B.Pharm 5th semester

BP501T. Medicinal Chemistry-II

Unit-V

Antidiabetic agents

Local Anaesthetics

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ANTIDIABETIC AGENTS

Agents which are used in the treatment of diabetes are called as antidiabetic agents. They used to lower the blood sugar level in patients suffering from hyperglycaemia. These are also called as anti-hyperglycaemic agents.

Diabetes mellitus: It is a chronic metabolic disorder which is characterized by hyperglycaemia (increased blood sugar level). The common symptoms are polydipsia (excess thirst), polyphagia (excess hunger), and polyurea (excess urination). The classification of diabetes has been presented in Table-1.

Table-1: Classification of diabetes mellitus

Type-1 (IDDM)	**Type-2 (NIDDM)**
Insulin dependent diabetes mellitus Juvenile onset diabetes mellitus Occurs in children	Non-insulin dependent diabetes mellitus Adult onset diabetes mellitus Occurs in adults
Pancreatic β-cells are destroyed No insulin secretion	Less insulin secretion or insulin resistance (cells don't respond to insulin)
Treatment: insulin injection	Treatment: oral hypoglycaemic agents

Insulin: It is a peptidic hormone secreted by β-cells of pancreas. It was discovered by Banting & Best in 1921. It regulates metabolism of carbohydrate, lipids and proteins. It decreases blood sugar level by decreasing gluconeogenesis, increasing glucose uptake and increasing glycogen synthesis.

Insulin structure: Its full structure was elucidated by Sanger in 1956. It is a polypeptide hormone with a molecular weight of 6000 Da. Inside body, the inactive pro-insulin is converted into active insulin which is composed of 2 chains (A & B). A chain has 21 amino acid residues, whereas B chain has 30 amino acid residues and both the chains are attached to each other by 2 disulphide (-S-S-) bonds. The structure of insulin has been depicted in Figure-1.

Sources of insulin: Bovine, Porcine, Recombinant human insulin

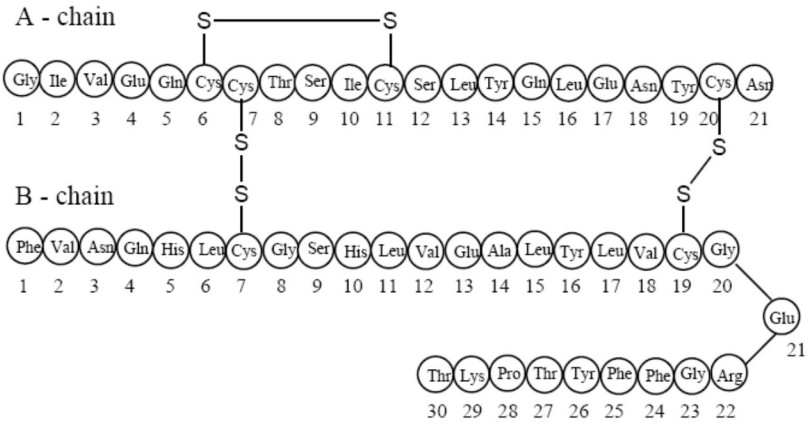


Figure-1: Structure of insulin

Insulin preparations: Various insulin preparations has been classified and presented in Table-2, according to their onset of action.

Table-2: Classification of various insulin preparations

Short acting	Intermediate acting	Long acting
Regular	Isophane (NPH)	Protamine zinc
Lispro	Lente	Ultra Lente
Insulin zinc	Biphasic insulin aspart	Insulin glargine
Insulin aspart		Insulin detemir
		Insulin degludec

Regular insulin: Also called as neutral or soluble insulin. Rapid acting with 0.5-1 hr duration of action.

Lispro insulin: Rapid acting with 6-8 hr duration of action. In the carboxyl terminal of B-chain, lysine and proline residues are reversed. It is a recombinant human insulin.

Insulin Zinc: It is a suspension of insulin and zinc chloride, having 6-8 hr duration of action.

Insulin aspart: Synthetic form of human insulin where a single amino acid, proline (B-28) is replaced by aspartic acid. It has 3-5 hr duration of action.

Isophane insulin: Also called as Neutral Protamine Hagedorn (NPH) insulin. It is intermediate acting with 18-24 hr duration of action. It is composed of zinc, protamine, and regular insulin.

Lente insulin: It is intermediate acting with 18-24 hr duration of action. It is composed of acetate buffer, zinc, and regular insulin.

Biphasic insulin aspart: It is intermediate acting with 24 hr duration of action. It is composed of 30% soluble insulin aspart and 70% protamine bound insulin aspart.

Protamine zinc insulin: It is composed of insulin, zinc chloride, and protamine. It has duration of action upto 36 hrs.

Ultra lente insulin: It contains 65% of lente insulin, having duration of action upto 36 hrs.

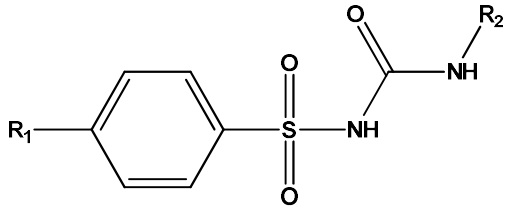
Insulin glargine: It is obtained by addition of two arginine residues in B-chain carboxy terminal and by replacement of asparagine with glycine in A-21 position of human insulin. It has duration of action upto 24 hrs.

Insulin detemir: It is obtained by addition of a fatty acid (myristic acid) to lysine residue in B-29 position of human insulin. It has duration of action upto 24 hrs.

Insulin degludec: It is obtained by addition of hexadecanedioic acid to lysine residue in B-29 position of human insulin. It has duration of action upto 24 hrs.

Oral hypoglycaemic agents

Sulfonyl ureas: These are the first class of oral hypoglycaemic agents used for treatment of diabetes. They are also called as insulin secretagogues.



