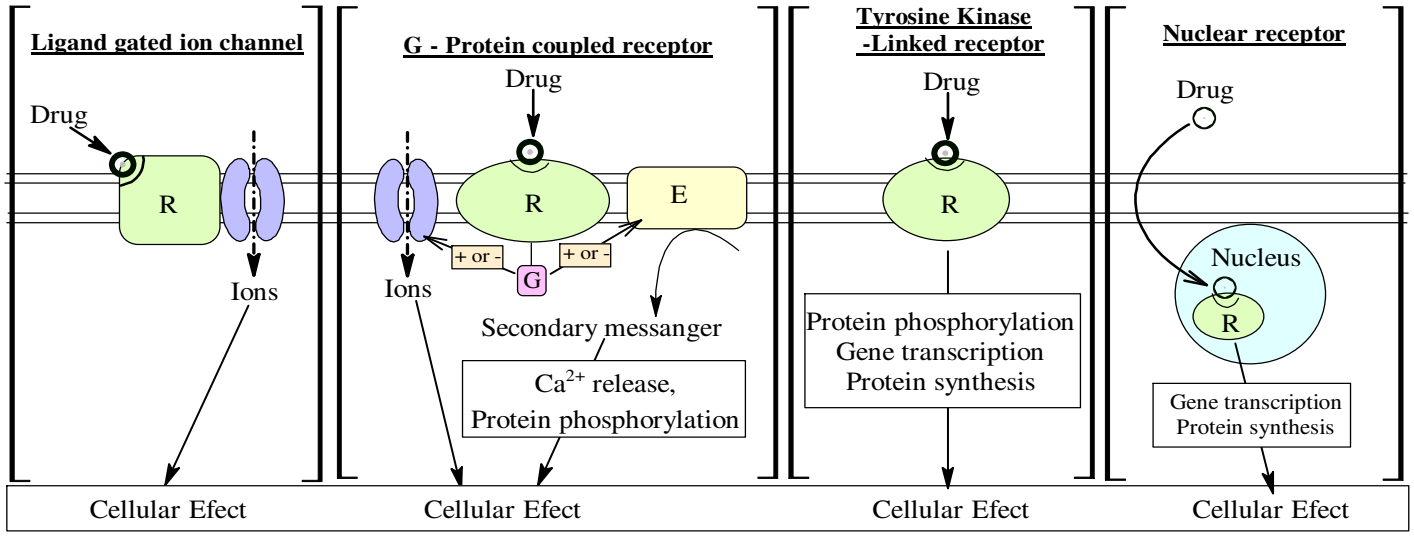
RECEPTOR TRANSDUCTION MECHANISM

Four types of receptor transduction mechanism are there

1. *Ligand – gated ion channel*. Ex: Nicotinic acetylcholine receptors, GABA receptors, 5 – HT_3 receptors, etc.
2. *G – Protein coupled receptors*. Ex: Cholinergic Muscarinic receptors, Histaminic receptors, Adrenergic receptors, etc.
3. *Kinase linked receptors*. Ex: Insulin recptors, Growth factor receptors, Cytokine receptors, etc.
4. *Nuclear receptors*. Ex: Steroid receptors, Hormone receptors, etc.

As shown below all the receptors get activated when they get occupied by the drug. Upon activation they under go some isomeric change or change in electronic field of the molecules to trigger out some signal which proceeds through several bio-chemical pathways which ultimately results into several cellular effects like muscle contraction, Secretion from glands, etc.



Type 1: Ligand – gated ion channel

Also called as ionotropic receptors. These are trans-membrane proteins, (i.e. spreading across the cell membrane) consisting of five different units – two α units, one β, one γ and one δ unit, etc. They form core with internal diameter of 0.7nm (Fig. 1).

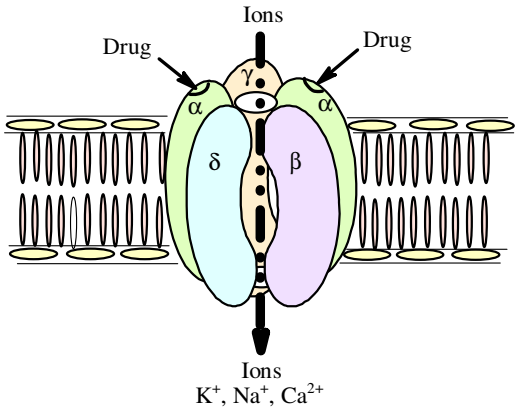


Fig. 1

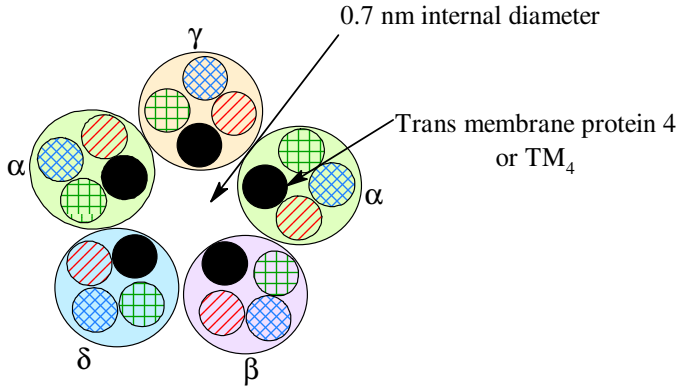


Fig. 2

Each member again consists of four Trans-membrane proteins among which the TM_4 resides to the inner wall of channel. The structural change in this particular protein alters channel permeability which is controlled by agonist attached to the receptor (Fig. 2). Receptors of this type control the fastest synaptic events. Most excitatory neurotransmitters like acetylcholine act by this method by causing increased permeability of Na^+, K^+ ions in the neurons. Thus increased influx of Na^+ ion depolarizes the neuron to generate an action potential. Inhibitory neurotransmitters like GABA also act by this method by increasing chloride ion permeability and causing hyper polarization of neurons.

Type2: G – Protein coupled receptors

Also called as Metabo-tropic receptors, these are receptors which are coupled to a G – protein that can bind to a GTP. Depending upon the type of ligand they may be classified into two categories:

Non peptide ligands: α- and β- adrenergic, Dopaminergic, Histaminergic, Muscarinic cholinergic receptor, etc.

Peptide ligands: Angiotensis, Bradykinin, FSH, LH, TRH, TSH, Thromboxane, etc.

The GPCRs consist of a polypeptide chain comprising of seven trans-membrane α – helices with an extra cellular N-terminal domain for agonist binding and an internal C-terminal to carry out signal transduction by coupling with a G – Protein that can bind to a GTP (Fig. 3).

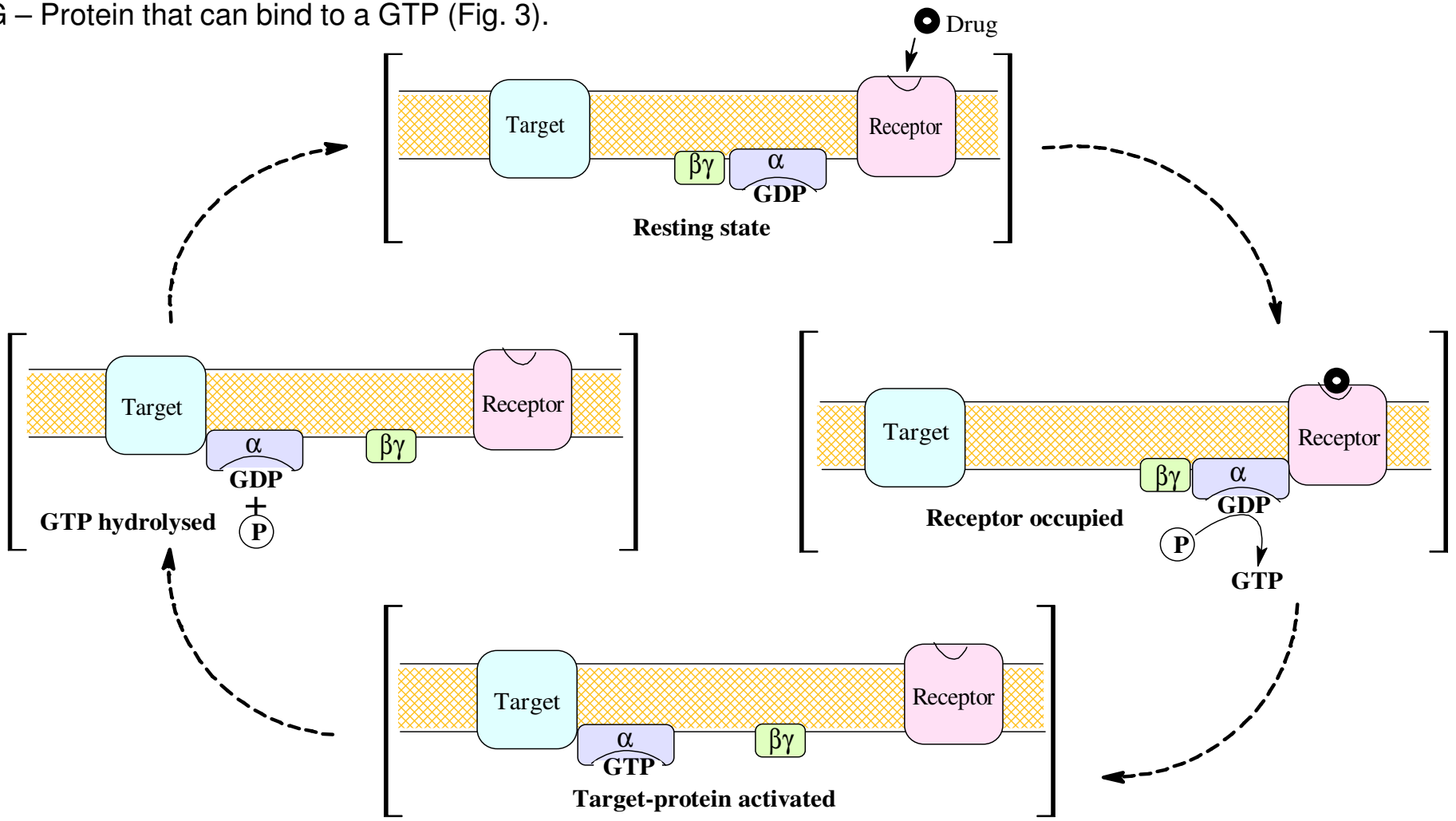


Fig. 4

The G – protein consists of three proteins α, β and γ. A guanine nucleotide binds to the α-sub unit which has enzymatic activity of catalyzing conversion of GTP to GDP. β and γ sub units remain as β – γ complex. All three proteins are anchored to the cell wall with fatty acids (Fig. 4). The G – protein can freely defuse in the membrane and a single G – protein can interact with several effectors and receptors inside the cell. In the resting stage the resting stage the G – protein exist as a αβγ trimer with GDP occupying the α–subunit. When the receptor is occupied by agonist a structural conformational change in the receptor occurs causing it to acquire high affinity for αβγ-trimer. With the attachment of αβγ-trimer with the receptor the GDP bound to α– subunit dissociates and get replaced by GTP, which in turn cause dissociation of αβγ-trimer into α–GTP and βγ-subunits. Now the α–GTP can interact a target protein to activate it. Some times βγ-subunit also can activate target proteins. The process is terminated by hydrolysis of GTP into GDP through GTPase activity of α–subunit which is regulated itself by the target protein. Now the α–GDP combines with βγ-subunit and returns to the resting stage.

