alkoxy
R_2 = alkoxyl, alkyl, or tertiary amine
X = a good leaving group
(e.g., F, CN, thiomalate, *p*-nitrophenyl)

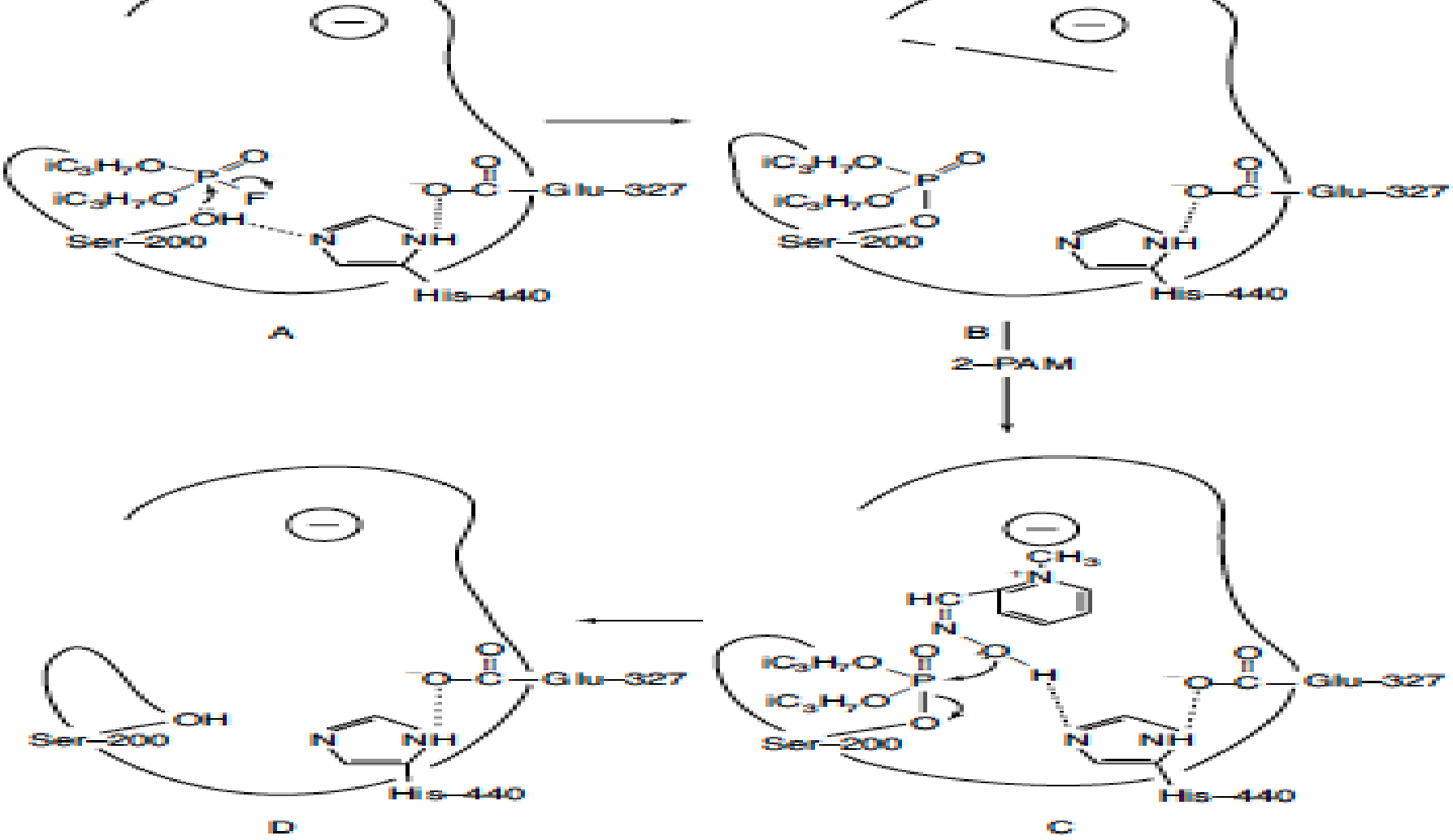
Inhibition of AChE

Inhibition of AChE by organophosphorous compounds takes place in two steps:

1. Association of enzyme and inhibitor, and
2. The phosphorylation step,

Inhibition of AChE

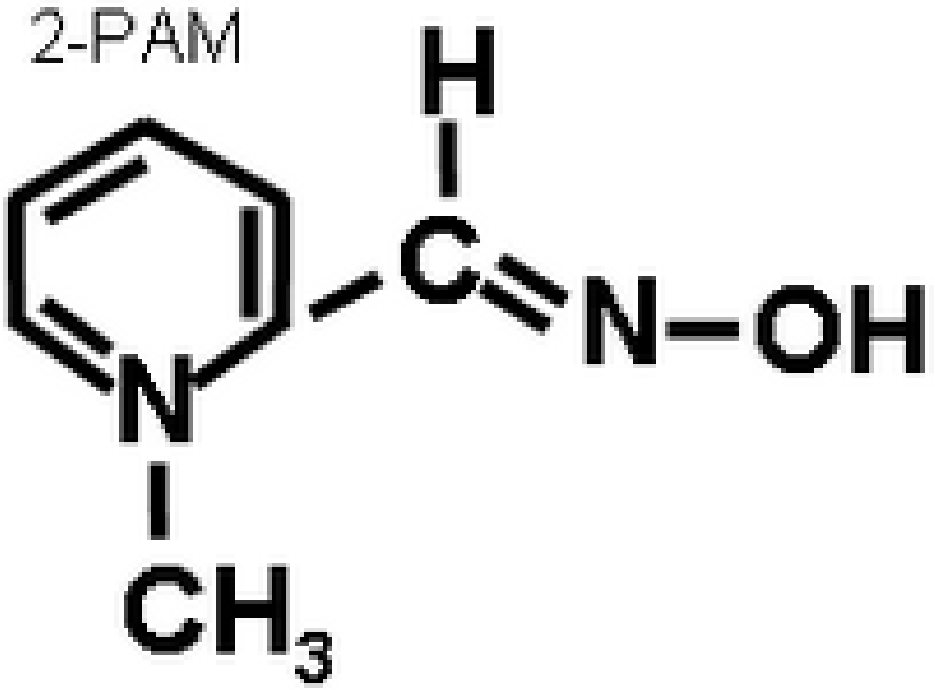
- Insecticides and nerve gases are irreversible inhibitors of cholinesterases by forming a phosphorylated serine at the esteratic site of the enzyme.
- It is possible to reactivate the enzyme if action is taken soon after exposure to these poisons.
- Basically, insecticides must be toxic to insects and safe for humans.



Phosphorylation and reactivation of cholinesterase. A. Phosphorylation of serine by isofluorphate. B. Phosphorylated serine at esteratic site. C. Nucleophilic attack on phosphorylated residue by 2-PAM. D. free enzyme.

Cholinesterase reactivators

- *pyridine-2-aldoxime methiodide (2-PAM).*

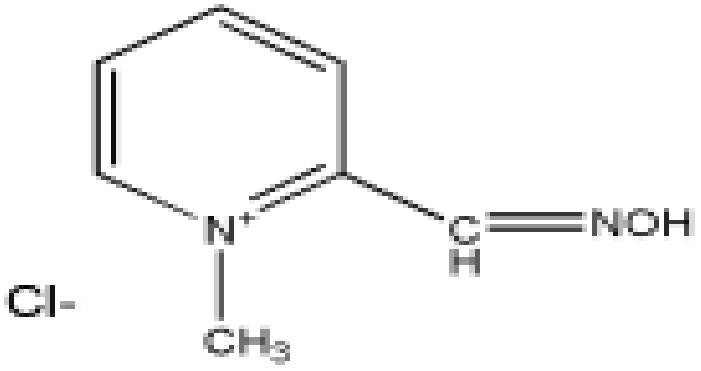


Pralidoxime chloride

- The biological half-life of pralidoxime chloride in humans is about 2 hours, and its effectiveness is a function of its concentration in plasma, which reaches a maximum 2 to 3 hours after oral administration.

Pralidoxime chloride

Pralidoxime chloride, a quaternary ammonium compound, is most effective by intramuscular, subcutaneous, or intravenous administration. Treatment of poisoning by an anticholinesterase will be most effective if given within a few hours.



Pralidoxime Chloride

Cholinergic Blocking Agents

- Anticholinergic action by drugs and chemicals apparently depends on their ability to reduce the number of free receptors that can interact with ACh.

The major chemical types for Cholinergic Blocking Agents

1. Solanaceous alkaloids and synthetic analogs
2. Synthetic aminoalcohol esters
3. Aminoalcohol ethers

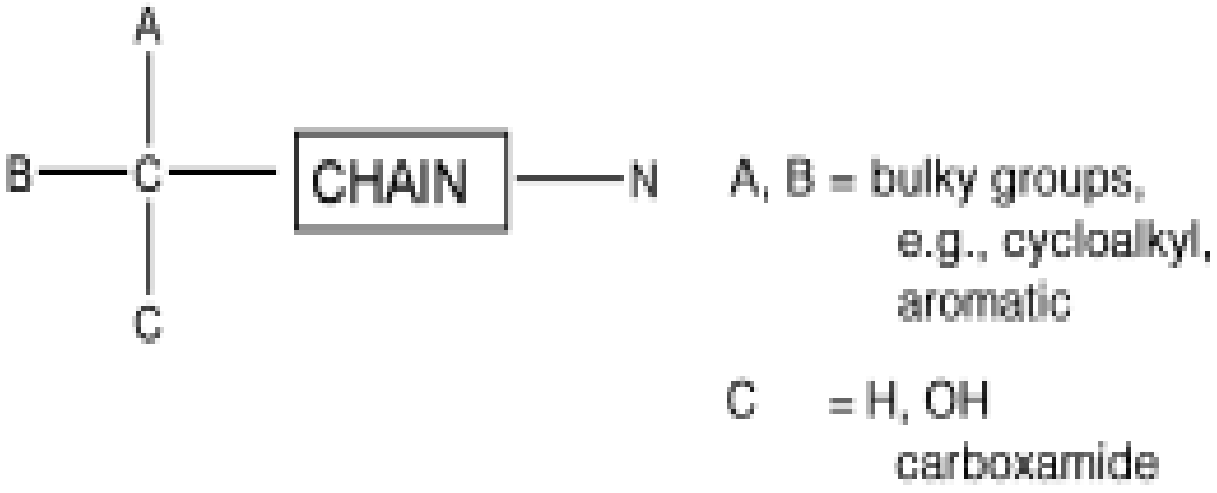
General Notes:

1. The chemical classification of anticholinergics is complicated because some agents act on the ganglia and at the neuromuscular junction in skeletal muscle.

2. Anticholinergics is considered as chemicals having a similarity to ACh but contain additional substituents that enhance their binding to the cholinergic receptor.

General Notes:

3. Anticholinergic agent may contain a quaternary ammonium function or a tertiary amine that is protonated in the biophase to form a cationic species.



4. The nitrogen is separated from a pivotal carbon atom by a chain.

Structure–Activity Relationships

The SAR of the chemical groups:

1. The Cationic Head
2. The Hydroxyl Group
3. The Esteratic Group
4. Cyclic Substitution

The Cationic Head

- Anticholinergics have a point of attachment to cholinergic sites via the cationic head.

- What about tertiary amines?

The Hydroxyl Group

- Is not essential for activity.
- It enhances antimuscarinic activity.
- Assumption of H-bonding is excist.

The Esteratic Group

- An esteratic function is not necessary for activity. Explain why?
- Useful for effective binding.

Cyclic Substitution

- At least one cyclic substituent (phenyl, thienyl, or other) is a common feature in *almost all anticholinergic molecules*

- Use of aromatic acids leads to low activity of these compounds as anticholinergics but potential activity as local anesthetics.

Parasympathetic Postganglionic Blocking Agents

- Also known as:

1. Antimuscarinic.
2. Anticholinergic.
3. parasympatholytic, or
4. cholinolytic drugs.

Therapeutic Actions

- 1. Mydriatic effect: dilation of the pupil of the eye; and cycloplegia, a paralysis of the ciliary structure of the eye, resulting in a paralysis of accommodation for near vision.
- 2. Antispasmodic effect: lowered tone and motility of the GI tract and the genitourinary tract.
- 3. Antisecretory effect: reduced salivation reduced perspiration and reduced acid and gastric secretions.

References:

- **Reference text**: Wilson and Gisvold Textbook of Organic Medicinal and Pharmaceutical Chemistry; Delgado JN, Remers WA, (Eds.); 12th ed., 2011.
- https://www.google.iq/search?q=2-PAM+structure&espv=2&biw=1150&bih=556&source=lnms&tbm=isch&sa=X&ei=cQMpVK6XHqbW7gatiYHwDQ&ved=0CAYQ_AUoAQ#facrc=_&imgdii=_&imgrc=2gKvfr-KqjRhwM%253A%3Bdi8bsg-nrlDNaM%3Bhttp%253A%252F%252Fwww.atsdr.cdc.gov%252Fcsem%252Fcholinesterase%252Fimages%252F2pam_action1.png%3Bhttp%253A%252F%252Fwww.atsdr.cdc.gov%252Fcsem%252Fcsem.asp%253Fcsem%253D11%2526po%253D23%3B489%3B368