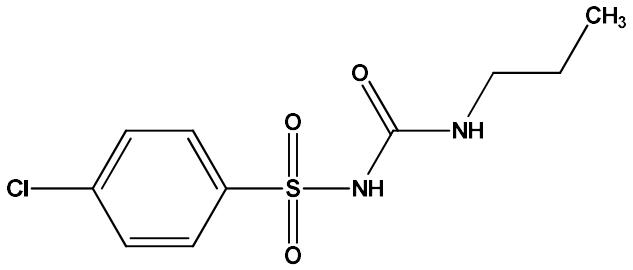
Mechanism of action- They bind to the sulfonyl urea receptors present in pancreatic β-cells. It leads to closure of ATP-sensitive K^+ channels and depolarises the β-cell membrane. Then it opens voltage gated Ca^{+2} channels and stimulates β-cells to secrete more insulin.

1st generation- **Chlorpropamide**, **Tolbutamide**, Acetohexamide

2nd generation- Glibenclamide, **Glipizide**, Glyburide

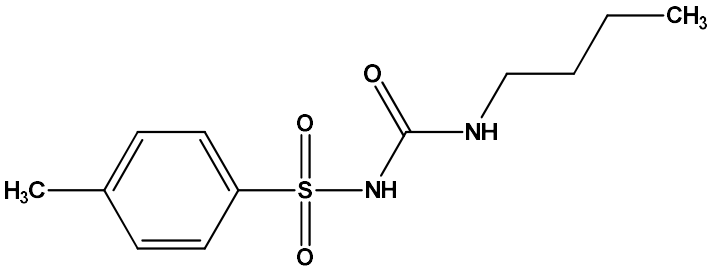
3rd generation- **Glimepiride**

Chlorpropamide- 1-(p-chlorophenyl)-sulfonyl-3-propyl urea



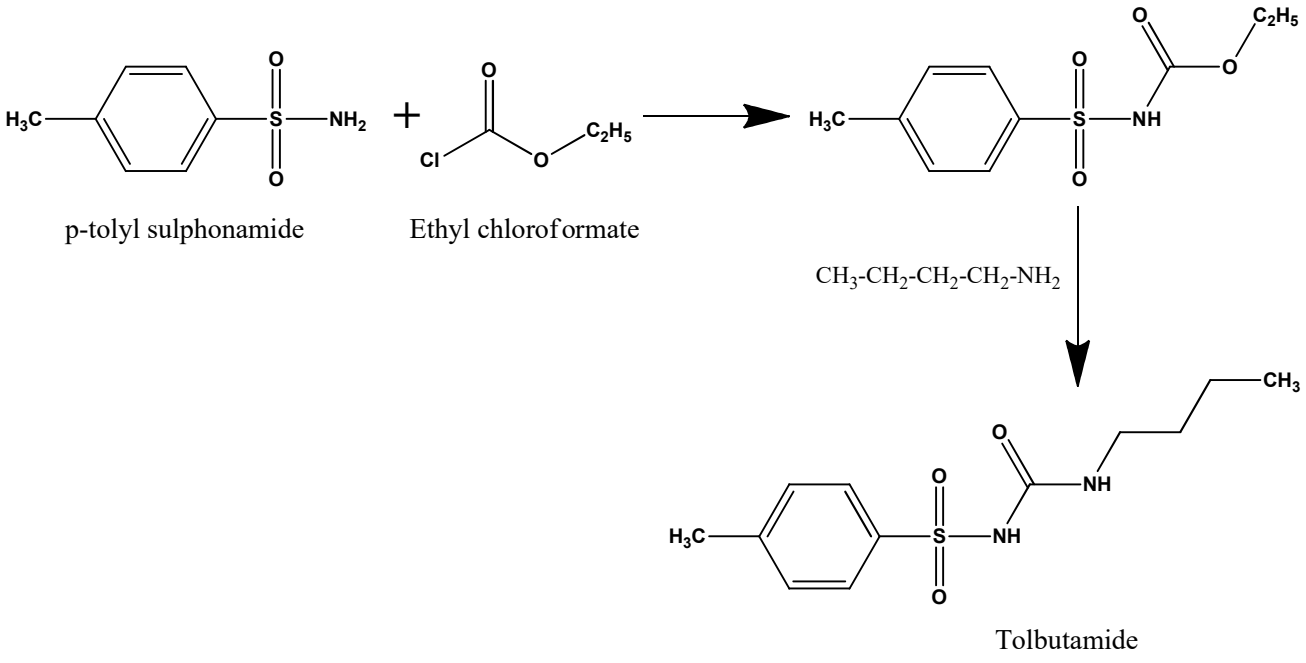
More resistant to metabolism than tolbutamide. So, it has longer duration of action. Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Tolbutamide- 1-(p-tolyl)-sulfonyl-3-butyl urea



It is the least potent and short acting sulfonyl urea. It is safely used for treatment of type-2 diabetes in elderly patients and those prone to hypoglycemia.

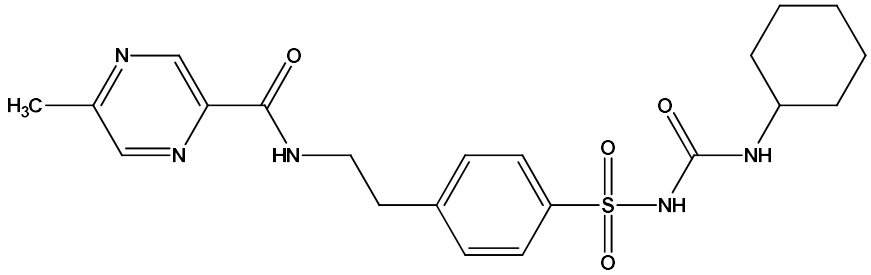
Synthesis:



p-tolyl sulphonamide Ethyl chloroformate

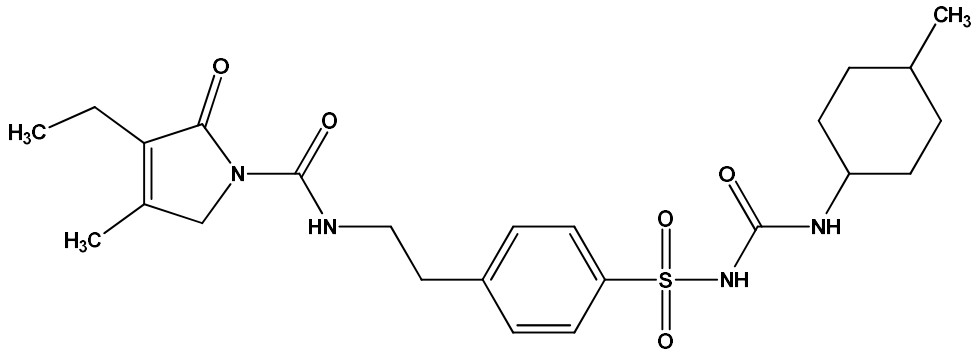
Tolbutamide

Glipizide- 1-cyclohexyl-3-[p-[2-[5-methyl pyrazin-2-yl]carboxamido]ethyl]phenyl]-sulfonyl urea



It has quick onset of action. Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Glimepiride- 1-[p-[2-[3-ethyl-4-methyl-2-oxo-3-pyrrolin-1-carboxamido]-ethyl]-phenyl] sulfonyl-3-(p-methyl cyclohexyl) urea

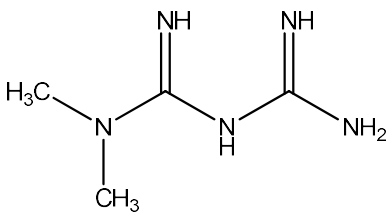


It's a long acting potent sulfonylurea. Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Biguanides: Phenformin, Metformin, Butformin

Mechanism of action- They reduce hepatic gluconeogenesis, decrease intestinal absorption of glucose, increase glucose uptake and utilization to decrease the blood sugar level. As they improve the insulin resistance, they are also known as insulin sensitizers.

Metformin- N,N-dimethyl biguanide

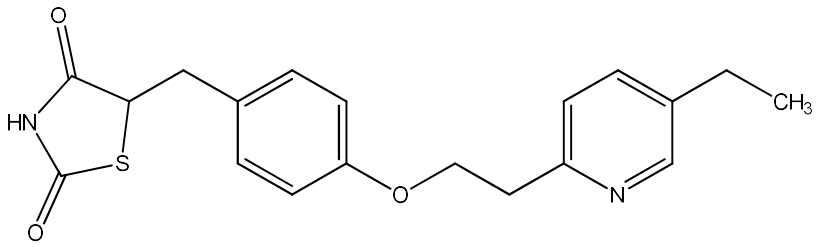


Used for treatment of type-2 diabetes in obese patients. Also used for treatment of polycystic ovarian syndrome.

Thiazolidinediones: Pioglitazone, Rosiglitazone

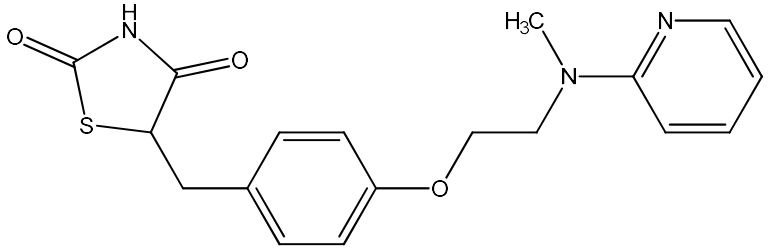
Mechanism of action- They binds to and stimulates Peroxisome Proliferator Activated Receptor-γ (PPAR-γ), due to which they are also known as PPAR- γ agonists. They increase the expression of GLUT-1 & GLUT-4 receptors on cell surface to increase glucose uptake. They reduce insulin resistance and hepatic gluconeogenesis. They decrease the post-prandial glucose level and also HbA1c level.

Pioglitazone- 5-[4-[2-[5-ethyl pyridin-2-yl]ethoxy]benzyl]thiazolidin-2,4-dione



Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Rosiglitazone- 5-[4-[2-[N-methyl-pyridin-2-yl]amino]ethoxy]benzyl]thiazolidin-2,4-dione



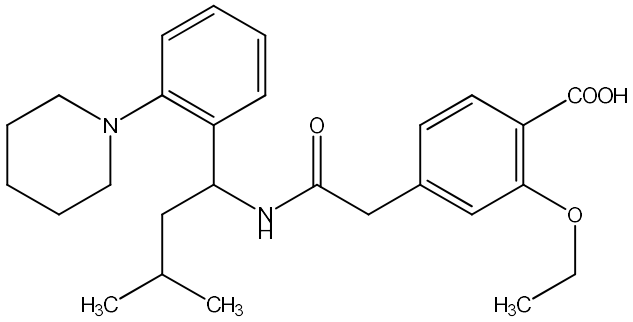
Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Meglitinides: Repaglinide, Nateglinide

Mechanism of action- Same as that of sulfonylureas. They bind to the sulfonyl urea receptors present in pancreatic β-cells. It leads to closure of ATP-sensitive K^+ channels and depolarises the β-cell membrane. Then it opens voltage gated Ca^{+2} channels and stimulates β-cells to secrete more insulin. These agents are also known as insulin secretagogues.

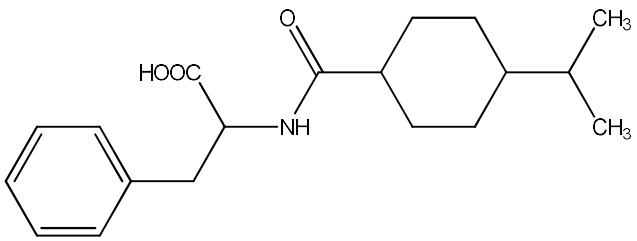
Repaglinide- 2-ethoxy-4-[2-[3-methyl-1-[2-(piperidin-1-yl)phenyl]butylamino]-2-oxo-ethyl] benzoic acid

It induces fast onset and short-lasting insulin secretion. Administered before each meal to control post-prandial hyperglycaemia.



Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Nateglinide- N-[{4-(propan-2-yl)cyclohexyl}carbonyl]-D-phenylalanine

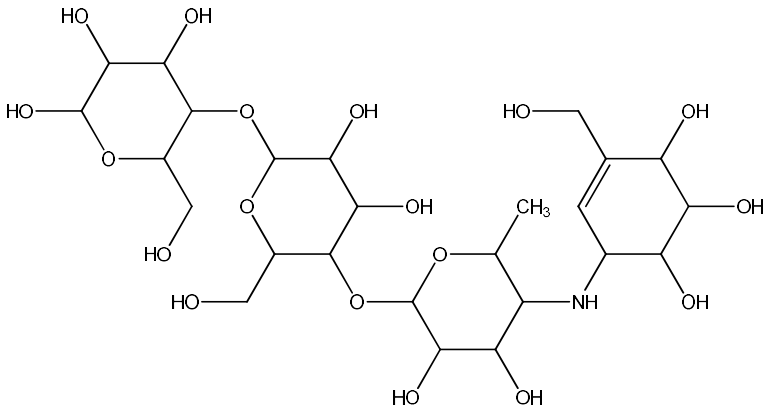


It's a phenylalanine derivative. Causes faster onset and short-lasting insulin secretion than repaglinide. Used as oral hypoglycaemic agent for treatment of type-2 diabetes.

Glucosidase inhibitors: Acarbose, Voglibose

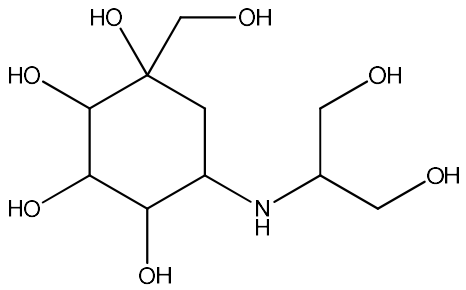
Mechanism of action- They delays the absorption and metabolism of carbohydrates by inhibiting α-glucosidase enzyme found in the brush border epithelium of small intestine. α-glucosidase helps in hydrolysing polysaccharides and oligosaccharides into monosaccharides and helps in their absorption. Flatulence and loose motion are the common side effects of this class of drugs. These drugs produce anti-hyperglycaemic effect but do not produce hypoglycaemia.

Acarbose- It is a complex oligosaccharide which is isolated from cultures of actinoplanes (a bacteria). It is composed of acarviosin moiety and a maltose moiety.



Used for treatment of type-2 diabetes.

Voglibose- 5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cylcohexan-1,2,3,4-tetraol It is obtained from validamycin-A (metabolic product of Streptomyces hygroscopius). It is a valiolamine derivative.



Used for treatment of type-2 diabetes.

References:

1. Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry.
2. Text book of Medicinal Chemistry- S. N. Pandeya
3. William Foye's Principles of Medicinal Chemistry.

LOCAL ANAESTHETICS

These are agents which upon topical application or local injection cause reversible loss of pain sensation in a restricted area of the body. They act by blocking both sensory and motor nerve conduction to produce temporary loss of sensation without loss of consciousness.

Mechanism of action- These drugs reversibly prevent the generation and propagation of impulses in all excitable membranes including nerve fibre by stabilising the membrane. Local anaesthetics block the nerve conduction by decreasing the entry of Na^+ during action potential. They interact with a receptor situated within the voltage sensitive Na^+ channel and raise the threshold of Na^+ channel opening. Therefore, Na^+ can't enter into the cell in response to an impulse which prevents depolarisation. Thus, action potential is not generated.

This action affecting the depolarisation which leads to failure of conduction of impulse without affecting the resting membrane potential (RMP) is known as membrane stabilising effect.

Uses- These are used for i) temporary relief of localised pain

ii) itching due to minor burns, insect bites & allergy

iii) minor surgery and in dentistry

Methods or sites of administration:

1. Surface anaesthesia- Applied directly to the mucosal surfaces of nose, mouth, bronchial tree, oesophagus & genito-urinary tract
2. Infiltration anaesthesia- It is injected under the skin in the area of operation
3. Nerve block anaesthesia- It is injected around the nerve trunks or plexuses. Used for peripheral anaesthesia.
4. Spinal anaesthesia- It is injected into the sub-arachnoid space so that the local anaesthetic mixes with the spinal fluid. Lower abdomen and hind limbs are paralysed. Used for operation in lower limbs, pelvis, abdomen, prostatectomy, fracture setting, obstetric procedures, caesarean surgery etc.
5. Epidural anaesthesia- It is injected into a narrow spinal dural space containing semiliquid fat where the nerve roots pass.

Ideal characteristics of Local anaesthetics:

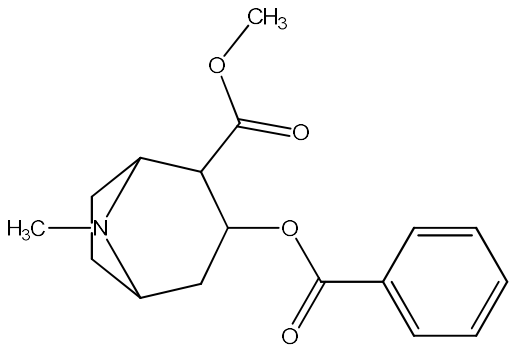
1. Non-irritating to the tissue.
2. Doesn't cause damage to the nerve structure.
3. Rapid onset & short duration of action.
4. Low systemic toxicity.
5. Must be effective whether injected or topically applied.