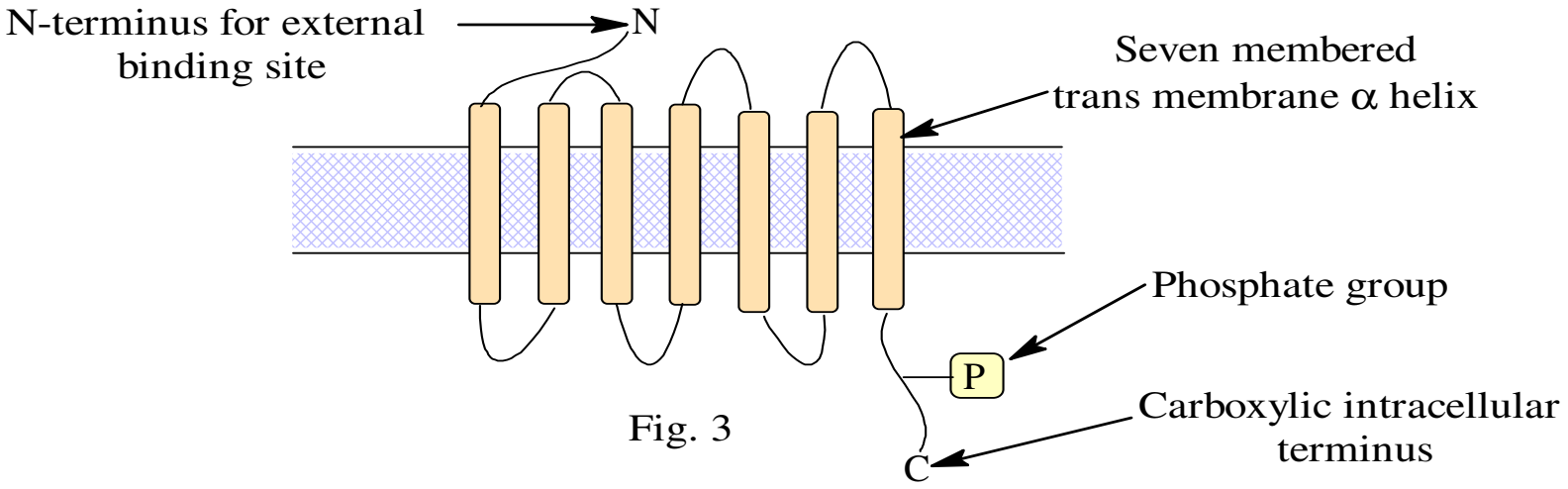


Fig. 3

The various targets for G – Protein coupled receptors are: *Adenylate cyclase* (the enzyme responsible for cAMP formation), Phospho –lipase C (the enzyme responsible for Inositol phosphate and Diacyl glycerol formation.), Ion channels (Particularly K^+ and Ca^{2+} ions), etc.

Type 3: Kinase-linked receptors

Also called as Tyrosine kinase receptor, these receptors differ from ion gated channels and G – protein coupled receptors. These are receptor for various hormones and growth factors with tyrosine kinase in their intracellular domain. Cytokine receptors have various intracellular kinases at the intracellular domain. They have a common structure with a single trans-membrane α – helix linked to an outer receptor domain and an intracellular domain. Signal transduction generally involves dimerisation of a pair of receptors followed by auto phosphorylation of tyrosine residue. Now the activated tyrosine acts as a high affinity binding sight for SH2 (*standing for src homology since it was first found in Src oncogen products*) domains of variety of intracellular proteins, which carry out further intracellular. These types of receptors are involved in various types of events controlling cellular growth and differentiation and they also act indirectly by regulating gene transcription. Two important path ways are involved in the mechanism are –

→ The Ras/ Raf/ MAP kinase pathway, which is important in cell division, growth and differentiation (Fig. 5).

→ The Jak/ Stat pathway, which is activated by many cytokines and control the synthesis of many inflammatory mediators (Fig. 6).

Few hormone receptors are there which have similar architecture but are linked to Guanylate cyclase.

The various targets for Tyrosine Kinase receptors are: various protein kinases and enzymes, Phospholipases, formation of IP_3 Ca^{2+} release, and various others stimulate transcription of gene needed for cellular growth and division.

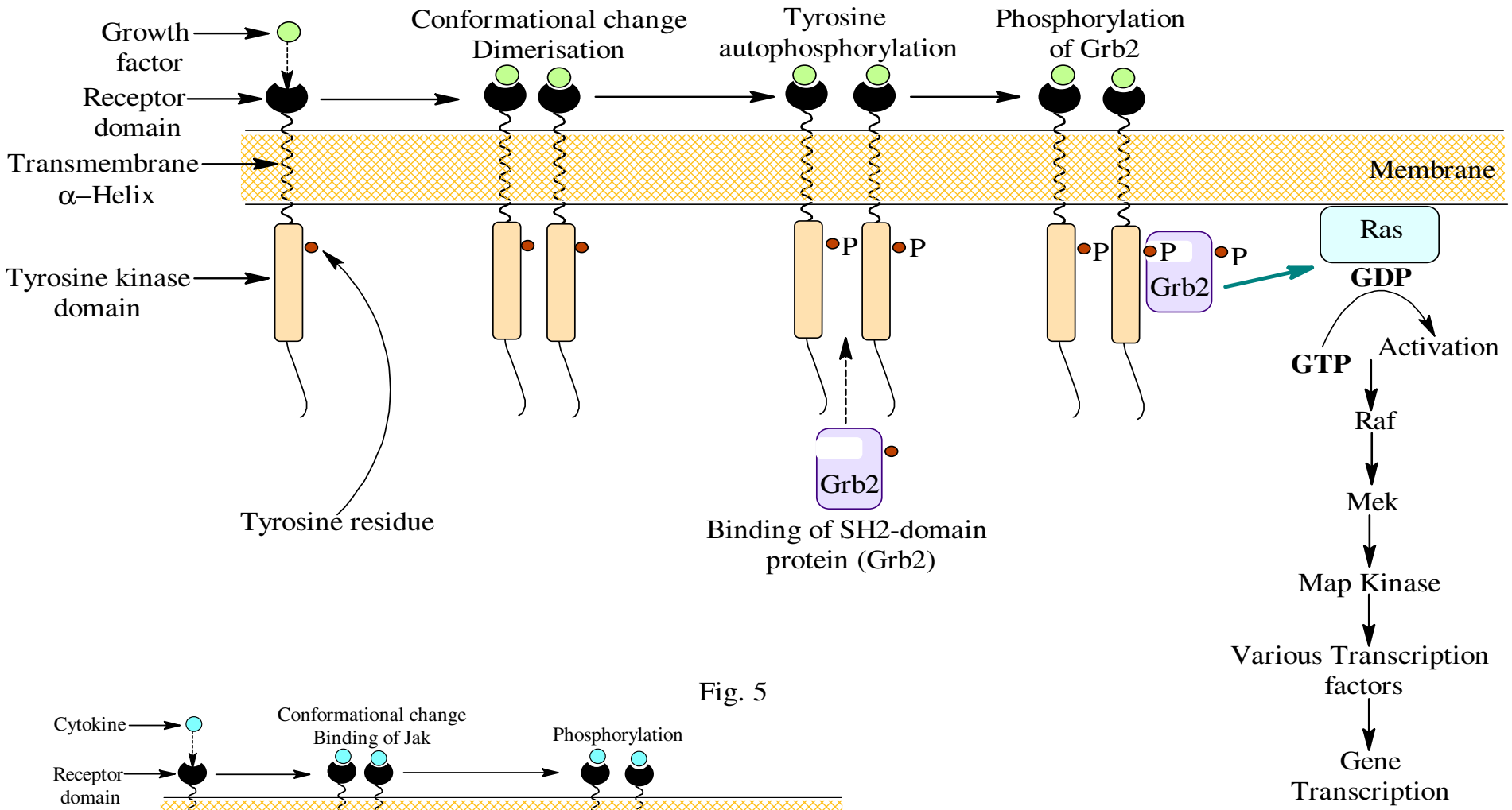

Growth factor
Receptor domain
Transmembrane α–Helix
Tyrosine kinase domain
Tyrosine residue
Conformational change Dimerisation
Tyrosine autophosphorylation
Phosphorylation of Grb2
Membrane
P
Grb2
Binding of SH2-domain protein (Grb2)
Ras
GDP
GTP
Activation
Raf
Mek
Map Kinase
Various Transcription factors
Gene Transcription

Fig. 5

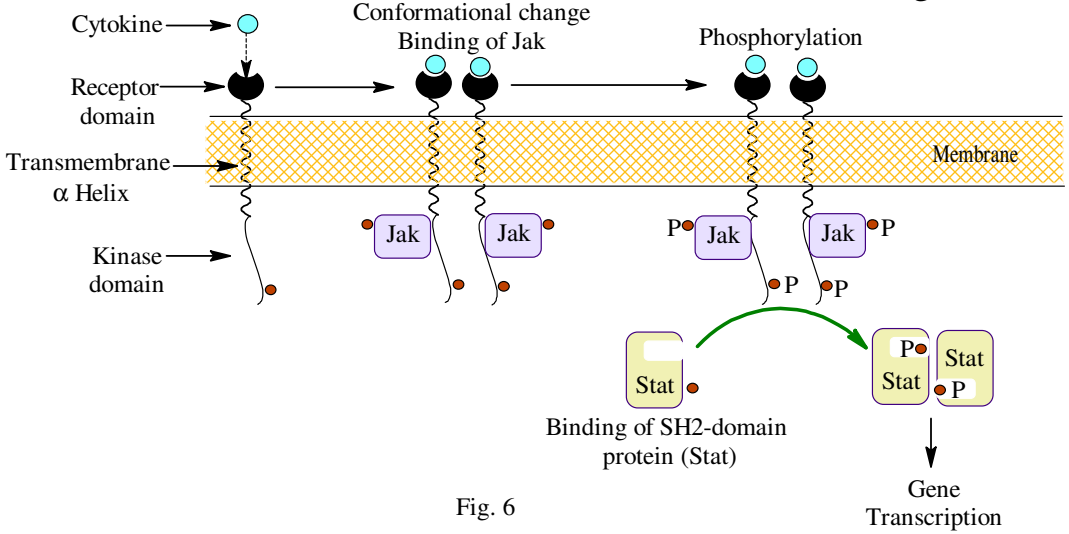
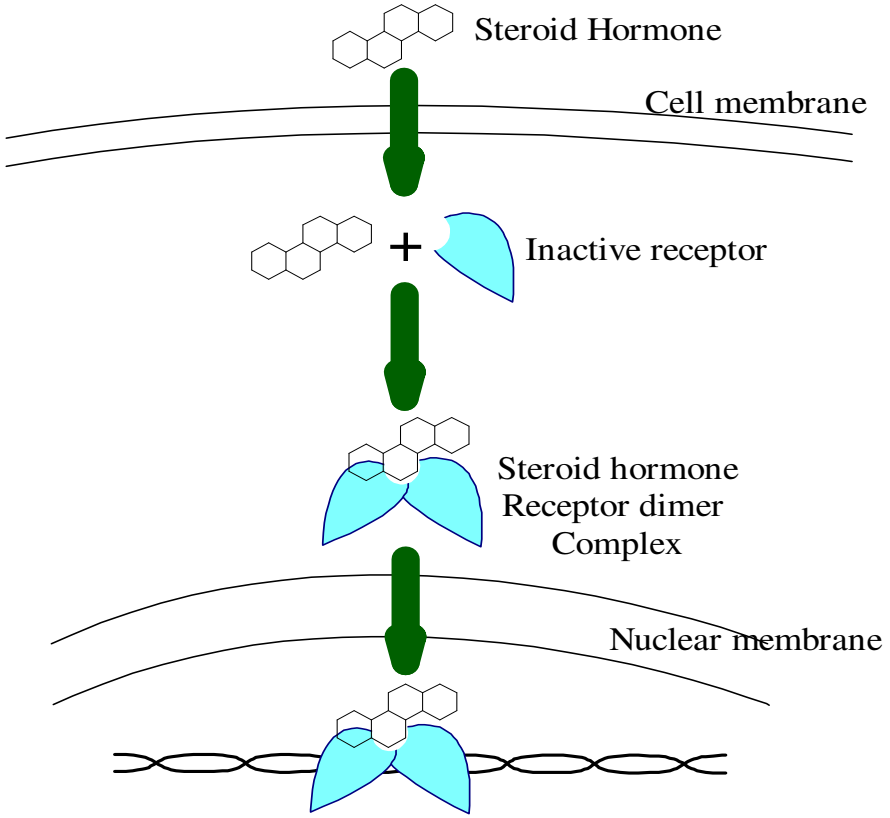

Cytokine
Receptor domain
Transmembrane α Helix
Kinase domain
Conformational change Binding of Jak
Phosphorylation
Membrane
Jak
P
Stat
Binding of SH2-domain protein (Stat)
Gene Transcription

Fig. 6

Type 4: Nuclear receptor

Also known as steroid or thyroid receptors, these receptors mediate regulation of DNA transcription. They induce synthesis of specific proteins and their cellular effects. Most of the receptors are located inside the nucleus and the ligands are all lipophillic compounds which can cross cell membrane. The receptor contain a highly conserved DNA binding site and the protein structures present in there regulate DNA transcription.

On binding of steroid, the receptor has a configurational change and forms a receptor dimer. Now the receptor binding domain can recognize specific DNA sequence thus suppressing or promoting that particular gene. The specific sequence of nuclear DNA known as *hormone – responsive – element* (*HRE*) (Fig. 7). An increase in RNA polymerase activity and production of specific mRNA with few minutes of steroid receptor interaction. This ultimately leads to synthesis of various physiological proteins of various physiological functions.

