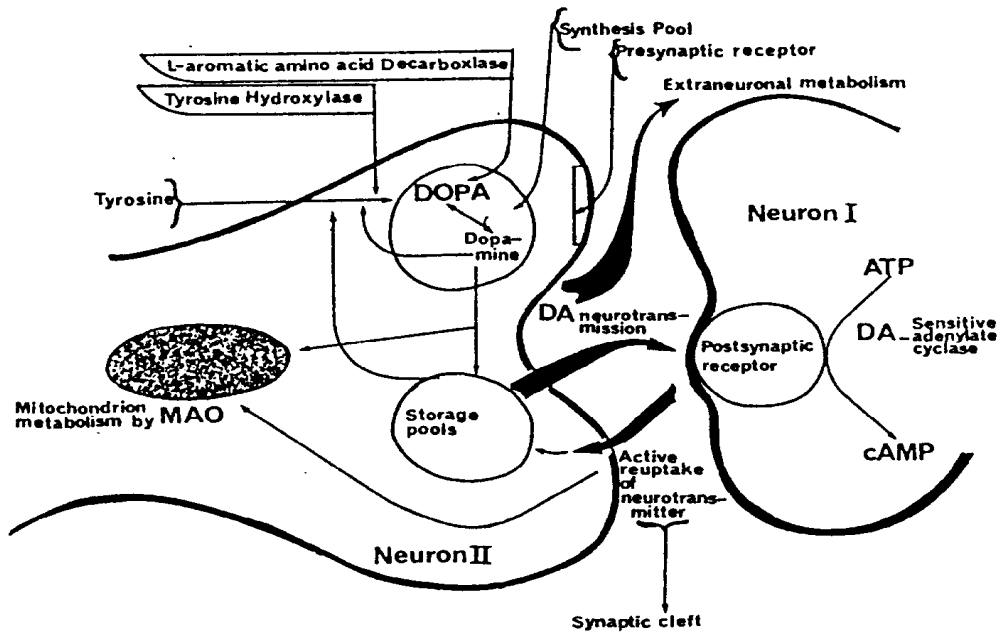
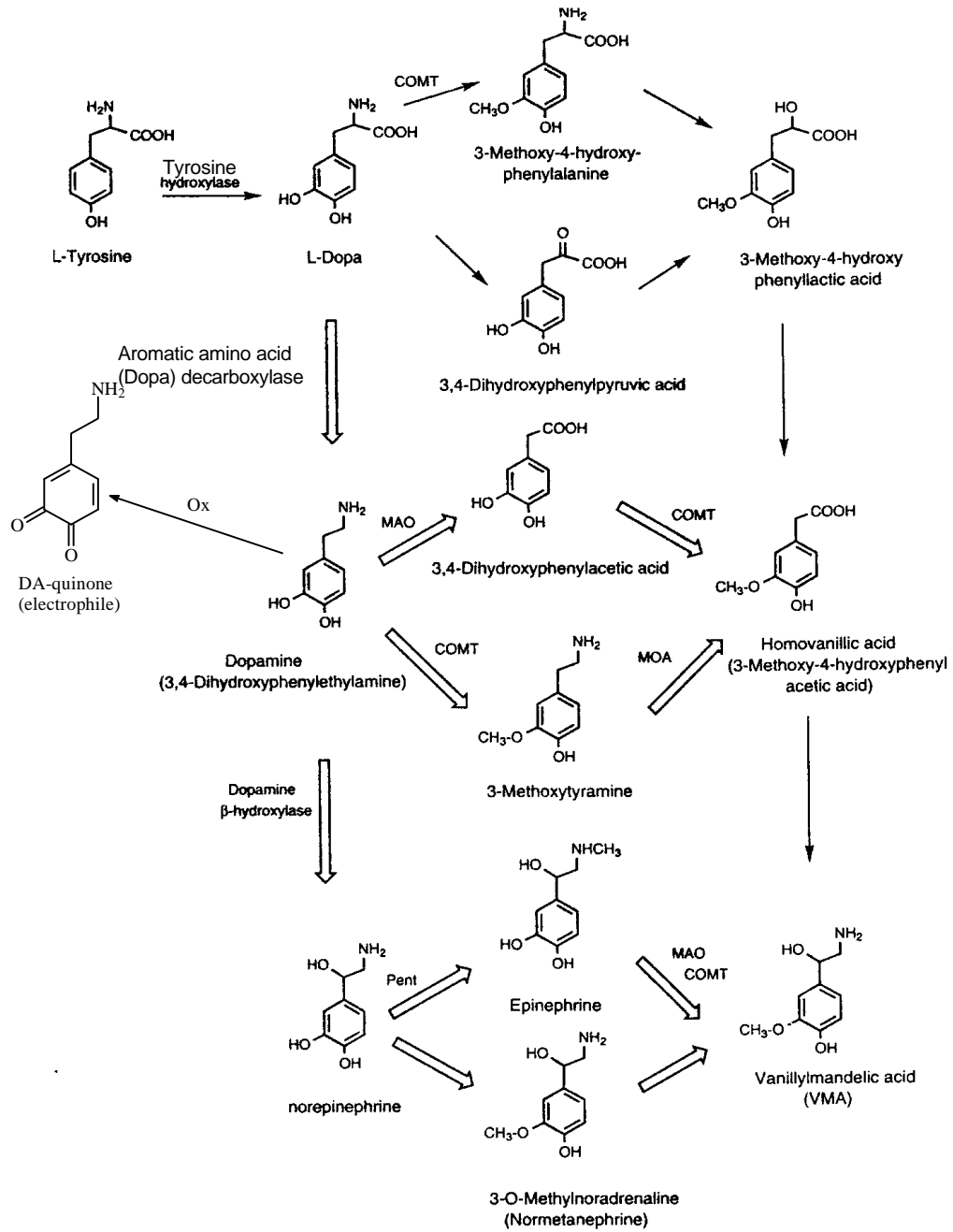


