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Sympathomimetic agents

Presented By;-

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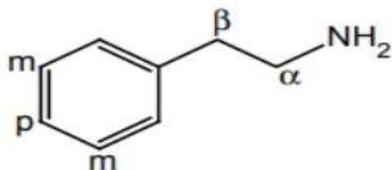
Specialization:- Pharmaceutical Chemistry

Sympathomimetic Agents

- ❑ **Sympathomimetics agents** are drugs that mimic the actions of the sympathetic nervous system by activating adrenergic receptors (α and β receptors).
- ❑ They either directly stimulate receptors or indirectly increase the levels of norepinephrine/epinephrine at synapses.
- ❑ These agents are used in medicine for various conditions, including asthma, COPD, low blood pressure, narcolepsy, ADHD, and nasal decongestion.

SAR of Sympathomimetic agents

Here is the β -Phenylethylamine (β -PEA) parent structure



β -Phenyl ethylamine

1. Aromatic Ring Substitution

A. Catechol group (3',4'-dihydroxy)

- Required for **maximum α and β activity**
- Rapid metabolism by **COMT**
- Poor oral bioavailability

Examples: Epinephrine, Norepinephrine, Isoproterenol

B. Non-catechol substitution

- Replacing catechol OH groups \downarrow COMT metabolism \rightarrow **longer duration, oral activity**