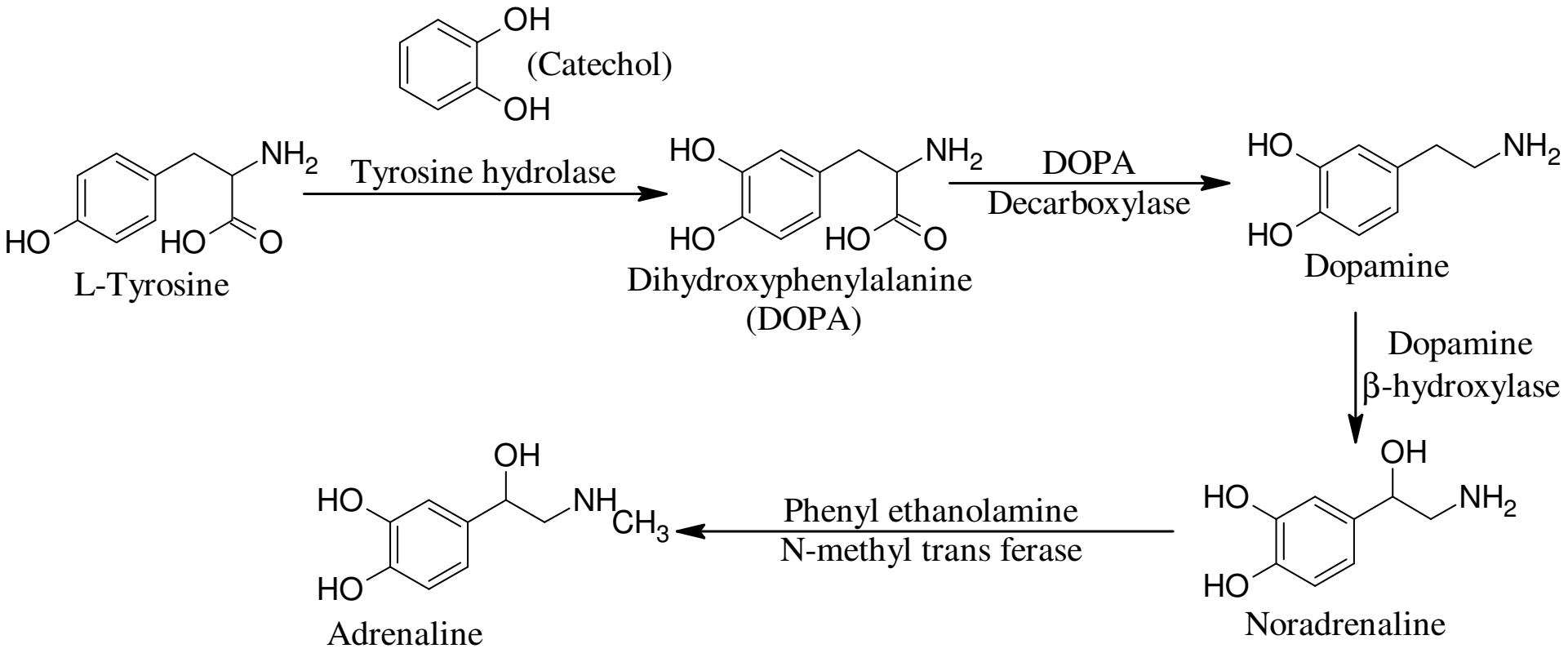


Binding of Hormone Receptor complex to promoter region of DNA or hormone responsive-element to cause transcription

Adrenergig Agents

- Adrenomimetic agents
- Adrenolytic agents

BIO-SYNTHESIS OF ADRENALINE



Regulation of synthesis

- The level of catecholamines within the nerve terminal
  - e.g., high catecholamine levels within the nerve terminal tend to inhibit tyrosine hydroxylase, serving as a negative feedback mechanism
- The rate of cell firing
  - e.g., when neurons are activated and firing at a high rate, such as during stress, tyrosine hydroxylase would be stimulated
- These elegant mechanisms enable dopaminergic and noradrenergic neurons to carefully control their rate of neurotransmitter formation.

Catecholamine synthesis, release, and inactivation

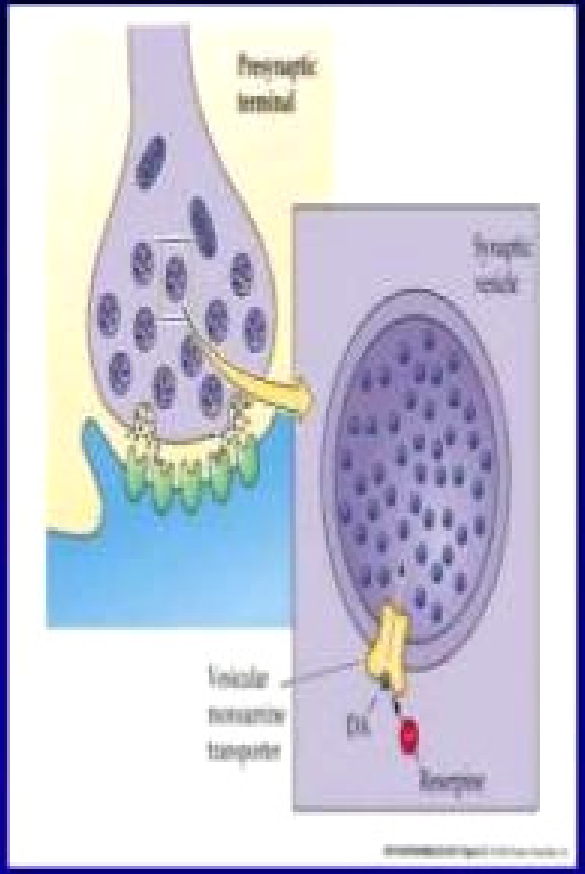
- Tyrosine hydroxylase catalyzes the rate-limiting step in catecholamine synthesis
- Catecholamine formation can be increased ↑ by the administration of a biochemical precursor (i.e., to be converted into a particular neurotransmitter) such as
  - L-DOPA (for the treatment of Parkinson's disease)
- Catecholamine formation can be decreased ↓ by the drug, AMPT (α-methyl-para-tyrosine)
- This compound blocks tyrosine hydroxylase, thus preventing overall catecholamine synthesis and causing a general depletion of DA and NE neurotransmitters
- AMPT treatment caused a return of depressive symptoms in patients who had previously recovered following treatment with antidepressants that act selectively on the noradrenergic system, indicating that the depressed patients' recovery depends on the maintenance of adequate levels of catecholamines in the brain

Storage and release

2. Catecholamines are stored in and released from synaptic vesicles

2.1 Once catecholamines have been synthesized, they are transported into synaptic vesicles for later release (Figure 5.3).

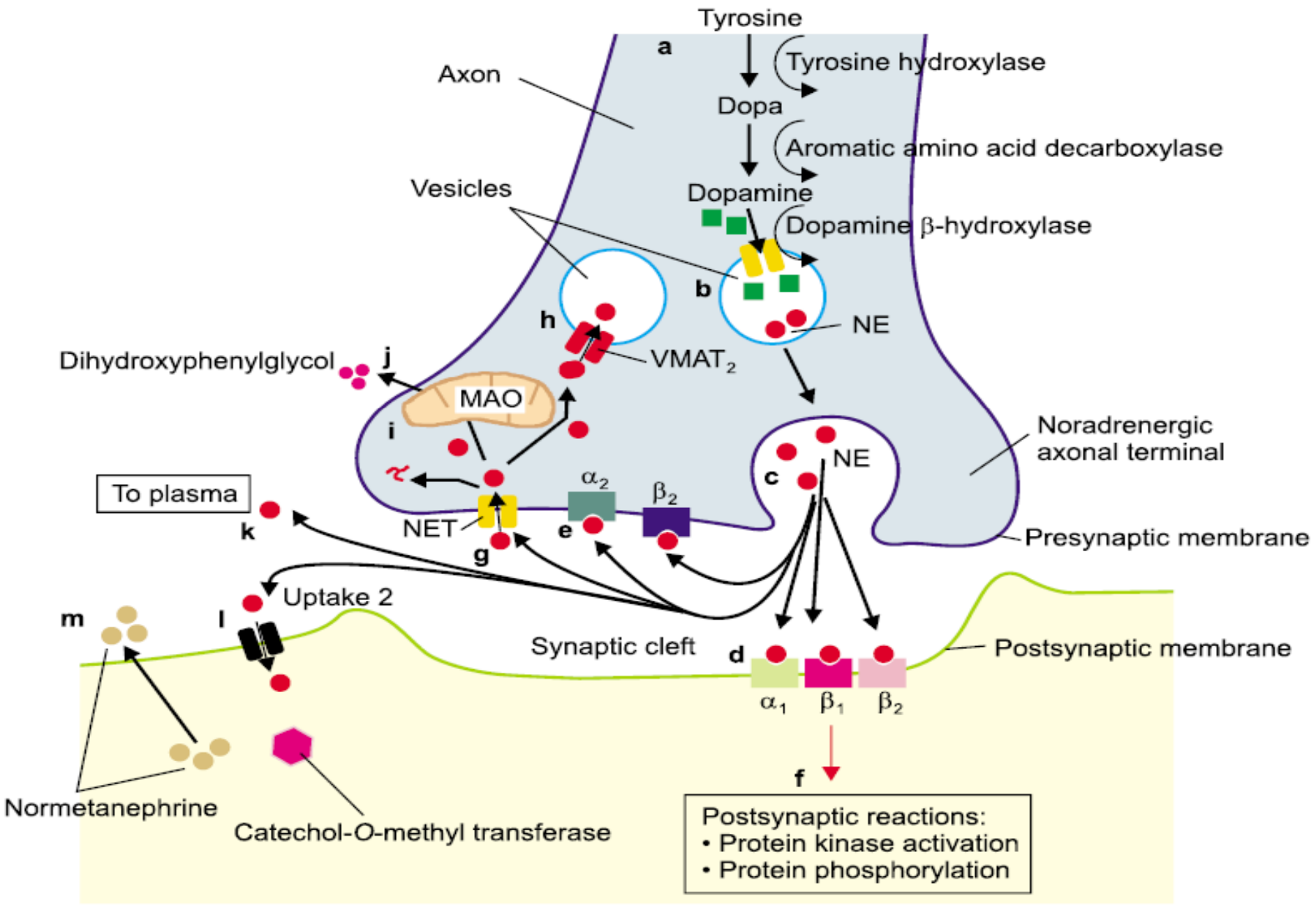
2.2 Catecholaminergic neurons use a vesicular monoamine transporter (VMAT) to transport neurotransmitter molecules from the cytoplasm of the cell to the interior of the synaptic vesicles (Figure 5.3).