CLASSIFICATION

1. Benzoic acid esters- Cocaine, Hexylcaine, Meprylcaine, Cyclomethycaine, Piperocaine
2. p-Aminobenzoic acid esters- Benzocaine, Butamben, Procaine, Butacaine, Propoxycaine, Tetracaine, Benoxinate
3. Amide/Anilide derivatives- Lignocaine/Lidocaine/Xylocaine, Mepivacaine, Prilocaine, Etidocaine
4. Miscellaneous agents-
   Amidine derivative- Phenacaine
   Carbamate derivative- Diperodon
   Quinoline derivative- Dibucaine

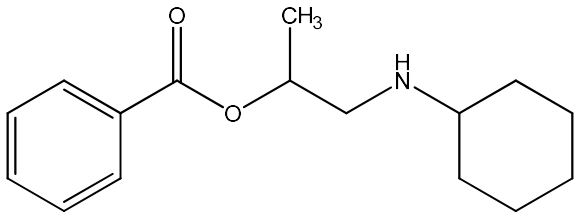
Cocaine- 2-methoxy carbonyl-tropan-3-yl-benzoate

It is a natural alkaloid, isolated from the leaves of Erythroxylon coca. It is the first drug to be used as local anaesthetic.



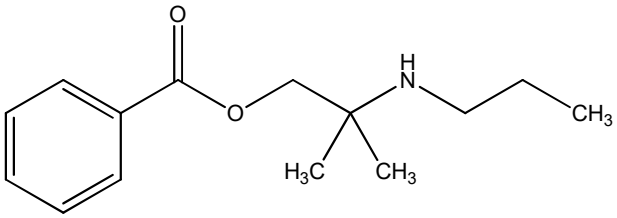
Used as anaesthesia for eye, ear, nose & throat.

Hexylcaine- 1-cyclohexyl amino-propan-2-yl-benzoate



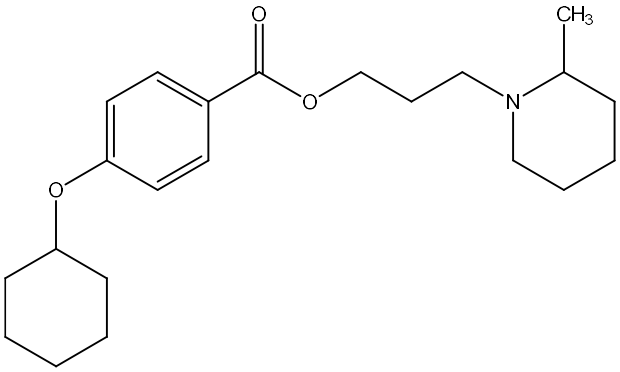
Used as surface anaesthesia.

Meprylcaine- 2-methyl-2-(propylamino) propyl benzoate



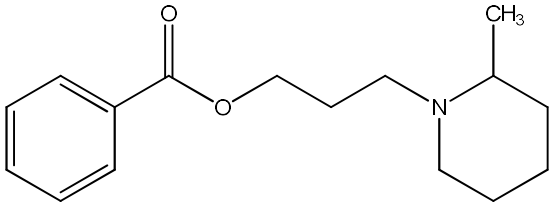
Used for dental anaesthesia.

Cyclomethycaine- 3-(2-methyl-1-piperidinyl) propyl-p-(cyclohexyloxy) benzoate



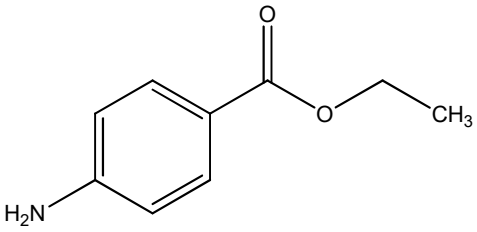
Used as topical anaesthesia.

Piperocaine- 3-(2-methyl-1-piperidinyl) propyl benzoate



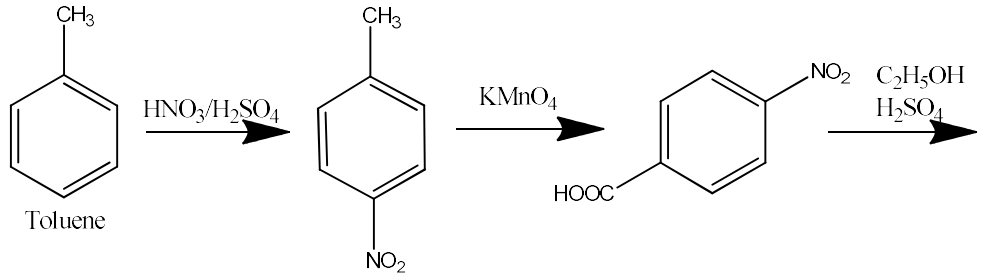
Used as ocular anaesthesia.

Benzocaine- Ethyl-p-aminobenzoate

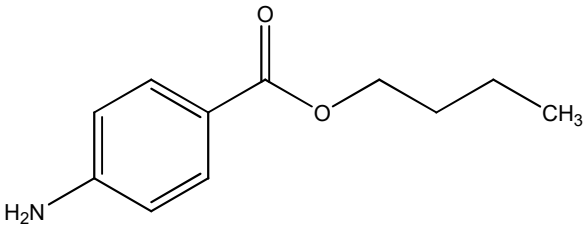


Used to reduce pain due to sunburn, teeth pain, piles, vaginal/rectal irritation.

Synthesis-



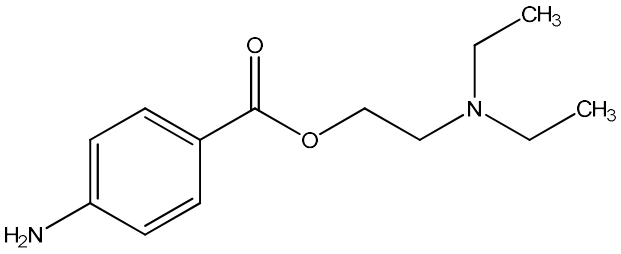
Butamben- Butyl-p-aminobenzoate



Used as surface anaesthesia for relief of pain and itching associated with anorectal disorders.