Examples: Salbutamol, Terbutaline

C. Meta/para substitutions

- 3',5'-OH \rightarrow increases **β_2 selectivity**

Example: Salbutamol

2. Side Chain (β -Carbon) Modification

A. β -OH group presence

- Enhances **α and β receptor affinity**
- Increases **direct-acting activity**

B. Absence of β -OH

- Increases **lipophilicity** \rightarrow better CNS penetration

- More **indirect action**

Example: Amphetamine

3. α -Carbon Substitution

A. α -CH₃ substitution

- Protects from **MAO metabolism**
- Increases **oral activity**

Example: Amphetamine, Ephedrine

B. No α -substitution

- Rapid MAO metabolism

Example: Norepinephrine, Epinephrine

4. Amine (Nitrogen) Substitution

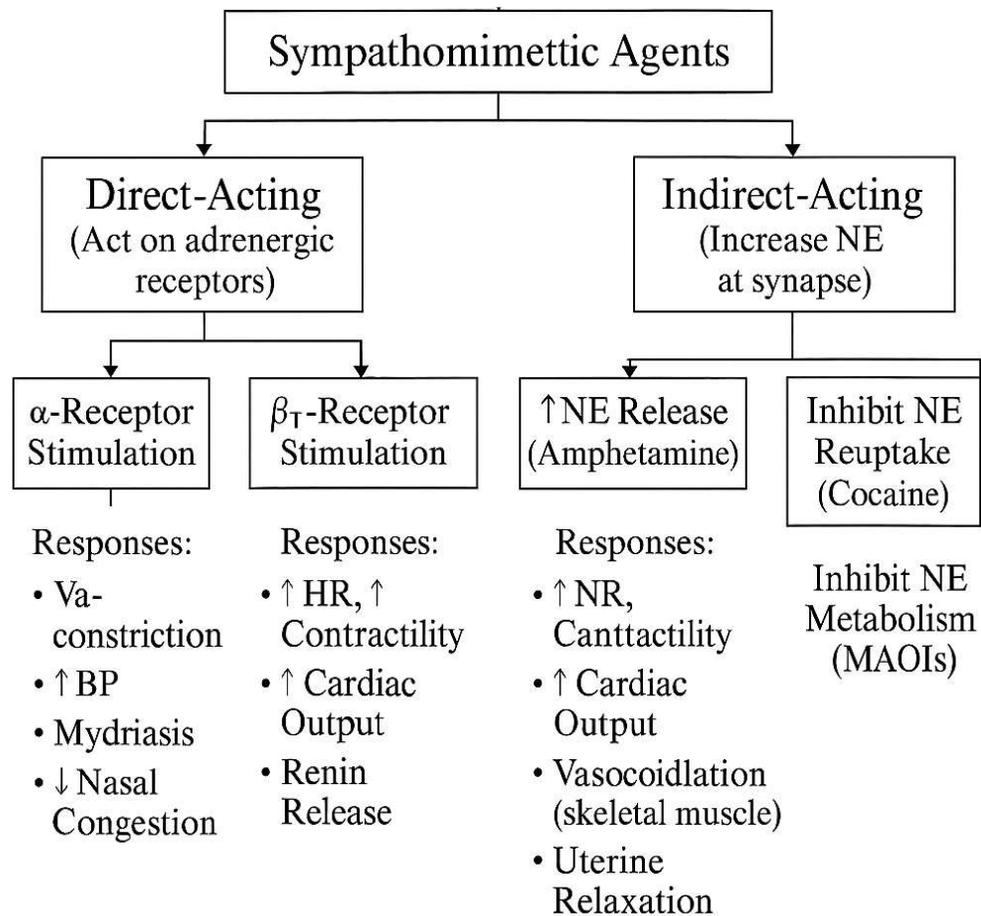
Effect of alkyl groups on N-atom

N-Substitution	Receptor Selectivity	Example
Small group (H)	α activity	Norepinephrine
Methyl (-CH ₃)	$\alpha + \beta$	Epinephrine
Isopropyl / tert-butyl	β_2 selectivity \uparrow	Isoproterenol, Salbutamol

Classification of Sympathomimetic Agents

- ❑ **Direct acting:-** Nor-epinephrine, Epinephrine, Phenylephrine*, Dopamine, Methyldopa, Clonidine, Dobutamine, Isoproterenol, Terbutaline, Salbutamol*, Bitolterol, Naphazoline, Oxymetazoline and Xylometazoline.
- ❑ **Indirect acting agents:-** Hydroxyamphetamine, Pseudoephedrine, Propylhexedrine.
- ❑ **Agents with mixed mechanism:-** Ephedrine, Metaraminol.