DRUGS AFFECTING BIOGENIC AMINE NEUROTRANSMISSION

Steps Involved in Dopaminergic Neurotransmission

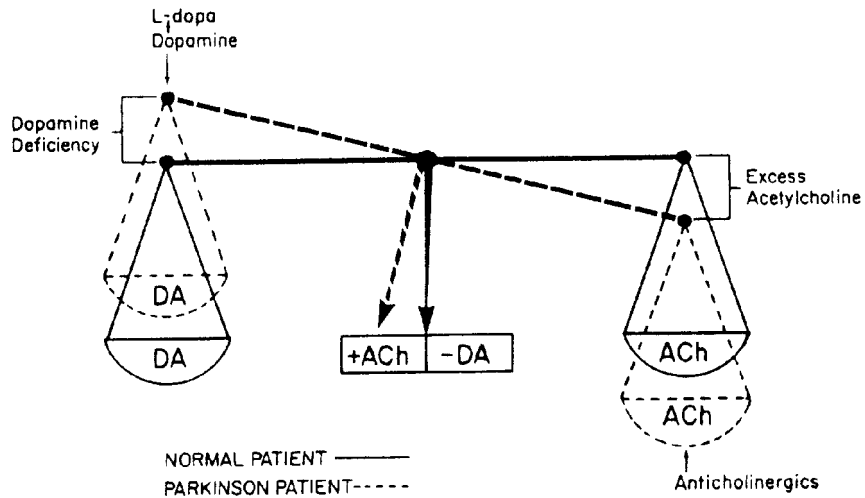


Biosynthesis and catabolism of Dopamine (heavy arrows = major pathways)



1. MEDICINAL CHEMISTRY OF DRUG THERAPY OF PARKINSON'S DISEASE (PD)

- Therapeutic goal: symptomatic relief through restoration of balance between neurotransmission by ACh and DA in the basal ganglia



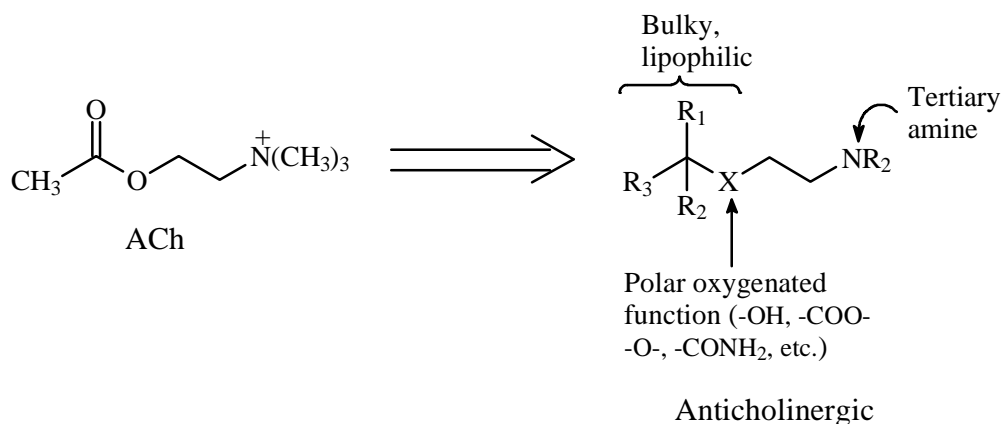
Schematic representation of the imbalance between the excitatory neurotransmitter acetylcholine (ACh) and the inhibitory neurotransmitter dopamine (DA) in the basal ganglia.