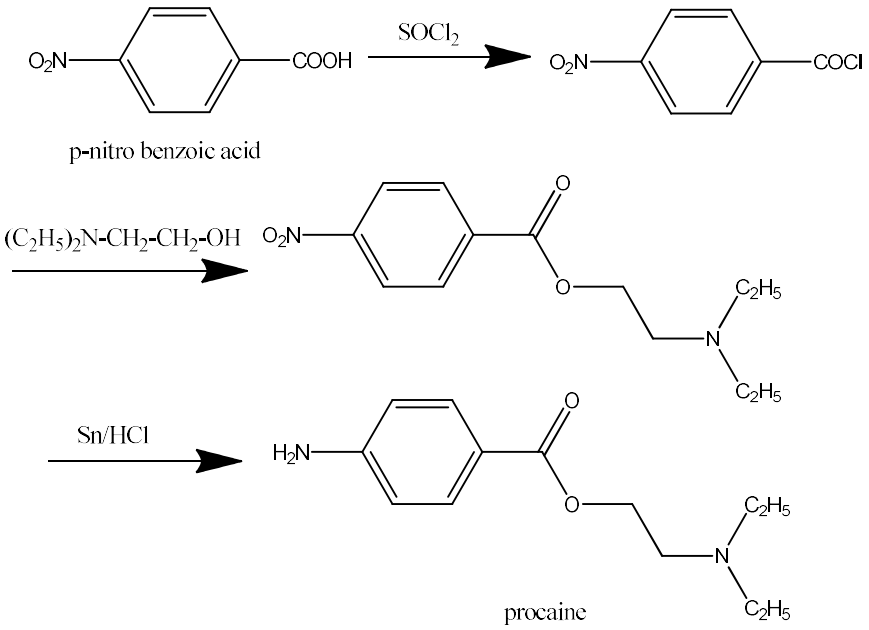
Procaine- Also called as novocaine.

2-(diethylamino) ethyl-p-amino benzoate

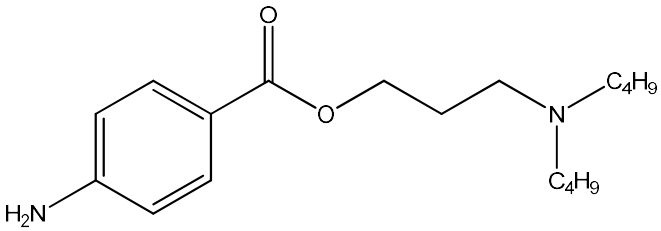


Used as infiltration, nerve block and spinal anaesthesia. It is a vassodilator. So, adrenaline is added to it to retard the absorption and prolong its duration of action.

Synthesis-

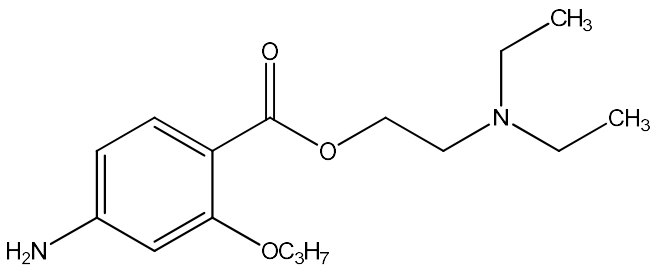


Butacaine- 3-(dibutylamino) propyl-p-amino benzoate



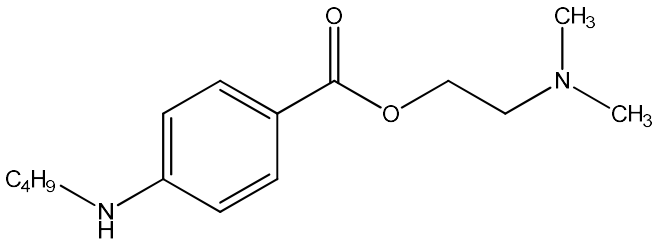
Used as topical anaesthesia.

Propoxycaine- 2-(diethylamino)ethyl-2'-propoxy-4'-amino benzoate



Used as dental anaesthesia.

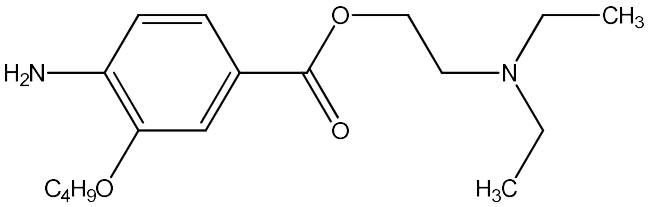
Tetracaine- 2-(dimethylamino)ethyl-p-(butylamino) benzoate



Used as topical and spinal anaesthesia.

Benoxinate- Also called as oxybuprocaine.

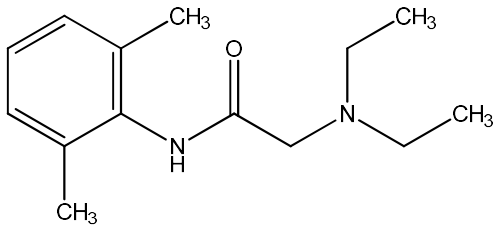
2-(diethylamino)ethyl-3'-butoxy-4'-amino benzoate



Used in ophthalmology.

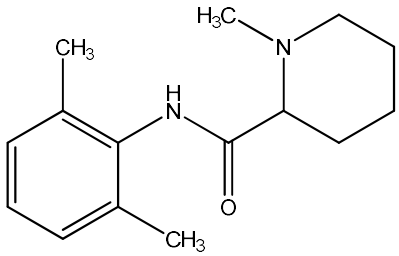
Lignocaine- Also called as Lidocaine or Xylocaine.

2-(diethylamino)-N-2,6-(dimethyl phenyl) acetamide



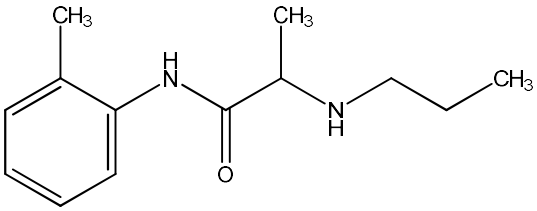
Used as infiltration, nerve block and surface anaesthesia. Also used for dental anaesthesia.