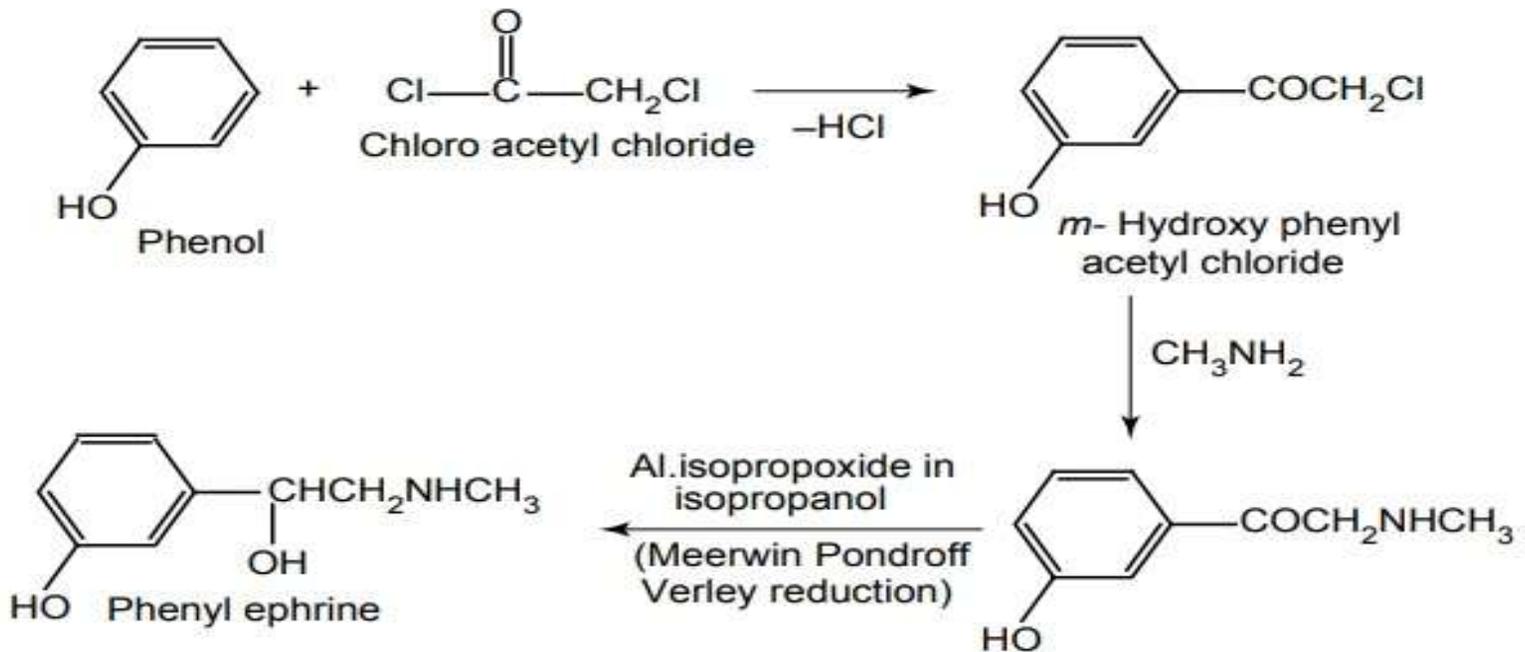
MOA
of
Sympathomimetic Agents



Here is a table summarizing the **Introduction, Mechanism of Action (MOA), and Uses** of the requested direct-acting adrenergic agonists:

Drug Name	Introduction	Mechanism of Action (MOA)	Uses
Norepinephrine	An endogenous catecholamine neurotransmitter and hormone.	Primarily stimulates $\alpha 1$ and $\alpha 2$ adrenergic receptors (vasoconstriction), with some $\beta 1$ activity (cardiac stimulation).	First-line treatment for acute hypotension in vasodilatory shock states (e.g., septic shock), and as an adjunct in cardiac arrest.
Epinephrine	A hormone and neurotransmitter (adrenaline) that plays a key role in the "fight-or-flight" response.	Potent agonist at both α and β adrenergic receptors, with dose-dependent effects.	Emergency treatment of anaphylaxis (severe allergic reactions), cardiac arrest, severe asthma attacks, and to prolong the action of local anesthetics.
Phenylephrine	A synthetic, selective sympathomimetic amine.	A potent, direct-acting selective $\alpha 1$ -adrenergic receptor agonist, causing significant vasoconstriction.	Used intravenously for hypotension (especially during anesthesia), as a nasal/oral decongestant, and as an ophthalmic solution for pupil dilation (mydriasis).
Dopamine	An immediate catecholamine precursor of norepinephrine and epinephrine.	Acts on dopaminergic, $\beta 1$, and $\alpha 1$ receptors in a dose-dependent manner (low dose: vasodilation; intermediate: cardiac stimulation; high dose: vasoconstriction).	Treatment of hemodynamic imbalances, poor organ perfusion, low cardiac output, and hypotension associated with shock (e.g., cardiogenic, septic) and impending renal failure.
Methyldopa	A centrally-acting adrenergic drug.	Converted to alpha-methylnorepinephrine in the CNS, which stimulates $\alpha 2$ -adrenergic receptors, reducing sympathetic outflow and lowering blood pressure.	Primarily used for the treatment of hypertension, especia