Vesicular packaging is important because it provides a means for releasing a predertermined amount neurotransmitter and

it protects the neurotransmitter from degradation by enzymes within the nerve terminal

Catecholamine Synthesis, Release, Uptake an Metabolism



Release of catecholamines

- Normally occurs when a nerve impulse enters the terminal and triggers one or more vesicles to release their contents into the synaptic cleft
- Psychostimulants, such as amphetamine and methamphetamine, can cause a release of catecholamines independently of nerve cell firing
- Catecholamine depletion: sedation and depressive symptoms
- Catecholamine release: behavioral activation

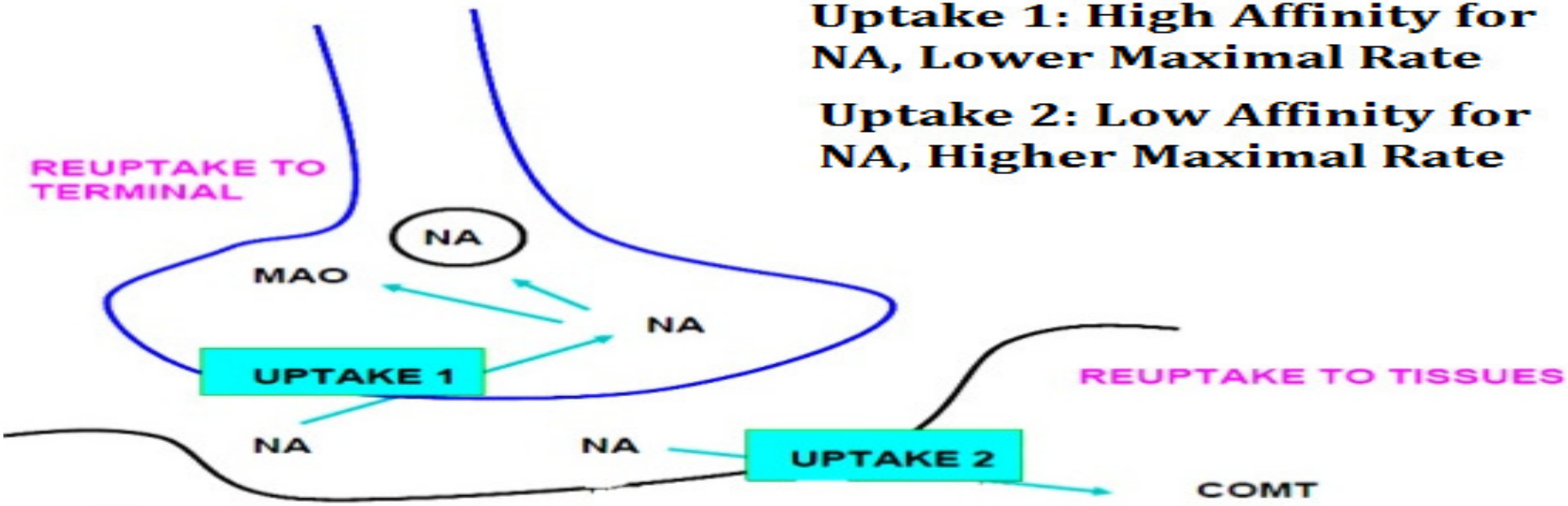
Modulation of catecholamine synthesis

1. Neuronal activity increase would enhance the amount of TH and DBH at both mRNA and protein levels
2. TH is modulated by end-product inhibition (catecholamine competes with pterin cofactor)
3. Depolarization would activate TH activity
4. Activation of TH involves reversible phosphorylation (PKA, PKC, CaMKs and cdk-like kinase

CaMKs: Ca^{2+}/calmodulin-dependent protein kinase

Uptake transporters

1. Released catecholamines will be up-take back into presynaptic terminals (DAT, NET)
2. Transporter is a Na^+ and Cl^+-dependent process
3. Uptake is energy dependent; can be blocked by tricyclic antidepressents, cocaine, amphetamine and MPTP



Catecholamine inactivation

- occurs through a combination of reuptake and metabolism
- Reuptake by transporters: After the neurotransmitter molecules are returned to the terminal through transporters, some of them are re-packaged into the vesicles for re-release while the remainder are broken down and eliminated
- transporters are necessary for the rapid removal of catecholamines from the synaptic cleft
- transporter-blocking drugs enhance the synaptic transmission of DA or NE by increasing the amount of neurotransmitter in the synaptic cleft
- Tricyclic antidepressants: to inhibit the reuptake of both NE and serotonin (5- HT) (i.e., reuptake blocker OR reuptake inhibitor).
- Cocaine: to inhibit the reuptake of DA, NE, and 5-HT.

Metabolic breakdown

- There are two enzymes mainly involved in the breakdown of catecholamines, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO)
- In humans, dopamine has only one major metabolite, homovanillic acid (HVA)
- Norepinephrine has two major metabolites, 3-methoxy-4-hydroxyphenylglycol (MHPG) and vanillymandelic acid (VMA)
- Measurement of these metabolites in various fluid compartments (i.e., blood, urine, and cerebrospinal fluid) facilitate in determining the possible involvement of these neurotransmitters in mental disorders such as schizophrenia and depression
- MAO inhibitors: the treatment of depression
- COMT inhibitors: as a supplemental therapy to enhance the effectiveness of L-DOPA in treating Parkinson's disease.

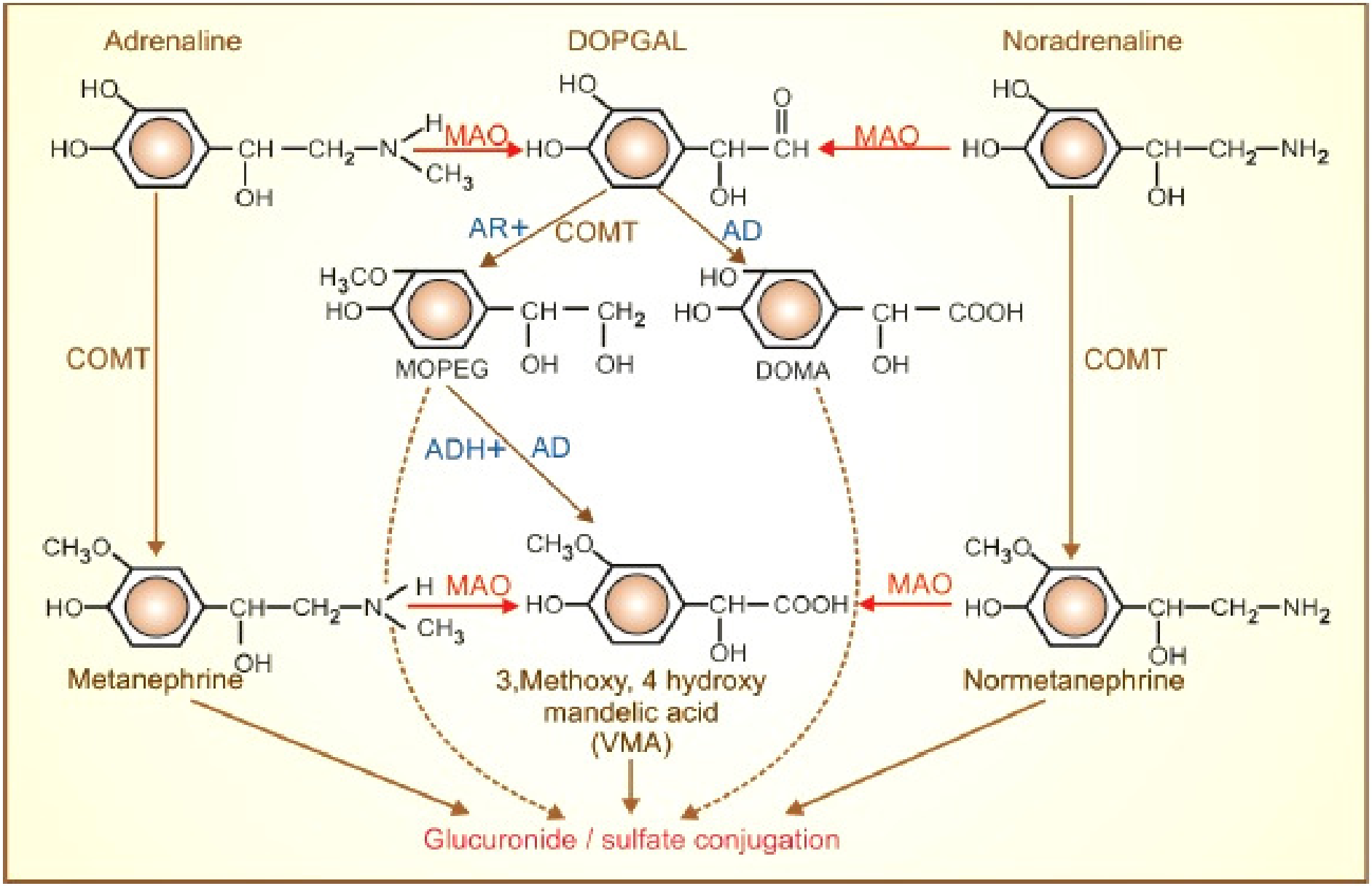


Fig. 9.2: Metabolism of catecholamines

MAO—Monoamine oxidase; COMT—Catechol-O-methyl transferase; AR—Aldehyde reductase; AD—Aldehyde dehydrogenase; ADH—Alcohol dehydrogenase; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-methoxy, 4-hydroxy phenyl glycol; VMA—vanillyl mandelic acid.

Distribution of adrenoceptor subtypes

Type	Tissue	Actions
Alpha$_1$	Most vascular smooth muscle **(innervated)**	Contraction (vasoconstriction)
	Pupillary dilator muscle	Contraction (dilates pupil = mydriasis)
	Pilomotor smooth muscle	Contraction (erects hair)
	Prostate	Contraction
	Heart	Increases force of contraction
Alpha$_2$	**POST**synaptic CNS adrenoceptors	Probably multiple (↓ SNS outflow)
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals (**PRE**synaptic)	Inhibition of transmitter release
	Some vascular smooth muscle	Contraction (vasoconstriction)
Beta$_1$	Heart	Increases HR, cardiac contractility and AV node conduction
	Kidney (juxtaglomerular cells)	Increases renin release
Beta$_2$ **(NOT innervated)**	Respiratory, uterine and vascular (skeletal muscle vessels and vessels to the liver) smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human Liver	Activates glycogenolysis - ↑glucose
	Heart	Increases HR, cardiac contractility and AV node conduction
Beta$_3$	Fat cells	Activates lipolysis
D$_1$	Smooth muscle	Dilates renal blood vessels

ADRENERGIC NERVOUS SYSTEM

Adrenergic nervous system is that which has adrenaline or epinephrine or nor-adrenaline or nor-epinephrine as neurotransmitter in the post synaptic neurons. Those agents which mimic the effect of adrenaline or augment the effect of adrenaline are called adreno mimetic or sympatho mimetic & those agents which antagonize the effect of adrenergic action are called sympatho-lytic or adreno-lytic.

Types of adrnoceptors: Two types receptors are there α & β, all are G-protein coupled receptors. α is again divided into α_1 (act through activation off IP_3 & DAG) & α_2 (act through lowering cAMP). β is divided into β_1 (increases cAMP) & β_2 (decreases cAMP).

Classification

1. Adrenergic agonists

Depending upon mode of action:

~ Directly acting: Epinephrine, nor-epinephrine, etc.
~ Indirectly acting: Tyramine, Phentermine, etc.
~ Mixed action: Amphetamine, Ephedrine, etc.

Depending upon chemical classification:

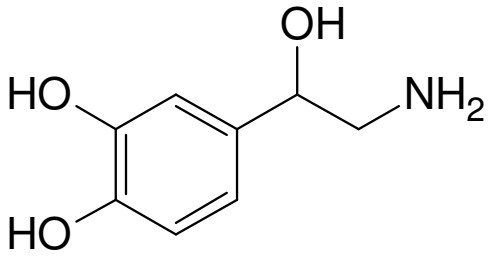
~ Phenyl ethylamine derivatives: Nor-adrenaline, Adrenaline,etc.
~ Imidazoline derivatives: Isoproterenol, Naphazoline, etc.

2. Adrenergic Antagonists

~ α-Adrenergic blockers: Phentolmine, Tolazoline, etc.
~ β-Adrenergic blocker: Propranolol, Practlol, Epanolol, etc.

Adrenomimetic Agents

Noradrenaline (Norepinephrine)

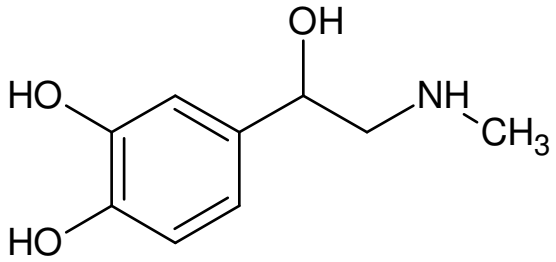


4-(2-amino-1-hydroxyethyl)benzene-1,2-diol

Use: Norepinephrine is a naturally occurring catecholamine and directly stimulates adrenergic receptors. Stimulation of α-1receptors causes constriction of the radial smooth muscle of the iris, arteries, arterioles, veins, urinary bladder, and the sphincter of the gastrointestinal tract. Stimulation of β-1 receptors causes an increase in myocardial contractility, heart rate, automaticity, and atrioventricular (AV) conduction, while stimulation of β-2 adrenergic receptors causes bronchiolar and vascular smooth muscle dilatation.

It is used in treatment of hypotension, cardio-pulmonary resuscitation

Adrenaline (Epinephrine)

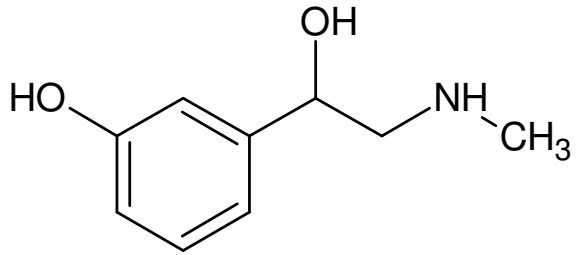


4-[1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol

Use: Epinephrine directly stimulates adrenergic receptors. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the HEART, and dilates bronchi and cerebral vessels.