B. ANTICHOLINERGIC THERAPY

Antagonists of muscarinic acetylcholine receptors (MACHRs) in the CNS tend to diminish the characteristic tremor of parkinsonism.

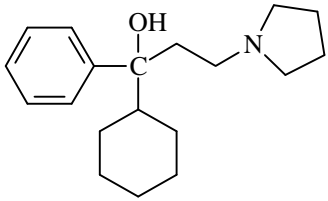
1. Structure-Activity Relationships

- structural modification of the natural MACHR ligand, Ach, leads to therapeutically useful anticholinergics:
 - replacement of the acetate moiety of ACh with a bulky, lipophilic structural feature:
 - conversion of the 4° ammonium ion of ACh to a 3° amine function ensures translocation of the drug to the CNS

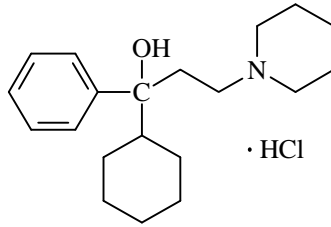


- 3° amines are less potent receptor antagonists but have greater selectivity for MACHRs vs. NACHRs but also have antagonistic affinity for other receptors, e.g. histamine H₁ and dopamine D₂
- 3°-amines > 4°-ammonium salts in lipid soly. and therefore exhibit more favorable bioavailability (systemic and CNS)