Mepivacaine- 1-methyl-N-(2,6-dimethyl phenyl)piperidin-2-carboxamide



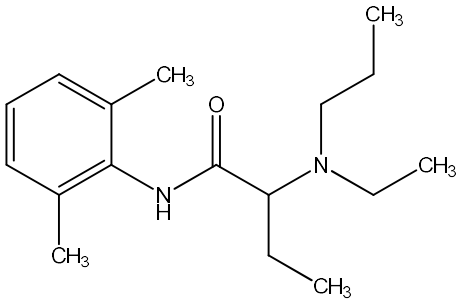
Used as epidural and nerve block anesthesia. Also used in dental procedures.

Prilocaine- N-(2-methyl phenyl)-2-propylamino propenamide



Used for infiltration, nerve block anaesthesia. A mixture of prilocaine and lignocaine (eutectic mixture) is used as topical dosage form.

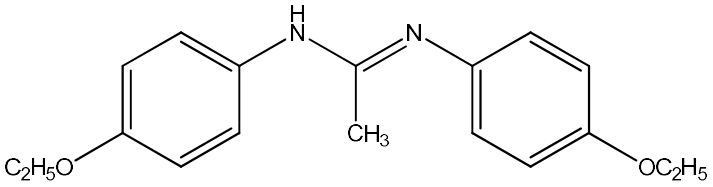
Etidocaine- N-(2,6-dimethyl phenyl)-2-(ethyl propyl amino)-butanamide



Used along with adrenaline for infiltration, epidural and nerve block anaesthesia.

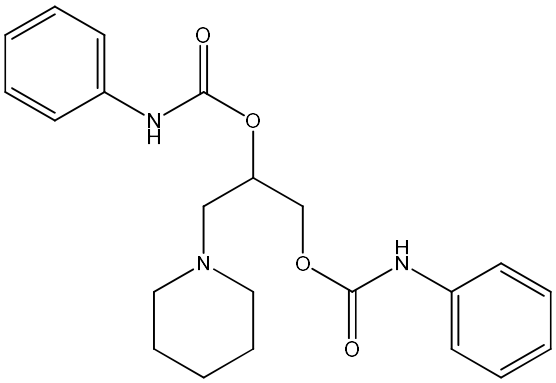
Phenacaine- Also known as holocaine.

N,N’-bis(p-ethoxyphenyl)ethan imidamide



Used in ophthalmology.

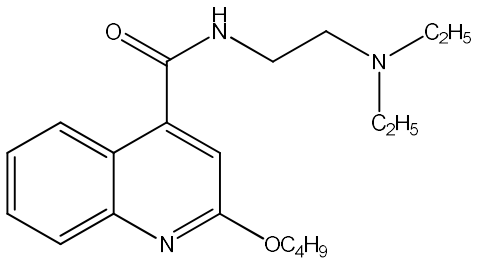
Diperodon- 3-(1-piperidinyl)-1,2-propandiol-bis-(phenyl carbamate)



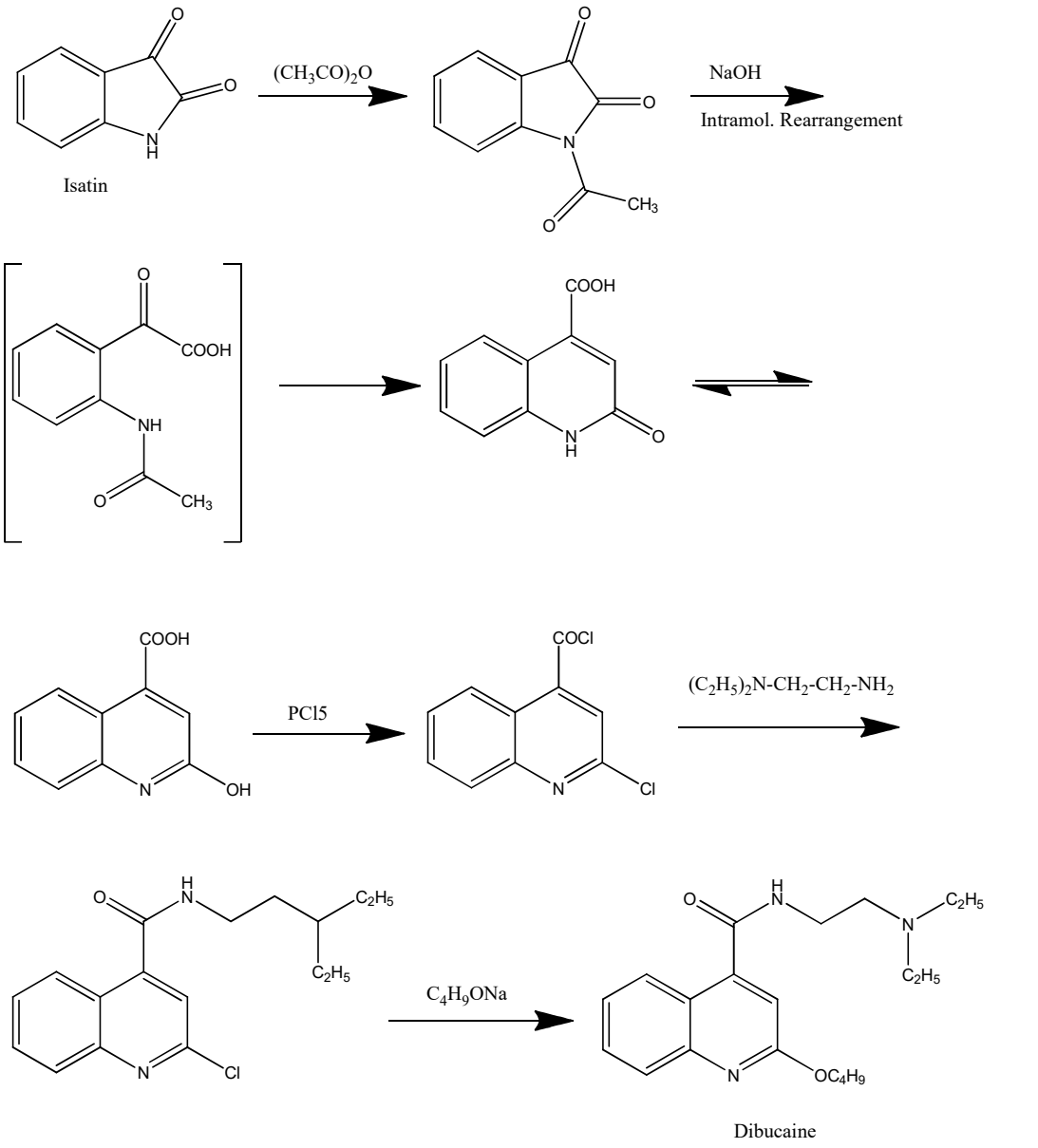
Used as topical anaesthetic.

Dibucaine- Also known as Cinchocaine. It is the most potent, most toxic, longest acting local anaesthetic.

N-(2-diethyl amino ethyl)-2-butoxy-quinolin-4-carboxamide



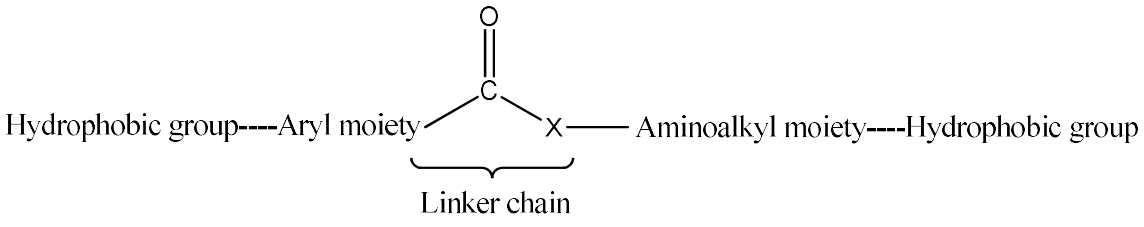
Synthesis-



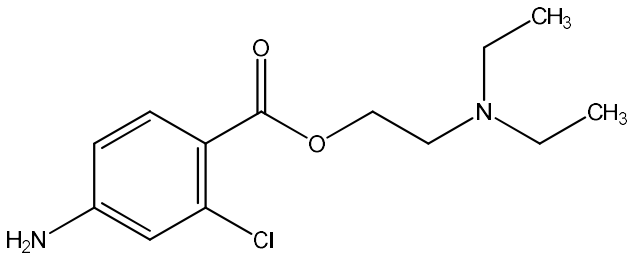
Dibucaine is used as surface anaesthetic on less delicate mucous membrane like anal canal. Can be used parenterally for spinal anaesthesia only.

SAR OF LOCAL ANAESTHETICS

1. Ester derivatives-

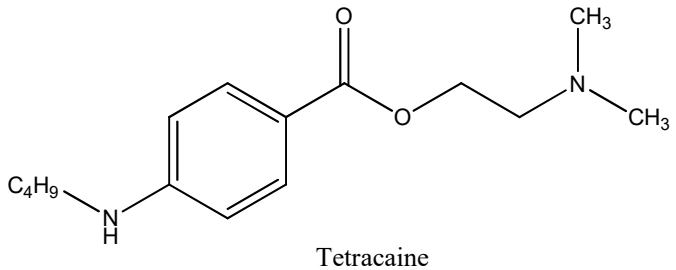


i) Presence of electron withdrawing group at 2nd position of aryl moiety provides rapid onset of action. Eg- Chloroprocaine has more rapid onset of action because it is 4 times faster hydrolysed than procaine.



Chloroprocaine

ii) Presence of non-polar groups on aromatic N atom imparts greater lipid solubility and good absorption. Eg- Tetracaine



Tetracaine

iii) Aryl group- It is attached directly to the carbonyl moiety.

- Conjugation of aromatic moiety with carbonyl group enhances local anaesthetic activity.
- Substituents like amino, alkoxy, alkyl amino groups increase the electron density on carbonyl oxygen and enhances the activity.
- Presence of alkyl group in between aryl and carbonyl results in inactive compounds.

iv) Bridge X- X may be C, O, N, or S

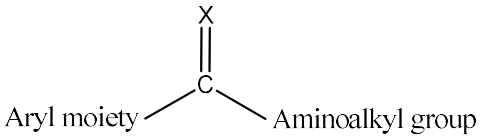
Anaesthetic potency: S > O > C > N

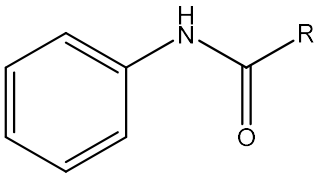
Amides (X=N) are resistant to metabolic hydrolysis.

v) Amino alkyl group- Tertiary amines have longer duration of action, but they are more irritating than primary amines. Alkyl groups also influence the lipid solubility.

2. Amide derivatives-

These are essentially anilide derivatives having the general structure:





Anilide

Aryl group- Phenyl group is attached to the sp^2 'C' atom through nitrogen bridge.

Substitution of phenyl group with a methyl in 2 or 6 position enhances the activity. It provides steric hindrance to hydrolysis and also increases the coefficient of distribution.

The amide bond is more stable to hydrolysis than esters.

Substituent X- X may be C (eg- isogramine), O (eg- lidocaine), N (eg- phenacaine)

Amino alkyl group- It is the hydrophilic part which helps in salt formation.

1° and 2° amines are more irritating than 3° amines.

References:

1. Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry.
2. Text book of Medicinal Chemistry- S. N. Pandeya
3. William Foye's Principles of Medicinal Chemistry.