Treatment of Respiratory distress, Status astheamaticus, Cardiac arrest, shock and as styptic(stop bleeding), and to delay absorption of local ANESTHETICS

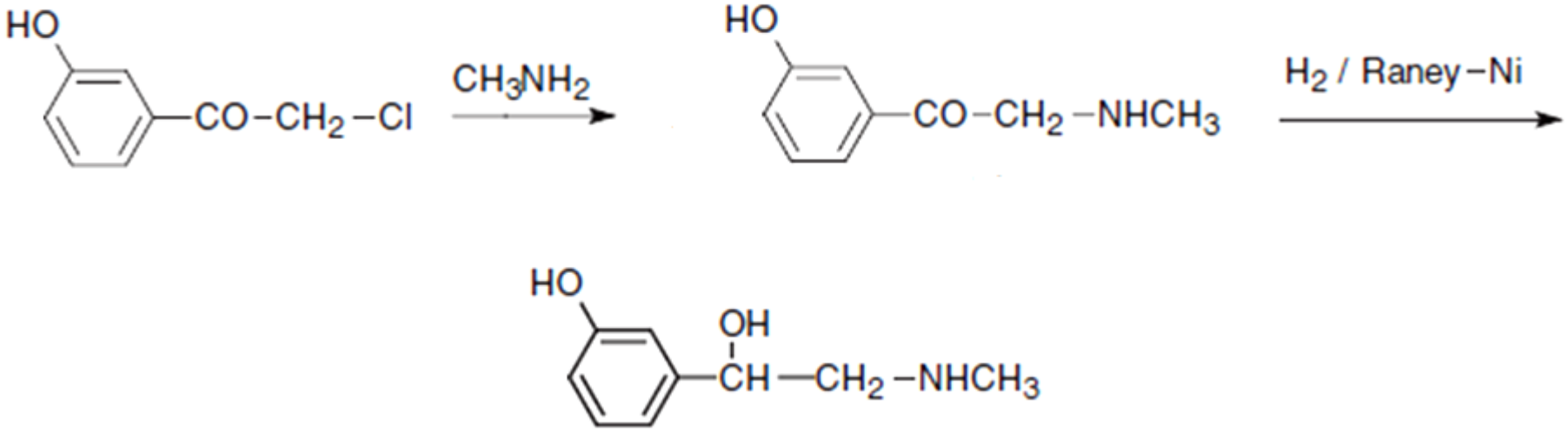
Phenylephrine:



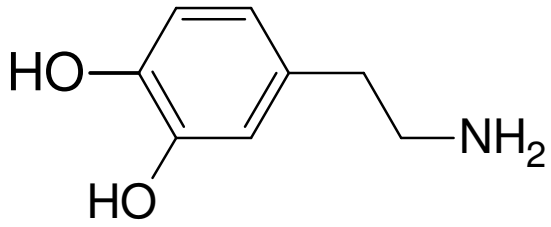
3-[1-hydroxy-2-(methylamino)ethyl]phenol

Uses: Phenylephrineis a postsynaptic α_1-receptor agonist with little effect on β-receptors of the heart and causes vasoconstriction, increases systolic/diastolic pressures, reflex bradycardia, and stroke output. Orally it causes arterial vasoconstriction, Used as nasal de-congestant, Mydriatic & to prolong local anesthetic action.

Synthesis:



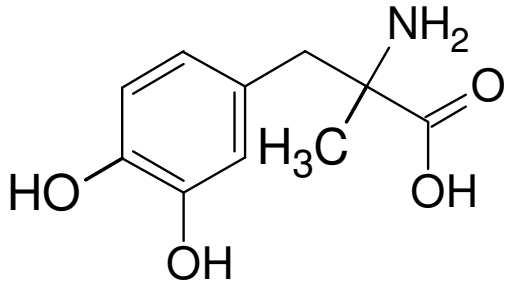
Dopamine:



4-(2-aminoethyl)benzene-1,2-diol

Uses: Dopamine is a natural catecholamine, is a precursor to norepinephrine in noradrenergic nerves. It produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. This is accomplished directly by exerting an agonist action on beta-adrenoceptors and indirectly by causing release of norepinephrine from storage sites in sympathetic nerve endings. It is used in the treatment of very low blood pressure, a slow heart rate that is causing symptoms, and, if epinephrine is not available, cardiac arrest.

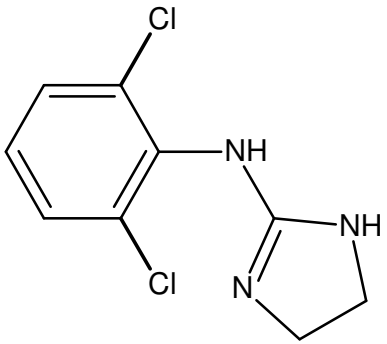
Methyldopa :



2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid

Uses: It is a competitive inhibitor of the enzyme DOPA decarboxylase, This inhibition results in reduced dopaminergic and adrenergic neurotransmission in the peripheral nervous system.
Hypertension, Gestational hypertension.

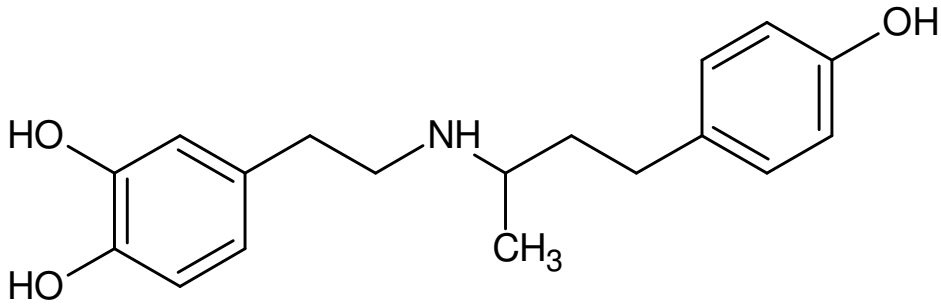
Clonidine :



_N_-(2,6-dichlorophenyl)-4,5-dihydro-1_H_-imidazol-2-amine

Uses: Clonidine treats high blood pressure by stimulating α2A receptors in the brain stem, which decreases peripheral vascular resistance, lowering blood pressure, used to treat high blood pressure, attention deficit hyperactivity disorder, anxiety disorders, withdrawal (from either alcohol, opioids, or smoking), migraine, menopausal flushing, diarrhea, and certain pain conditions.

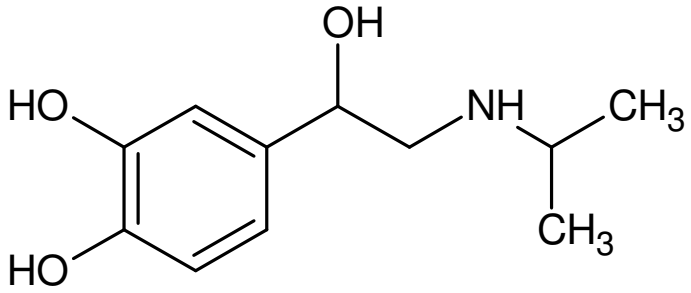
Dobutamine:



4-(2-{[4-(4-hydroxyphenyl)butan-2-yl]amino}ethyl)benzene-1,2-diol

Uses: Dobutamine is a direct-acting agent whose primary activity results from stimulation of the β1-adrenoceptors of the heart, increasing contractility and cardiac output, used to treat acute but potentially reversible heart failure, such as which occurs during cardiac surgery or in cases of septic or cardiogenic shock, on the basis of its positive inotropic action.

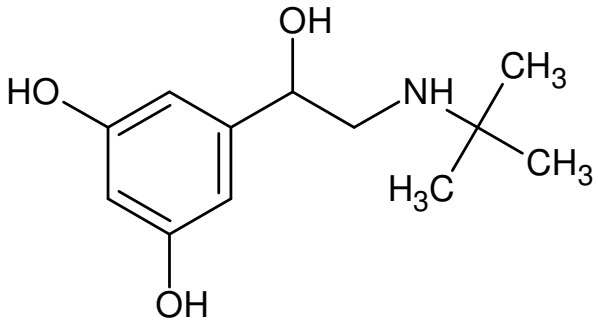
Isoproterenol:



4-[1-hydroxy-2-(propan-2-ylamino)ethyl]benzene-1,2-diol

Uses: Isoprenaline is a β1 and β2 adrenoreceptor agonist and has almost no activity against alpha adrenergic receptors. It is used to treat heart block and episodes of Adams-Stokes syndrome that are not caused by ventricular tachycardia or fibrillation, in emergencies for cardiac arrest until electric shock can be administered, for bronchospasm occurring during anesthesia, and as an adjunct in the treatment of hypovolemic shock, septic shock, low cardiac output (hypoperfusion) states, congestive heart failure, and cardiogenic shock.

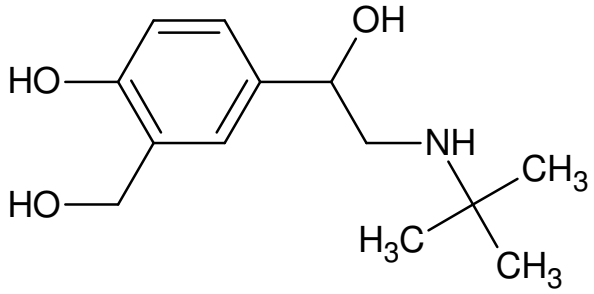
Terbutaline



5-[2-(T*ert*-butylamino)-1-hydroxyethyl]benzene-1,3-diol

Uses: Terbutaline is a relatively selective beta2-adrenergic bronchodilator that has little or no effect on alpha-adrenergic receptors. It stimulates beta-receptors of the bronchial, vascular, and uterine smooth muscles (beta2 receptors) than on the beta-receptors of the heart (beta1 receptors). This drug relaxes smooth muscle and inhibits uterine contractions, but may also cause some cardiostimulatory effects and CNS stimulation.

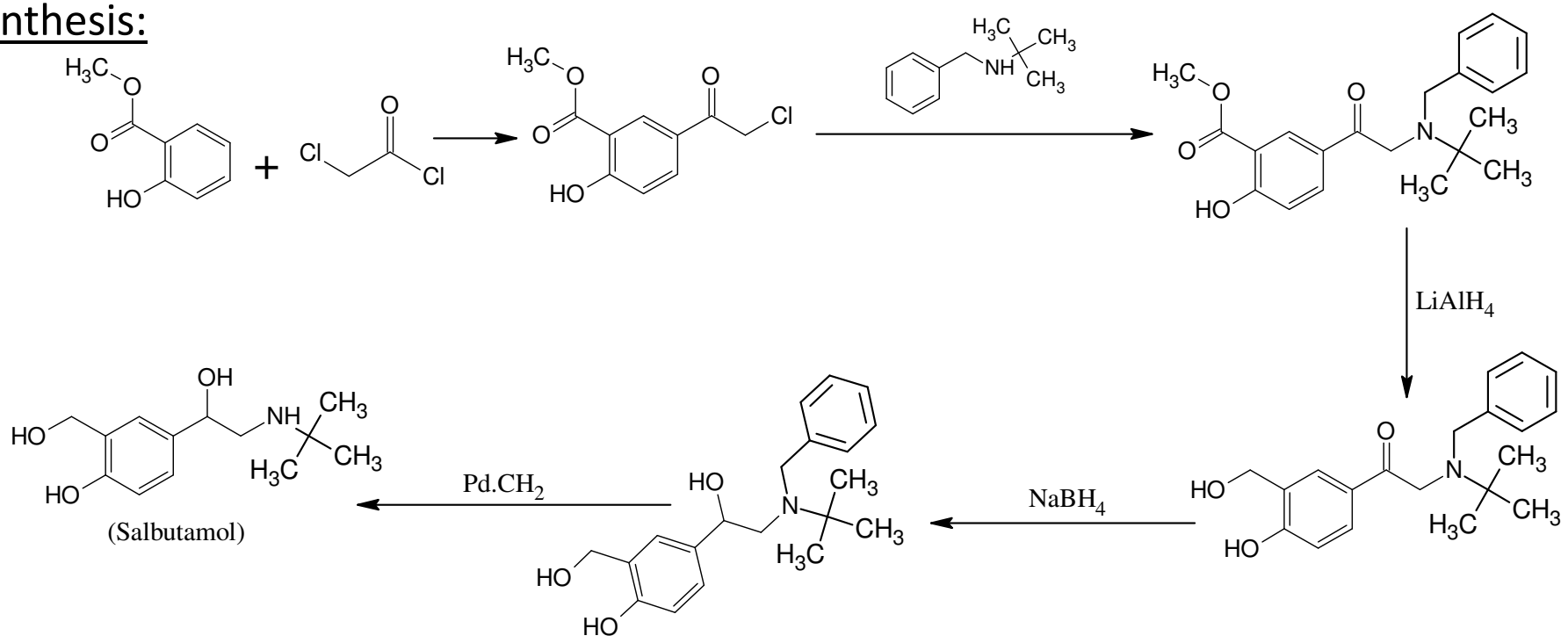
Salbutamol:



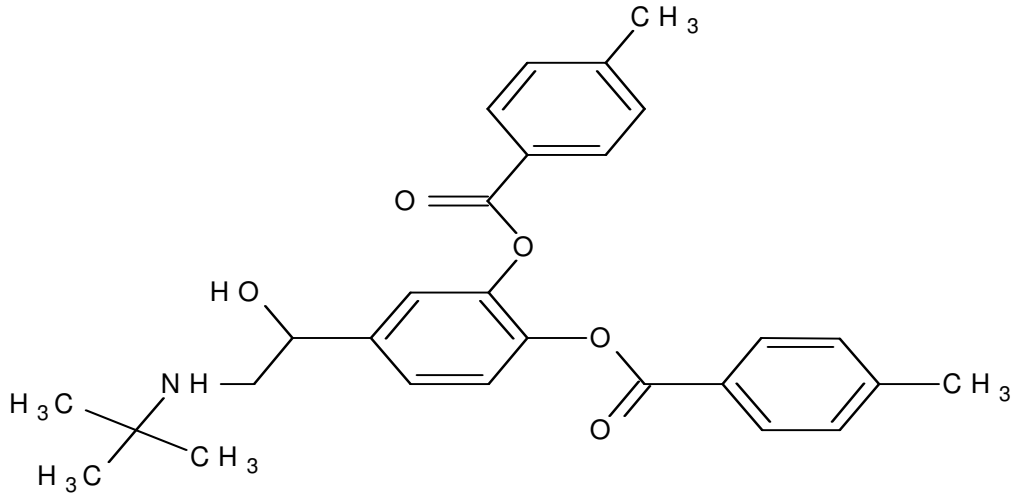
4-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol

Uses: Salbutamol is a moderately selective beta(2)-receptor agonist similar in structure to terbutaline, is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. The R-isomer, levalbuterol, is responsible for bronchodilation while the S-isomer increases bronchial reactivity.

Synthesis:



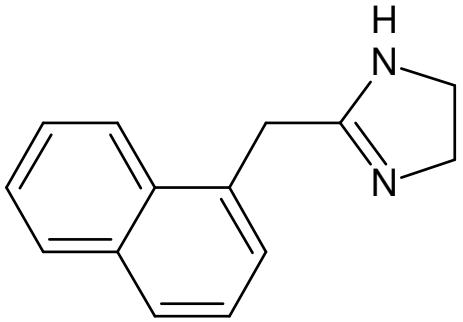
Bitolterol:



[4-[2-({tert}-butylamino)-1-hydroxyethyl]-2-(4-methylbenzoyl)oxyphenyl] 4-methylbenzoate

Uses: Bitolterol, an adrenergic bronchodilator, is a prodrug that widens constricted airways in the lungs by relaxing the smooth muscles that surround the bronchial passages. Bitolterol probably does not affect the inflammation in the lung, such as in bronchitis. Bitolterol is unique in that it is a prodrug because it must first be metabolized by the body before it becomes active.

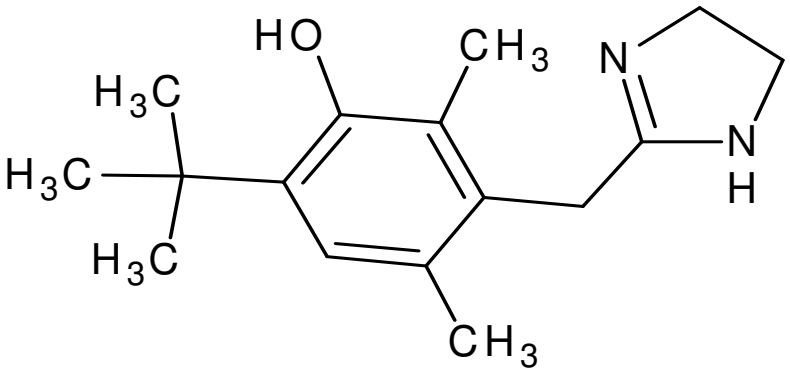
Naphazoline



2-(naphthalen-1-ylmethyl)-4,5-dihydro-1H-imidazole

Uses: Naphazoline is a direct acting sympathomimetic adrenergic alpha-agonist used to induce systemic vasoconstriction, thereby decreasing nasal congestion and inducing constriction around the conjunctiva. It also decreases itching and irritation of the eyes.

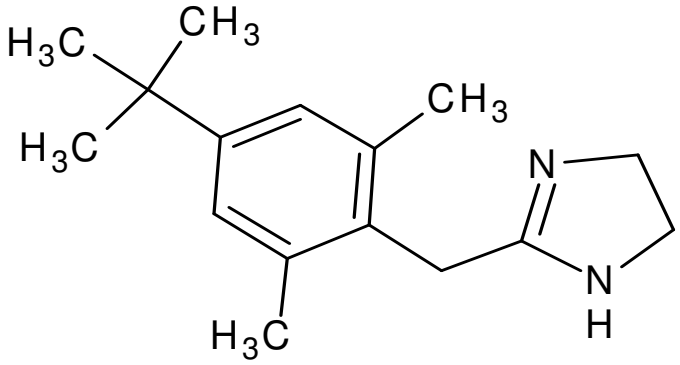
Oxymetazoline



6-tert-butyl-3-(4,5-dihydro-1H-imidazol-2-ylmethyl)-2,4-dimethylphenol

Uses: Oxymetazoline a adrenergic alpha-agonists, direct acting sympathomimetic used as a vasoconstrictor to relieve nasal congestion The sympathomimetic action of oxymetazoline constricts the smaller arterioles of the nasal passages, producing a prolonged (up to 12 hours), gentle and decongesting effect. Oxymetazoline elicits relief of conjunctival hyperemia by causing vasoconstriction of superficial conjunctival blood vessels and used in various conjunctivitis.

Xylometazoline



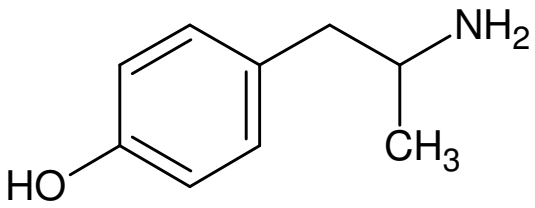
2-(4-tert-butyl-2,6-dimethylbenzyl)-4,5-dihydro-1H-imidazole

Uses: Xylometazoline is a direct acting sympathomimetic adrenergic alpha-agonist used to induce systemic vasoconstriction, thereby decreasing nasal congestion. The sympathomimetic action of xylometazoline constricts the smaller arterioles of the nasal passages, producing a prolonged (8-12 hours) decongesting effect.

Indirect acting agents:

Indirect-acting (interaction not between drug and receptor), such as MAOIs, COMT inhibitors, release stimulants, and reuptake inhibitors that increase the levels of endogenous catecholamines

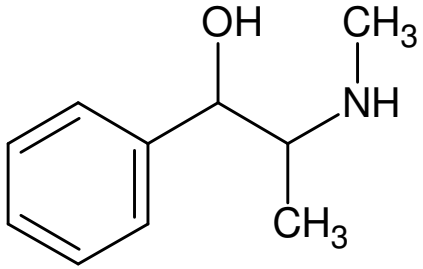
Hydroxyamphetamine:



4-(2-aminopropyl)phenol

Uses: It is an indirect-acting sympathomimetic amine with adrenergic property. Hydroxyamphetamine, when applied topically to the eye, stimulates the release of norepinephrine from postganglionic adrenergic nerves resulting in the stimulation of both alpha and beta adrenergic receptors. Local alpha stimulatory effects include dilation of the pupil, increased flow of aqueous humor, and vasoconstriction; whereas beta stimulatory effects include relaxation of the ciliary muscle and a decreased production in aqueous humor.

Pseudoephedrine

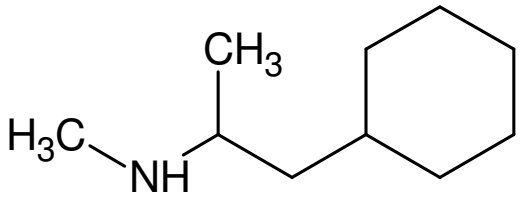


2-(methylamino)-1-phenylpropan-1-ol

Uses: Pseudoephedrine is a sympathomimetic agent, structurally similar to ephedrine, used to relieve nasal and sinus congestion and reduce air-travel-related otalgia in adults.

Pseudoephedrine displaces norepinephrine from storage vesicles in presynaptic neurones, thereby releasing norepinephrine into the neuronal synapses where it stimulates primarily alpha-adrenergic receptors. It also has weak direct agonist activity at alpha- and beta- adrenergic receptors. Receptor stimulation results in vasoconstriction and decreases nasal and sinus congestion.

Propylhexedrine :



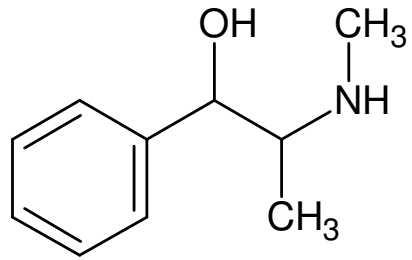
1-cyclohexyl-N-methylpropan-2-amine

Uses: Like other monoamine releasing stimulants propylhexedrine is active as a norepinephrine and dopamine releaser in the central nervous system. Propylhexedrine binds to and activates alpha-adrenergic receptors in the mucosa of the respiratory tract, thereby mimicking the actions of norepinephrineand epinephrine. This results in vasoconstriction and reduces swelling and inflammation of the mucous membrane lining, therefore relieving nasal and sinus congestion.

Mixed Adrenergic Agonist:

Mixed-acting adrenergic agonists are compounds that cause activation of adrenergic receptors by both direct binding as well as release of endogenously-stored norepinephrine from presynaptic terminals. Ephedrine is the prototype mixed-acting agonist.

Ephedrine:



2-(methylamino)-1-phenylpropan-1-ol

Uses: Ephedrine is similar in structure to the derivatives amphetamine and methamphetamine. Chemically, it is an alkaloid derived from various plants in the genus Ephedra (family Ephedraceae). It works mainly by increasing the activity of noradrenaline on adrenergic receptors.

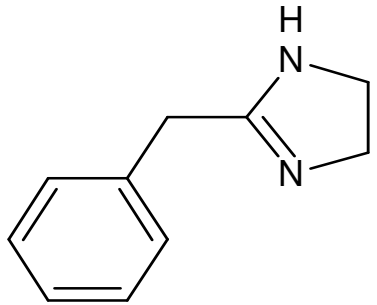
Adrenolytic agents (Adrenergic Antagonists):

Alpha adrenergic blockers:

SAR of α-Adreneric Blocker:

By changing the furan ring in prazosin to tetrahydrofuran ring (as in alfuzosin) the half-life is greatly increased, allowing once-a-day dosing. Silodosin is the most selective for α-1A receptors. The affinity and selectivity for α-1 receptors seems to be determined by structure between the quinazoline and the furan ring. Piperazine is present in prazosin, terazosin and doxazosin which seems to contribute to the non-selective inhibition of α-1 receptors.