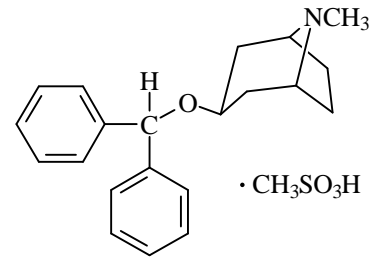
2. Antiparkinsonism Anticholinergics



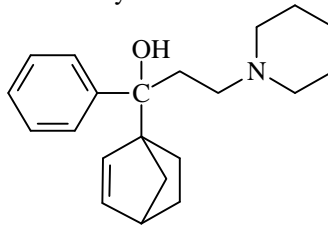
Procyclidine



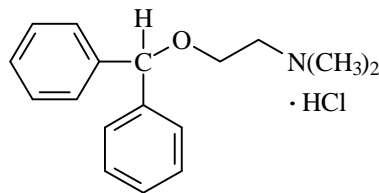
Trihexyphenidyl HCl



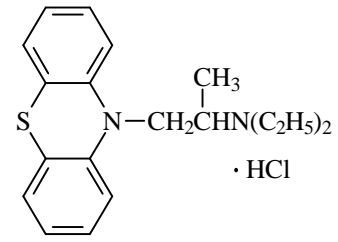
Benztropine Mesylate



Biperiden



Diphenhydramine HCl

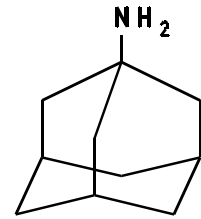


Ethopropazine HCl

B. DOPAMINERGIC THERAPY OF PARKINSONISM

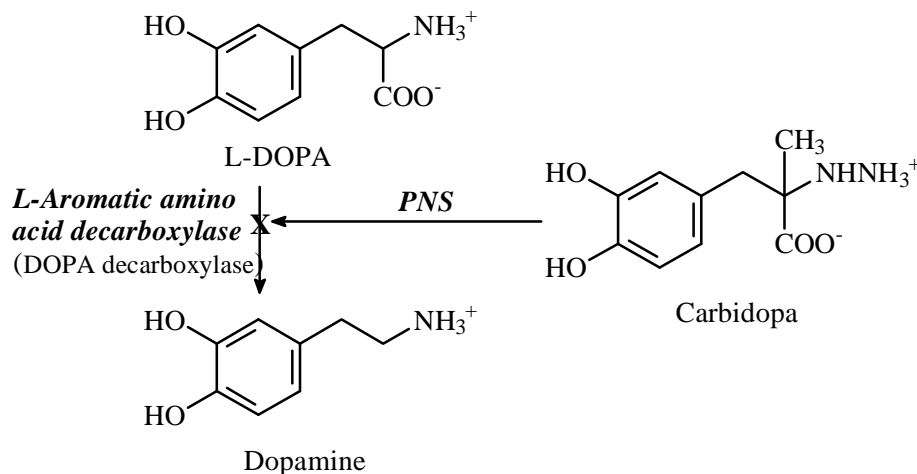
1. Dopamine-Releasing Agents

- Amantadine – displaces presynaptically stored DA into synaptic cleft
- This compound has a high pKa (10.8) and therefore is extensively ionized at physiological pH. However, its "cage-like" hydrocarbon (*adamantane*) structure of this compound provides lipophilicity and prevents oxidative metabolism so that significant quantities of the drug can penetrate the CNS,
- Disadvantages associated with the use of amantadine include low efficacy and a dependence on the presence of pre-synaptic DA stores.

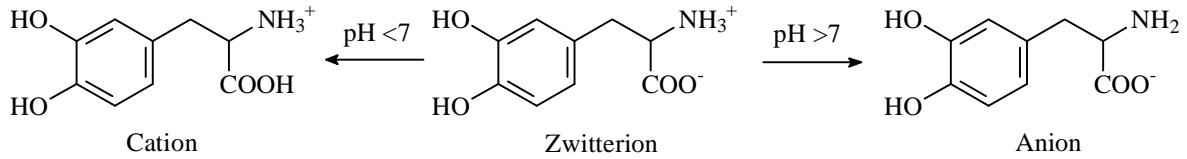


2. Dopamine Replacement (L-DOPA)

- exogenous replacement of dopamine in PD is unsuccessful because DA cannot access the CNS from the periphery because of
 - (1) structural hydrophilicity and
 - (2) ionization (a basic compound with pKa of NH₂ is 10.6, therefore it is primarily protonated at physiological pH)
- metabolic lability (peripheral deamination and conjugation) also limits systemic utility
- exogenous administration of DA produces a variety of adverse effects as a result of DA-interacting with various monoamine (NE, 5-HT, DA) receptors in both the CNS and PNS.
- effective delivery of DA to the CNS is achieved by use of the exogenous biosynthetic precursor, L-dihydroxyphenylalanine (L-DOPA) which:
 - a. accesses CNS sites via an amino acid transporter and
 - b. is readily decarboxylated in dopaminergic neurons to DA by *dopa decarboxylase*
- Significant concentrations of DA are formed in the PNS related to peripheral DOPA decarboxylase activity giving rise to peripheral DA stimulation (primarily cardiovascular effects). Addition of a *DOPA decarboxylase* inhibitor, **carbidopa**, improves the CNS bioavailability of L-DOPA

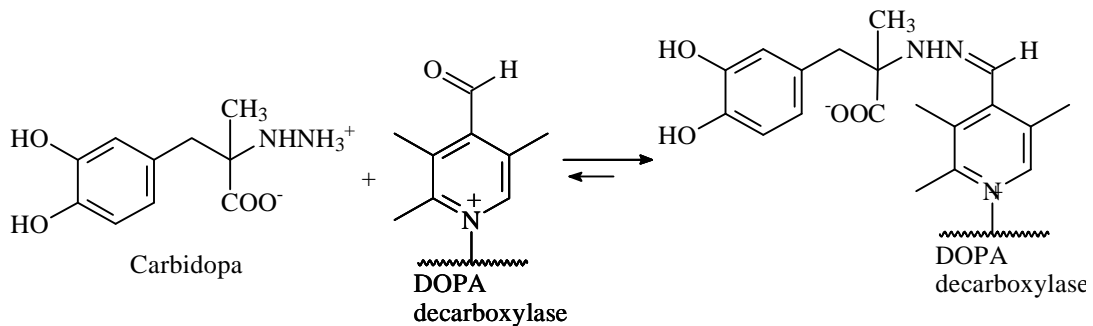


- Levodopa is absorbed from the small bowel; peak plasma levels occur in 0.5 to 2 hours, and may be delayed in the presence of food. The rate of absorption is dependent upon the rate of gastric emptying, pH of gastric juice, and the length of time the drug is exposed to degradative enzymes of gastric mucosa and intestinal flora.