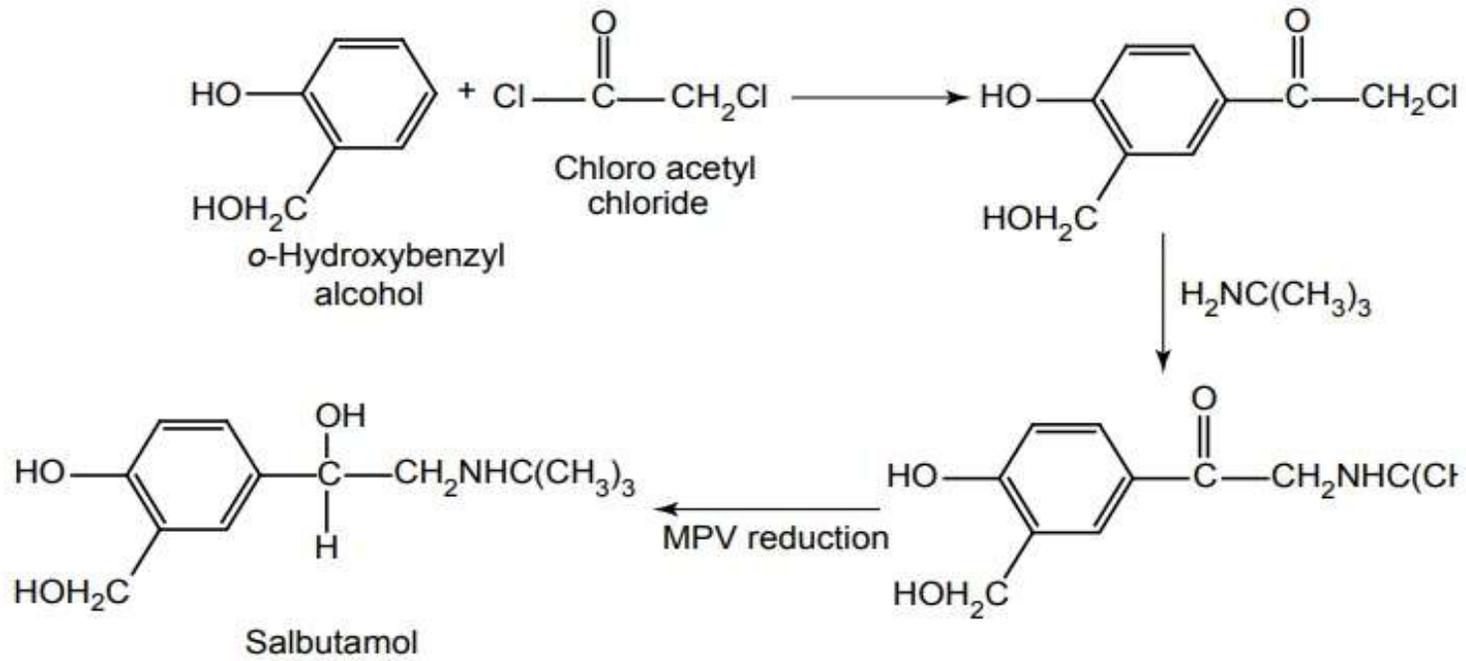
Synthesis of Phenylephrine

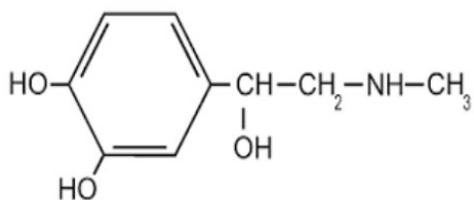


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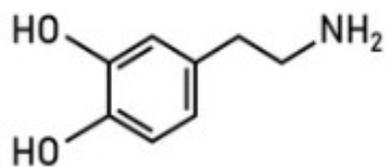
Drug Name	Introduction	Mechanism of Action (MOA)	Uses
Dobutamine	A synthetic direct-acting sympathomimetic.	Primarily a direct agonist at β_1 -adrenergic receptors, with weak β_2 and α_1 activity. Its main effect is strong positive inotropy (increased heart contractility) with minimal chronotropy (heart rate increase).	Management of acute heart failure and cardiogenic shock, especially where an increase in cardiac output is needed without significant vasoconstriction.
Isoproterenol	A potent, non-selective synthetic catecholamine.	Potent agonist at all β_1 and β_2 adrenergic receptors, with little or no effect on α receptors.	Historically used for heart block, certain bradycardias, and as a bronchodilator for severe asthma, though more selective drugs are now preferred.
Terbutaline & Salbutamol	Selective β_2 -adrenergic receptor agonists (Salbutamol is also known as Albuterol).	Stimulate β_2 receptors in the bronchial smooth muscle, leading to relaxation and bronchodilation.	Management and prevention of bronchospasm in patients with asthma, bronchitis, and emphysema.
Bitolterol	A selective β_2 -adrenergic receptor agonist (prodrug of colterol).	Converted in the body to the active form, colterol, which stimulates β_2 receptors, causing bronchodilation.	Used as a bronchodilator for the treatment of asthma and reversible bronchospasm.
Naphazoline, Oxymetazoline, Xylometazoline	Imidazoline derivatives.	Act as direct agonists, primarily stimulating α_1 and α_2 adrenergic receptors in nasal blood vessels, causing local vasoconstriction.	Topical use as nasal/ocular decongestants to relieve redness, itching, and swelling associated with rhinitis, sinusitis, and allergies
Clonidine	A centrally-acting selective adrenergic agonist.	Potent agonist at central nervous system α_2 -adrenergic receptors, which decreases sympathetic outflow to the periphery, lowering heart rate and blood pressure.	Treatment of hypertension, severe cancer pain, and attention deficit hyperactivity disorder (ADHD); also used for withdrawal symptoms (alcohol, opioids) and managing menopausal flushing.

Synthesis of Salbutamol

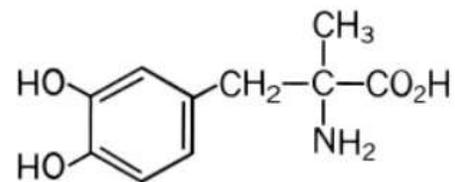




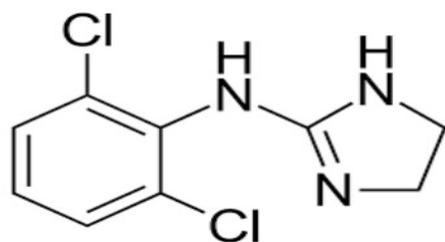
Epinephrine



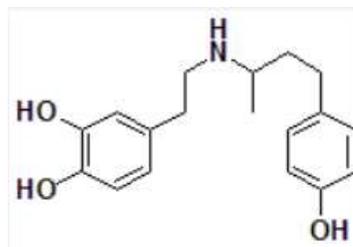
Dopamine



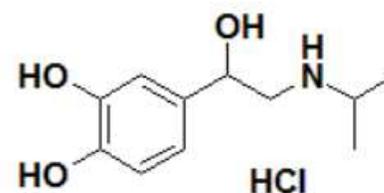
Methyldopa



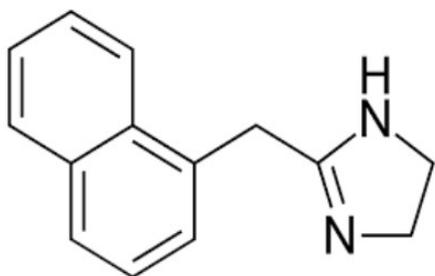
Clonidine



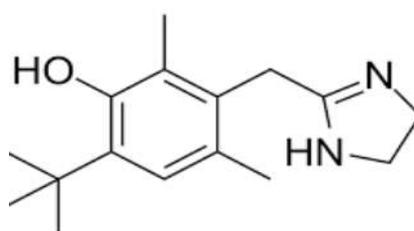
Dobutamine



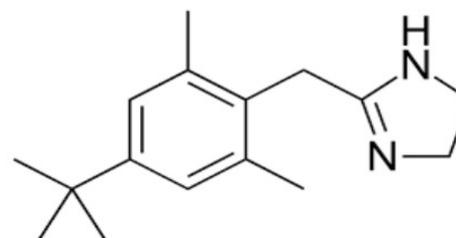
Isoproterenol
HCl



Naphazoline



Oxymetazoline



Xylometazoline

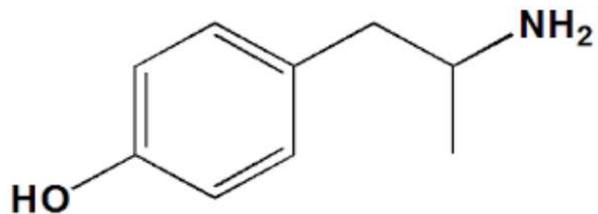


Here is a table summarizing the **Introduction, Mechanism of Action (MOA), and Uses** of the requested **Indirect acting** adrenergic agonists:

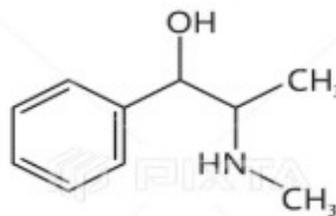
Drug Name	Introduction	Mechanism of Action (MOA)	Uses
Hydroxyamphetamine	A sympathomimetic amine, it is a major metabolite of amphetamine and is mainly intended for local ophthalmic use.	Primarily an indirect agent that stimulates the release of stored norepinephrine (NE) from postganglionic adrenergic nerve terminals. The released NE then acts on both alpha and beta receptors, with a prominent alpha-stimulatory effect in the eye.	Used in eye drops to dilate the pupil (mydriasis) during eye examinations or surgery and to help in the diagnosis of Horner's syndrome.
Pseudoephedrine	A naturally occurring alkaloid, stereoisomer of ephedrine, available as an over-the-counter (OTC) decongestant.	Mixed mechanism: it acts both indirectly by promoting NE release from storage vesicles and directly on alpha- and beta-adrenergic receptors. The alpha-adrenergic stimulation in the nasal mucosa causes vasoconstriction.	Primarily used as an orally effective nasal and sinus decongestant for colds and allergies. It may also be used to relieve ear pain/blockage during air travel or diving and to increase urinary sphincter tone.
Propylhexedrine	A cycloalkylamine used as a topical decongestant in inhalers, developed as a safer alternative to older agents like amphetamine.	Works mainly as an alpha-adrenergic agonist when used at therapeutic doses via inhalation, causing vasoconstriction in the nasal passages. At higher doses (abuse), it also acts as a norepinephrine-dopamine releasing agent.	Used for the temporary relief of nasal congestion associated with colds, hay fever, and allergic rhinitis.

Here is a table summarizing the **Introduction, Mechanism of Action (MOA), and Uses** of the requested Agents with mixed mechanism adrenergic agonists:

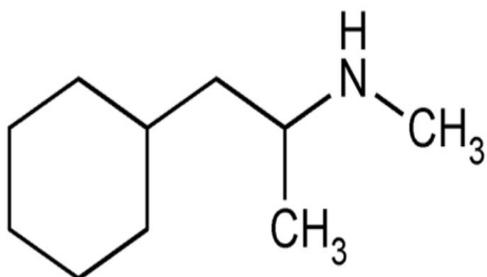
Drug Name	Introduction	Mechanism of Action (MOA)	Uses
Ephedrine	An alkaloid derived from Ephedra plants, it has been used in traditional medicine for centuries and is now used in modern medicine for treating hypotension.	Has a mixed mechanism of action: it binds directly to both alpha and beta adrenergic receptors and indirectly causes the release of stored norepinephrine from sympathetic nerve endings. It also weakly inhibits NE reuptake and MAO.	The primary FDA-approved use is to treat clinically significant hypotension (low blood pressure), especially during general or spinal anesthesia. It has also been used as a bronchodilator for asthma and a CNS stimulant for narcolepsy.
Metaraminol	A sympathomimetic amine used as a powerful vasopressor.	It acts as an alpha-1 adrenergic agonist and also releases norepinephrine from its storage sites (mixed action). This causes peripheral vasoconstriction, leading to an increase in systemic blood pressure.	Used to treat acute hypotension resulting from spinal anesthesia, surgical complications, or head trauma.



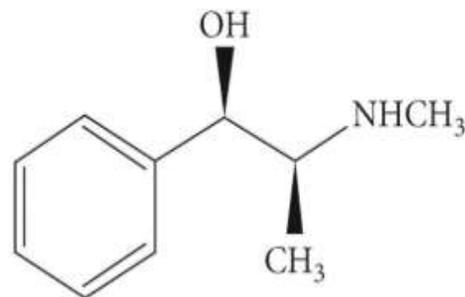
Hydroxyamphetamine



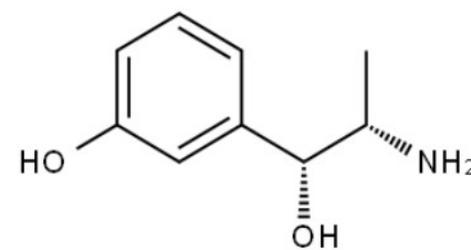
Pseudoephedrine



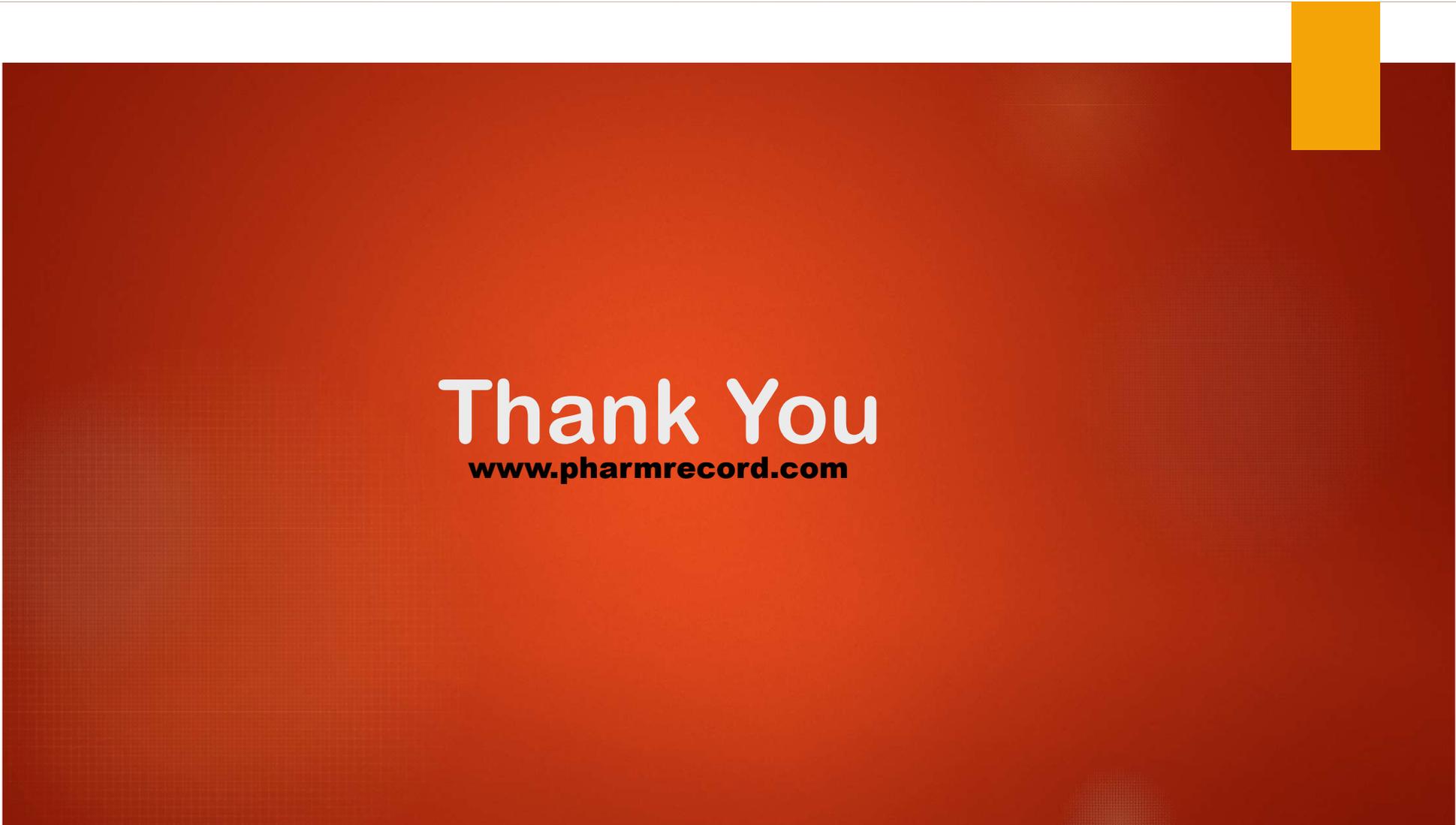
Propylhexedrine



Ephedrine



Metaraminol



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