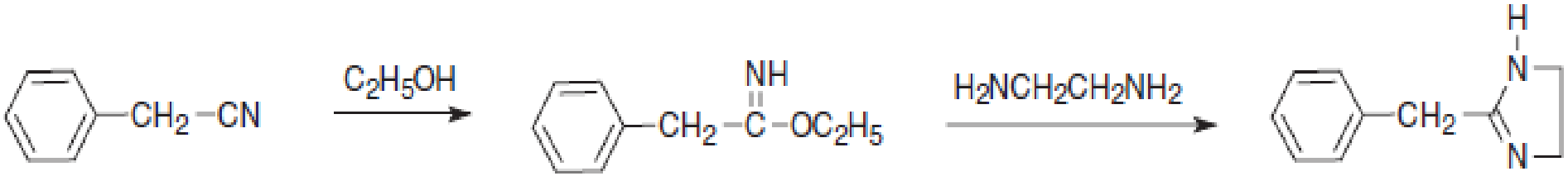
Tolazoline:



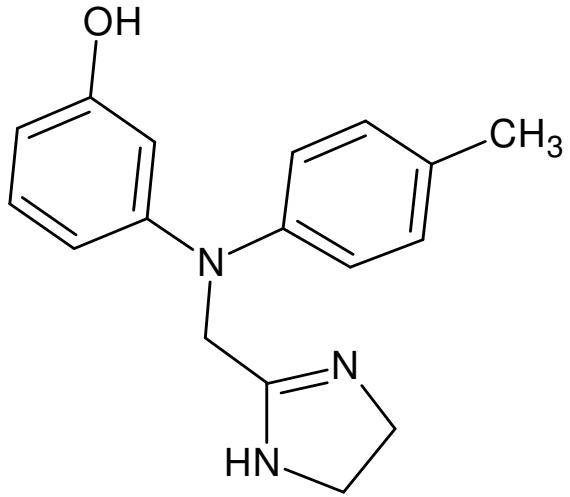
2-benzyl-4,5-dihydro-1*H-imidazole*

Ues: Drugs that bind to but do not activate alpha-adrenergic receptors thereby blocking the actions of endogenous or exogenous adrenergic agonists. Adrenergic alpha-antagonists are used in the treatment of hypertension, vasospasm, peripheral vascular disease, shock, and pheochromocytoma (neuroendocrine tumor of the medulla of the adrenal glands).

Synthesis:



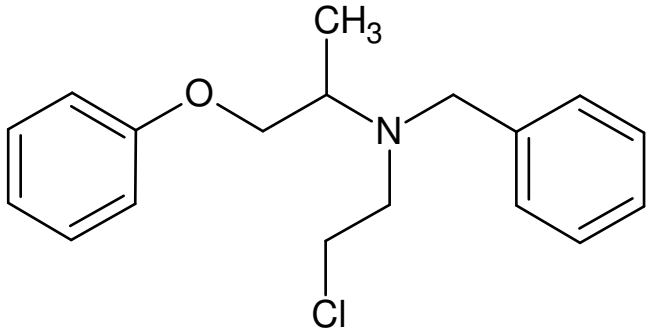
Phentolamine :



3-[(4,5-dihydro-1*H-imidazol-2-ylmethyl)(4-methylphenyl)amino]phenol*

Uses: Phentolamine is a synthetic imidazoline with alpha-adrenergic antagonist activity. As a competitive alpha-adrenergic antagonist, phentolamine binds to alpha-1 and alpha-2 receptors, resulting in a decrease in peripheral vascular resistance and vasodilatation.

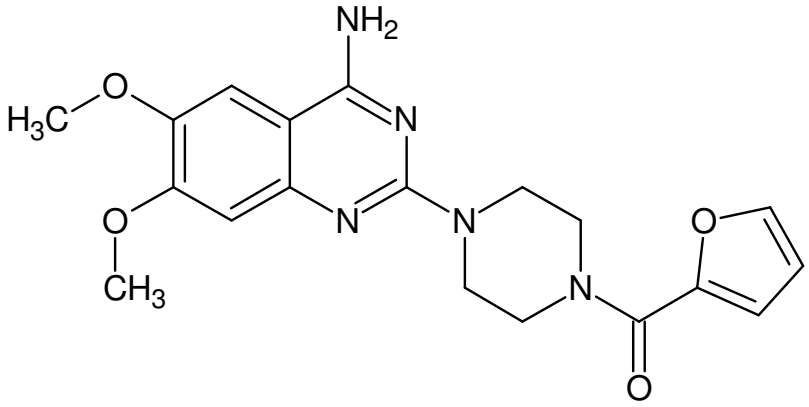
Phenoxybenzamine :



N-benzyl-N-(2-chloroethyl)-1-phenoxypropan-2-amine

Uses: Phenoxybenzamine is a synthetic, dibenzamine alpha adrenergic antagonist with antihypertensive and vasodilatory properties. Phenoxybenzamine non-selectively and irreversibly blocks the postsynaptic alpha-adrenergic receptor in smooth muscle, thereby preventing vasoconstriction, relieving vasospasms, and decreasing peripheral resistance and fall in BP. Reflex tachycardia may occur and may be enhanced by blockade of alpha-2 receptors which enhances norepinephrine release.

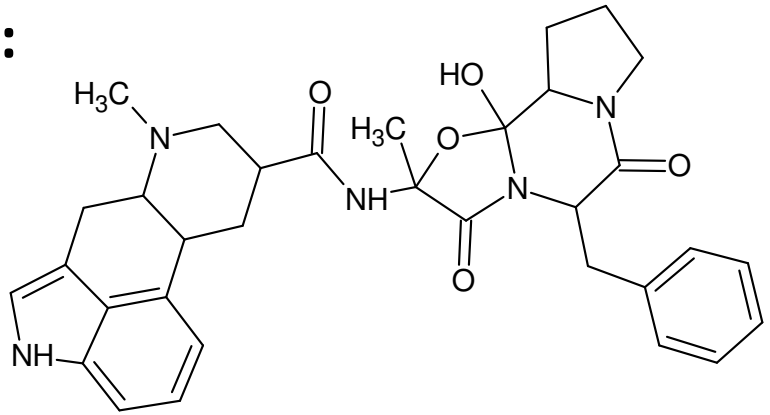
Prazosin :



[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl](furan-2-yl)methanone

Uses: Prazosin is a synthetic piperazine derivative and an alpha-1 adrenergic receptor inhibitor used primarily as an anti-hypertensive. Prazosin's effects are most pronounced in the large resistance vessels (i.e. arterioles) and result in a decrease in total systemic vascular resistance (SVR) without a rebound or reflex tachycardia.

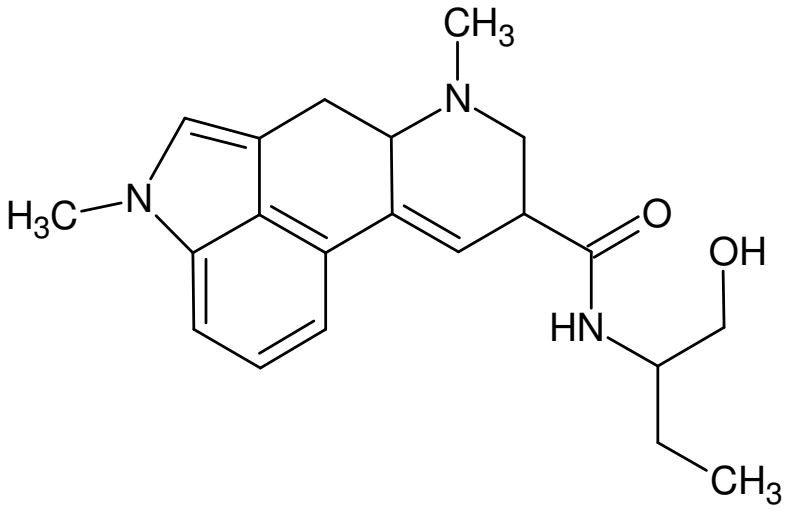
Dihydroergotamine :



(5'α)-9,10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-ergotaman-3',6',18-trione

Uses: Dihydroergotamine is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes. Dihydroergotamine binds with high affinity to 5-HT1Da and 5-HT_{1D}b receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline a2A, a2B and a receptors, and dopamine D2L and D3 receptors.

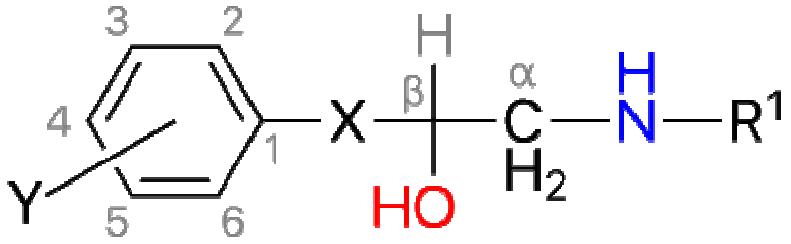
Methysergide:



(6a*R*,9*R*)-*N*-[(2*S*)-1-Hydroxybutan-2-yl]-4,7-dimethyl-6,6a,8,9-tetrahydroindolo[4,3-*fg*]quinoline-9-carboxamide

Uses: Methysergide inhibits or block the effects of serotonin, a substance which may be involved in the mechanism of vascular headaches. Serotonin (5-HT) has been variously described as a central neurohumoral agent or chemical mediator, as a "headache substance" acting directly or indirectly to lower pain threshold, as an intrinsic "motor hormone" of the gastrointestinal tract, and as a "hormone" involved in connective tissue reparative processes.

SAR of β-Adrenergic blockers:

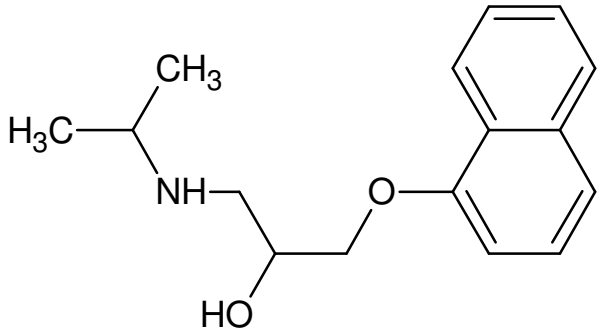


For the function of a β-blocker it's essential for the compound to contain an aromatic ring and a β-ethanolamine. The aromatic ring can either be benzoheterocyclic (such as indole) or heterocyclic (such as thiadiazole). This is mandatory. The side chains can be variable:

1. The X part of the side chain can either be directly linked to the aromatic ring or linked through a —OCH2— group.
2. When X is —CH2CH2—, —CH=CH—, —SCH2— or —NCH2—, there is little or no activity.
3. The R1 group can only be a secondary substitution and branched is the optimal choice.
4. Alkyl (—CH3) substituents on the α, β or γ carbon (if X = —OCH2—) lower beta blockade, especially at the α carbon.

The general rule for aromatic substitution is: ortho > meta > para. This gives non-selective β-blockers. Large para-substituents usually decrease activity but large ortho-groups retain some activity. Polysubstitution on carbon 2 and 6 makes the compound inactive but when the substitution is on carbon 3 and 5 there's some activity. For the highest cardioselectivity, the substituents should be as following: para > meta > ortho. All the β-blockade is in one isomer, (S)-aryloxypropylamine and (R)-ethanolamine.

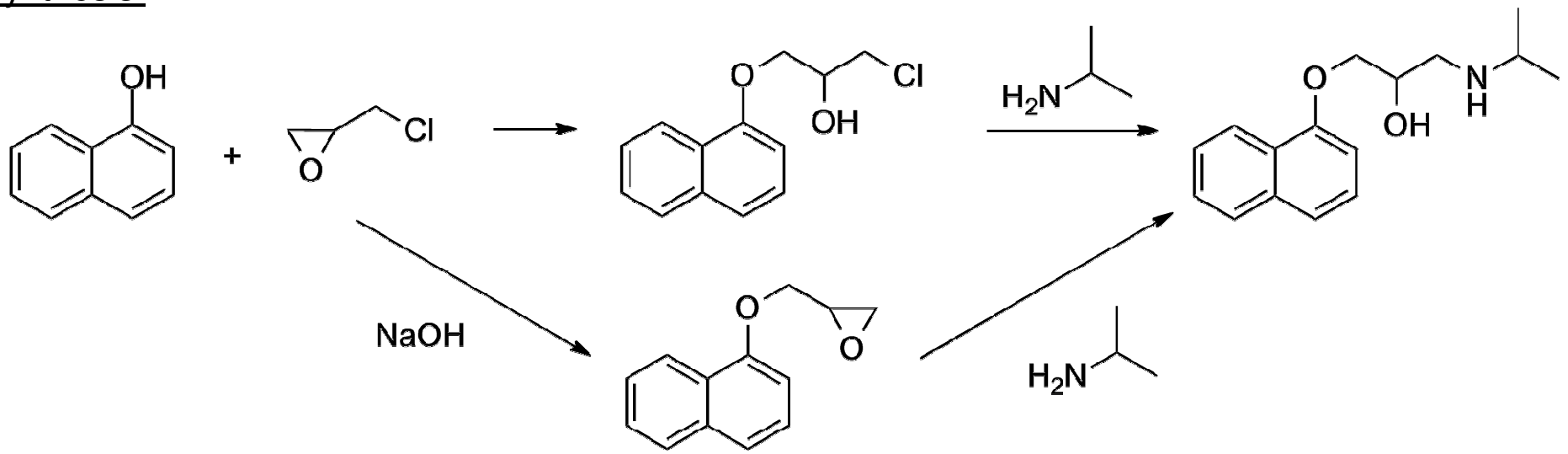
Propranolol :



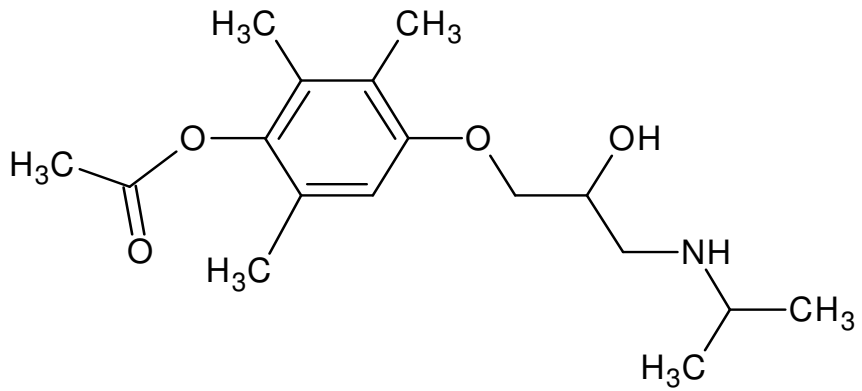
1-(naphthalen-1-yloxy)-3-(propan-2-ylamino)propan-2-ol

Uses: Propranolol, the prototype of the beta-adrenergic receptor antagonists, is a competitive, nonselective beta-blocker without having any intrinsic sympathomimetic activity. Propanolol is a racemic compound; the levo-isomer is responsible for adrenergic blocking activity.