- Metabolism/Excretion** - The drug is extensively metabolized (> 95%) in the periphery and by the liver; <1% of unchanged drug penetrates the CNS. Plasma half-life ranges from 1 to 3 hours. It is excreted primarily in the urine. The major urinary metabolites of levodopa appear to be dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (**Page 2**). In 24 hour urine samples, HVA accounts for 13% to 42% of the ingested dose of levodopa.

- Carbidopa** is a pyridoxal- (DOPA decarboxyase cofactor) trapping agent:

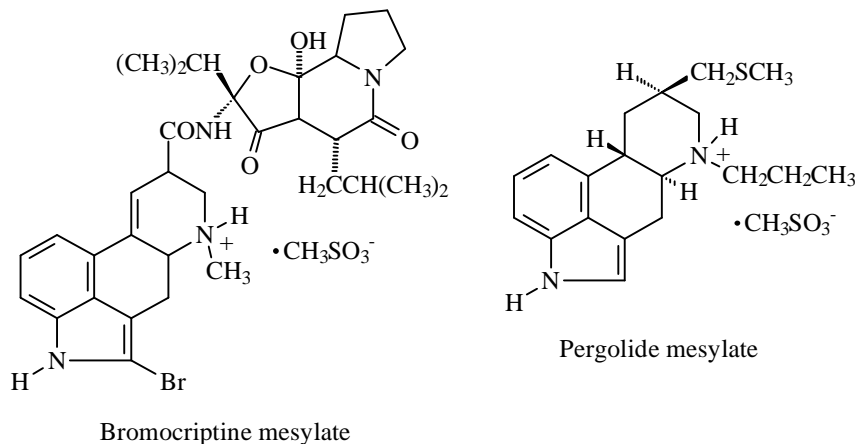
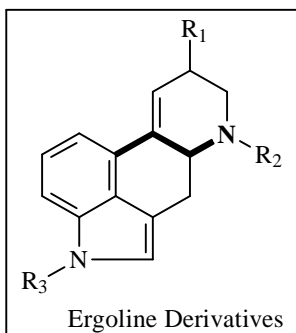


3. Dopamine Receptor Agonists

In addition to reinforcing DA neurotransmission in the substantia nigra via postsynaptic receptor activation, DA receptor agonists also reduce DA biosynthesis and turnover by activating presynaptic autoreceptors.

a. Ergoline (Ergot) Derivatives

- Natural and semi-synthetic compounds having high affinity (both agonistic and antagonistic) for monoamine (NE, DA) receptors
- All ergoline derivatives are structurally derived from alkaloid products produced by the grain fungus *Claviceps purpurea*
- **Bromocriptine** mesylate and the more potent **pergolide** mesylate are DA-receptor agonists used as adjunctive treatment to levodopa in controlling the symptoms of PD
- Affinity of ergoline derivatives for DA receptors is presumably related to the presence of a β -arylethylamine structural feature in these drugs.



b. Non-ergoline Derivatives

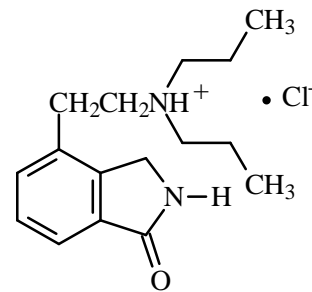
- much structurally simpler DA receptor agonists compared to ergots
- spectrum of receptor activities much more focused than ergots

Receptor Interactions of DA Agonists			
Agonist	DA	NE	5-HT
Bromocriptine [¶]	D ₂	(+)	(+)
Pergolide [¶]	D ₂ > D ₁	(+)	(+)
Ropinirole [¶]	D ₃ > D ₂ > D ₄	(-)	(-)
Pramipexole [¶]	D ₃ > D ₂ > D ₄	(+)	(-)
Lisuride	D ₂	(+)	(+)
Cabergoline	D ₂ > D ₁	(±)	(±)

[¶]Approved for PD therapy

• Ropinirole

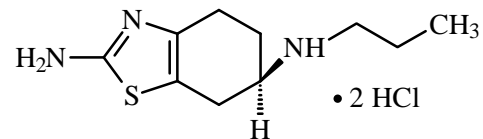
- an indolinone derivative unrelated in structure to the ergolines
- high affinity for the D₂ family of DA receptors (D₂, D₃ and D₄ subtypes)
- formulated for PO administration as HCl salt



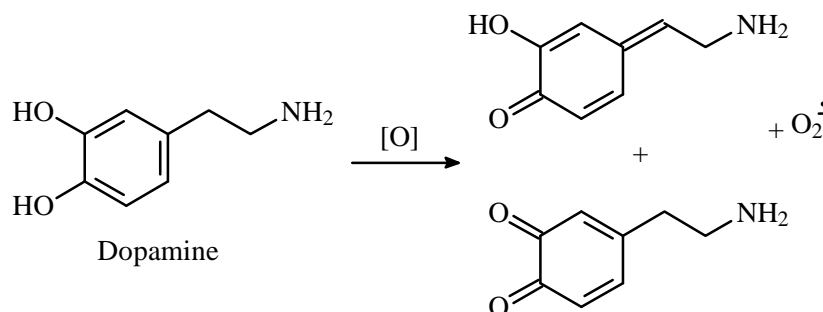
Ropinirole HCl

• Pramipexole

- a tetrahydrobenzothiazole derivative
- formulated as di-HCl salt (side chain NH and hetero N) of pharmacologically-active single (*S*-(-)) isomer
- high affinity for D₂ receptor family
- possesses a low oxidation potential which may function to scavenge (neuroprotection) DA-derived free radicals and electrophiles:



Pramipexole dihydrochloride

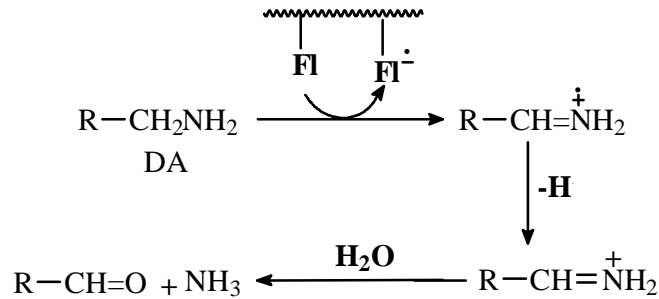


4. Metabolic Protective Agents (MPAs)

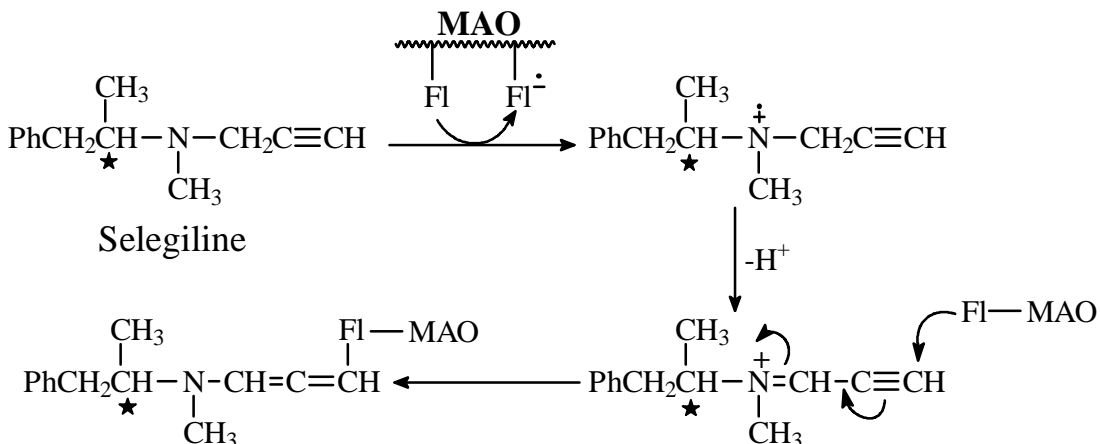
a. LAAD Inhibitors - see carbidopa

b. MAO-B inhibitors

- conservation of presynaptic DA by retardation of its catabolism by monoamine oxidase is therapeutic in managing the symptoms of PD
- early use of nonselective MAOIs confirmed their therapeutic benefit in PD but attendant adverse reactions, primarily involving cardiovascular stimulation as a result of peripheral MAOI, limited the utility of these drugs
- **Selegiline hydrochloride**
 - marketed as pharmacologically active (*R*)-enantiomer
 - an irreversible inhibitor of MAO by acting as a 'suicide' substrate for the enzyme; ie, it is converted by MAO to an electrophilic species that combines irreversibly with the flavin cofactor attached to the active-site of the enzyme,
 - selective for the *B*-type of MAO at therapeutic concentrations. MAO-B is found in high concentrations in the brain while the A-type is restricted to the intestines, liver, etc.. An important function of MAO-A, which remains intact with selegiline therapy, is that the enzyme provides protection from exogenous amines (eg, tyramine) having potent cardiovascular stimulant activity.
 - Substrate reaction:

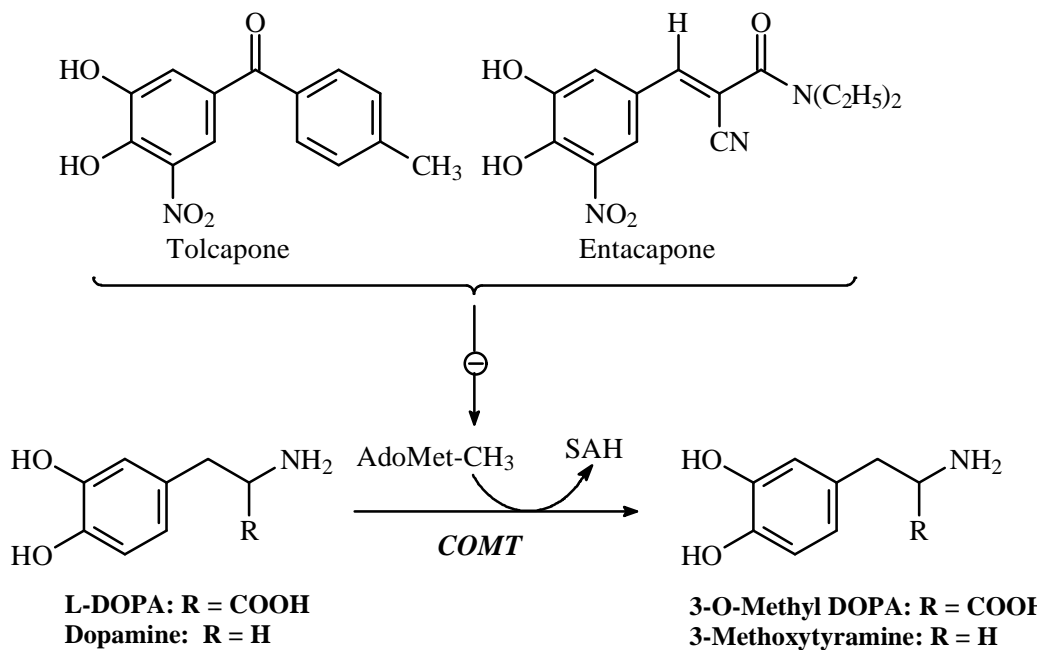


- Inhibitor (selegiline) reaction:



c. COMT inhibitors

- Inhibition of COMT activity in both the periphery and the CNS enhances the bioavailability of L-DOPA
- Two COMTIs are now available in the U.S.; **tolcapone**, an inhibitor of COMT (IC_{50} liver 36 nM; brain 2.2 nM) in both the periphery and the CNS and **entacapone**, a somewhat less potent COMT (IC_{50} liver 160 nM; brain 10 nM) that is less readily distributed to the CNS
- The nitrocatechol structural feature of both drugs confers affinity for the active site of COMT while the acetophenone moiety produces an antagonistic action
- Tolcapone has been characterized as a “tight binding” competitive inhibitor of COMT
- Entacapone has the *E*-stereochemistry about the double bond. The major metabolite of entacapone is its *Z*-isomer
- Therapeutic activity results from (1) increased bioavailability of L-DOPA to site of action and (2) reduction in formation of the potentially toxic metabolite, 3-O-methyl-L-DOPA
- Substrate reaction with tolcapone:



- The rationale for the use of the MPAs, carbidopa (AADC inhibitor) and tolcapone (COMT inhibitor) with L-DOPA therapy is depicted as follows:

