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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

- **Local Anesthetics :** SAR of Local anesthetics

Local Anesthetics — Structure Activity Relationship (SAR)

- **Local anesthetics (LAs)** are drugs that **reversibly block nerve conduction** near their site of application, causing **loss of sensation (especially pain)** without loss of consciousness.
- They act by **blocking voltage-gated sodium channels** in the neuronal membrane, preventing the propagation of action potentials.
- Commonly used in **dentistry, surgery, ophthalmology, and minor procedures.**

General Chemical Structure of Local Anesthetics

All local anesthetics share a **common structural pattern** consisting of **three essential components:**

Aromatic Ring — Intermediate Linkage — Amino Group

Component	Function	Example
Aromatic ring (lipophilic part)	Responsible for **lipid solubility** → enhances membrane penetration and potency	Benzene ring or substituted aromatic group
Intermediate chain (linkage)	Determines **type of LA** — *Ester or Amide* linkage → affects stability and metabolism	–COO– (ester), –NHCO– (amide)
Amino group (hydrophilic part)	Ensures **water solubility** and interaction with sodium channels (ionized form binds receptor)	Tertiary or secondary amine

Classification Based on Linkage

Type	Example	Metabolism	Stability	Allergic Potential
Ester type	Procaine, Benzocaine, Tetracaine	Hydrolyzed by plasma pseudocholinesterase	Less stable	Higher
Amide type	Lidocaine, Bupivacaine, Mepivacaine,	Metabolized in liver (amidases)	More stable	Lower

	Prilocaine			

Mechanism of Action

1. Unionized (lipid-soluble) form crosses nerve membrane.
2. Inside the neuron, equilibrium forms between ionized and unionized forms.
3. **Ionized form binds to Na^+ channel receptors** → blocks Na^+ influx.
4. Prevents depolarization → inhibits nerve impulse conduction.
5. Effect is reversible once the drug diffuses away.

Structure–Activity Relationship (SAR) of Local Anesthetics

The **activity, potency, duration, and toxicity** of local anesthetics depend on **modifications** in each structural part:

A. Aromatic (Lipophilic) Group

- Provides **lipid solubility**, essential for membrane penetration.
- **Higher lipophilicity → higher potency and duration of action.**
- **Electron-donating substituents** (e.g., $–CH_3$, $–OCH_3$) on the aromatic ring **increase potency.**
- **Example:** Tetracaine (with butyl group) > Procaine (no substitution).

SAR Notes:

- Lipophilic aromatic ring essential for anesthetic potency.
- Ortho or para substitutions enhance lipid solubility.

B. Intermediate Chain (Ester or Amide Linkage)

- Determines **stability and metabolism**.
- **Ester link (–COO–):** Rapidly hydrolyzed by plasma cholinesterase → shorter duration.
- **Amide link (–NHCO–):** Stable, metabolized in liver → longer duration.

- Increasing **chain length** increases **lipid solubility and potency** up to a certain limit, after which toxicity increases.

SAR Notes:

- Ester linkage → short-acting, unstable.
- Amide linkage → long-acting, stable.
- Optimal chain length → balance between potency and toxicity.

C. Amino (Hydrophilic) Group

- Usually a **tertiary amine** ($-NR_2$), sometimes secondary (–NHR).
- Exists in **ionized and unionized forms** depending on pH.
- The **unionized form** penetrates the membrane, while the **ionized form** binds to the sodium channel receptor inside the neuron.
- **Electron-donating groups** on nitrogen increase activity.
- **Quaternary amines** (permanently charged) are **inactive** (cannot cross membranes).

SAR Notes:

- Tertiary amine required for activity.
- Alters solubility and onset of action (pKa affects ionization ratio).
- Optimum pKa ~7.5–9.0 for effective action.