Synthesis:



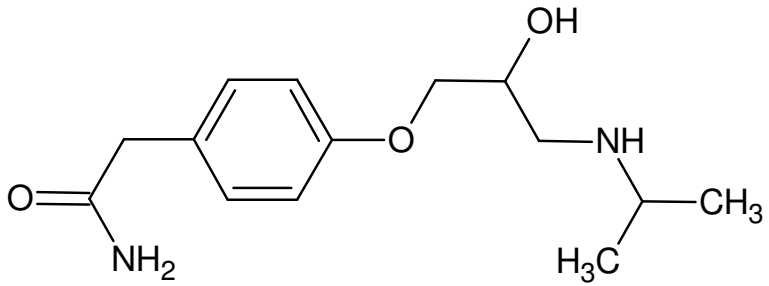
Metipranolol :



4-[2-hydroxy-3-(propan-2-ylamino)propoxy]-2,3,6-trimethylphenyl acetate

Uses: Metipranolol is a beta1 and beta2 (non-selective) adrenergic receptor-blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Metipranolol is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Metipranolol reduces intraocular pressure with little or no effect on pupil size or accommodation in contrast to the miosis which cholinergic agents are known to produce.

Atenolol :

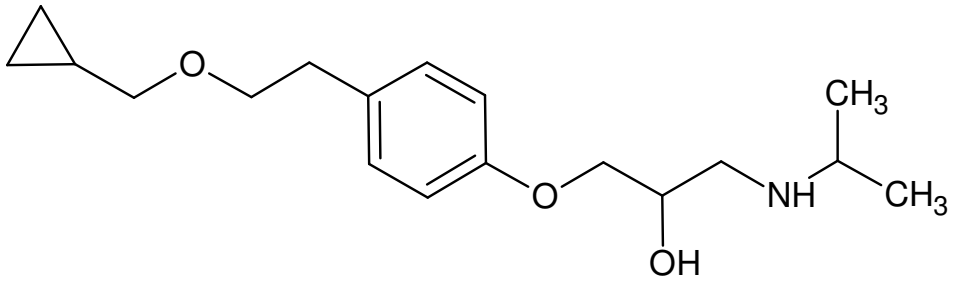


2-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide

Uses: Atenolol, a competitive beta(1)-selective adrenergic antagonist, has the lowest lipid solubility of this drug class. Although it is similar to metoprolol, atenolol differs from pindolol and propranolol in that it does not have intrinsic sympathomimetic properties or membrane-stabilizing activity. Atenolol is used alone or with chlorthalidone in the management of hypertension and edema.

Betazolol :

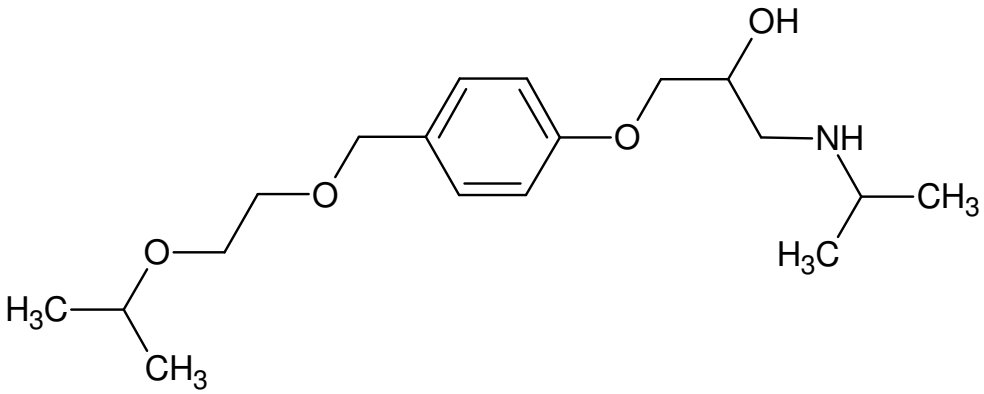
Also Called Betaxolol



(*RS*)-1-{4-[2-(cyclopropylmethoxy)ethyl]-phenoxy}-3-(isopropylamino)propan-2-ol

Uses: Betaxolol is a competitive, beta(1)-selective (cardioselective) adrenergic antagonist. Betaxolol is used to treat hypertension, arrhythmias, coronary heart disease, glaucoma, and is also used to reduce non-fatal cardiac events in patients with heart failure. Activation of beta(1)-receptors (located mainly in the heart) by epinephrine increases the heart rate and the blood pressure, and the heart consumes more oxygen. Drugs such as betaxolol that block these receptors therefore have the reverse effect: they lower the heart rate and blood pressure and hence are used in conditions when the heart itself is deprived of oxygen.

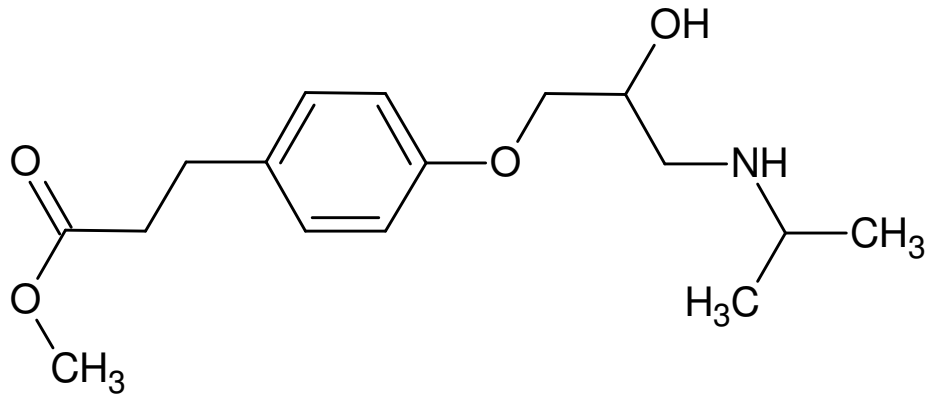
Bisoprolol :



2-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide

Uses: Bisoprolol is a competitive, cardioselective β1-adrenergic antagonist. Activation of β1-receptors (located mainly in the heart) by epinephrine increases heart rate and the blood pressure causing the heart to consume more oxygen. β1-adrenergic blocking agents such as bisopolol lower the heart rate and blood pressure and may be used to reduce workload on the heart and hence oxygen demands. They are routinely prescribed in patients with ischemic heart disease.

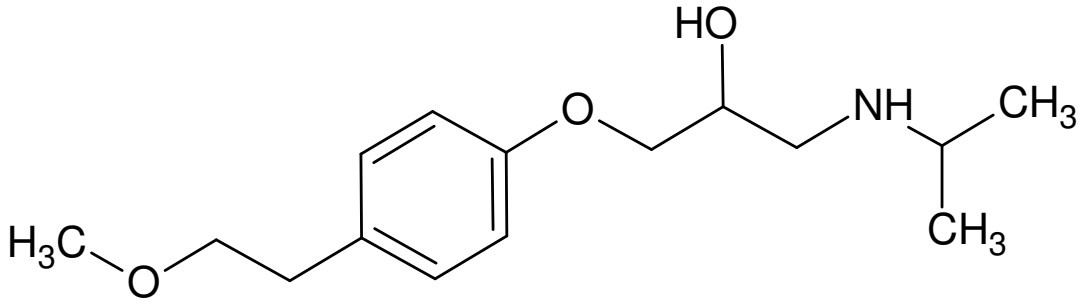
Esmolol:



(*RS*)-1-{4-[2-(cyclopropylmethoxy)ethyl]-phenoxy}-3-(isopropylamino)propan-2-ol

Uses: Drugs that bind to and block the activation of ADRENERGIC BETA-1 RECEPTORS. It is used to terminate supraventricular tachycardia, episodic atrial fibrillation or flutter, arrhythmia during anaesthesia, to reduce HR and BP during and after cardiac surgery, and in early treatment of myocardial infarction.

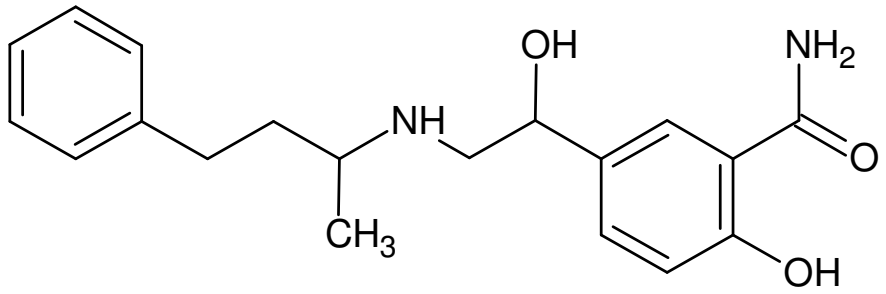
Metoprolol:



1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol

Uses: Metoprolol, marketed under the tradename Lopressor among others, is a medication of the selective β1 receptor blocker type. It is used to treat high blood pressure, chest pain due to poor blood flow to the heart, and a number of conditions involving an abnormally fast heart rate. It is also used to prevent further heart problems after myocardial infarction and to prevent headaches in those with migraines.

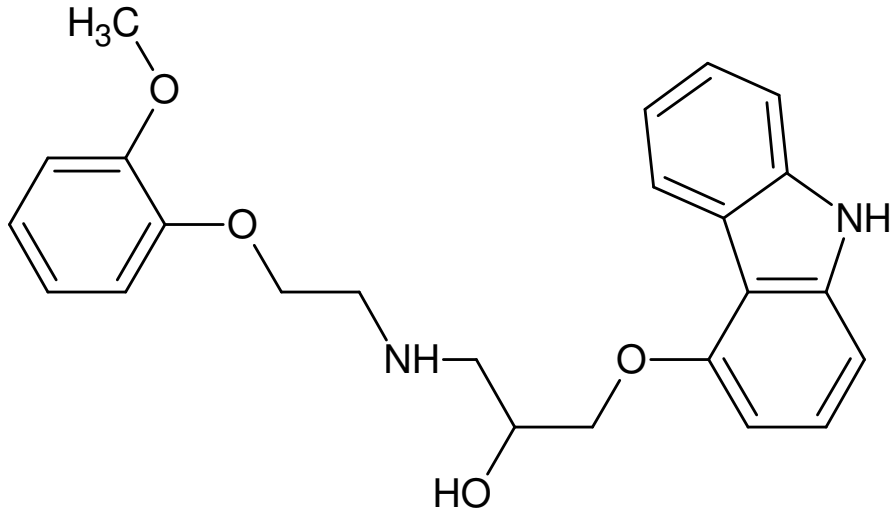
Labetolol:



2-hydroxy-5-{1-hydroxy-2-[(4-phenylbutan-2-yl)amino]ethyl}benzamide

Uses: Labetalol is an selective alpha-1 and non-selective beta adrenergic blocker used to treat high blood pressure. It works by blocking these adrenergic receptors, which slows sinus heart rate, decreases peripheral vascular resistance, and decreases cardiac output.

Carvedilol:



1-(9H-Carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol

Uses: Carvedilol is a nonselective beta-adrenergic blocking agent with alpha1-blocking activity and is indicated for the treatment of hypertension and mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency.