Metabolic Changes of Drugs and Related Organic Compounds

Organic Pharmaceutical Chemistry I

3rd Year Pharmacy

2018-2019

Methylation

- Methylation constitutes a minor way for conjugating drugs and xenobiotics.
- Methylation reactions play important role in the biosynthesis of endogenous compounds such as epinephrine, melatonin, norepinephrine, dopamine, serotonin and histamine.
- Methylation does not lead to polar metabolites, except when it creates a quaternary ammonium derivatives.
- Most methylated products tend to be pharmacologically inactive.
- The methyl group is supplied by the coenzyme S-adenosylmwthionine, SAM.

Substrates for Methylation

Substrates for methylation include;

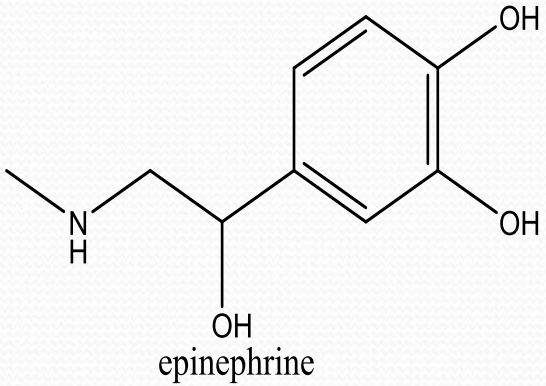
Catechols, phenols, amines and N-heterocyclic and thiol compounds. The antihypertensive drug (S)α-methyldopa (Aldomet), Isoprel, Dobutrex are examples of substrates undergoing methylation.

COMT selectively O-methylates only the phenolic OH at C-3. Bismethylation does not occur.

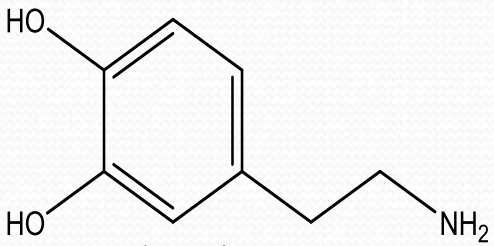
Catechol metabolites from aromatic hydroxlation of phenols and from the arene oxide dihydrodiol-catechol pathway and catechol metabolites of phenytoin undergo O-methylation.

Substrates undergoing O-methylation by COMT must have 1,2-dihydroxy groups i.e. catechol group.

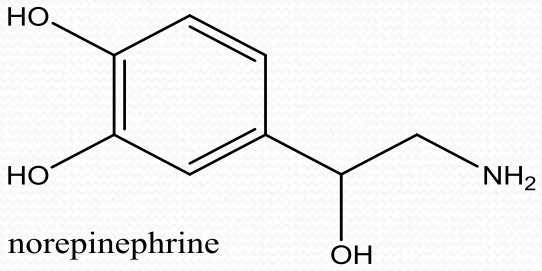
Endogenous Substrates for Methylation



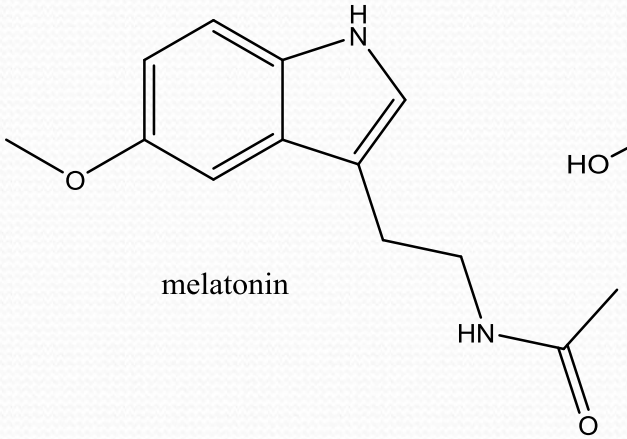
epinephrine



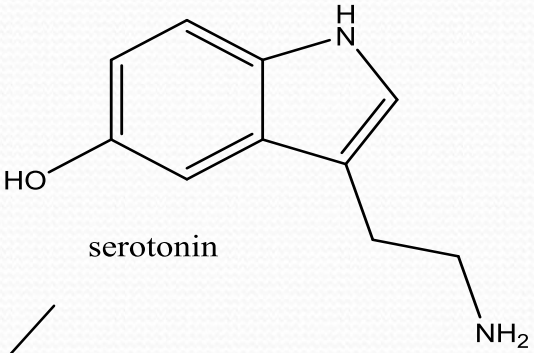
dopamine



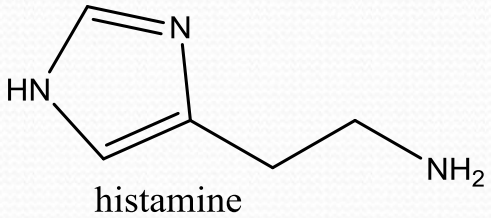
norepinephrine



melatonin

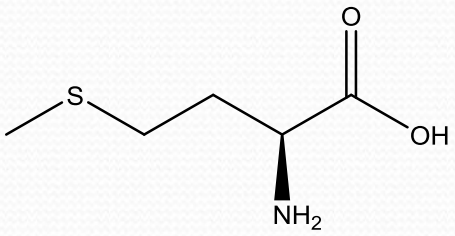


serotonin

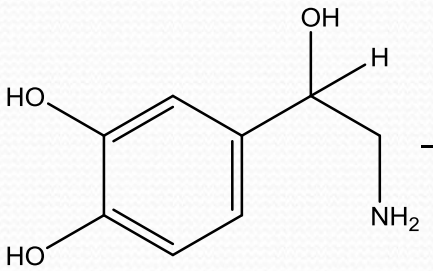


histamine

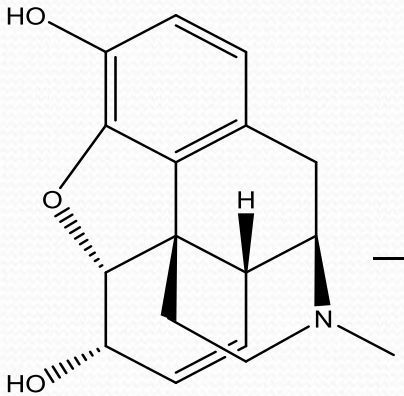
Methylation, coenzyme and



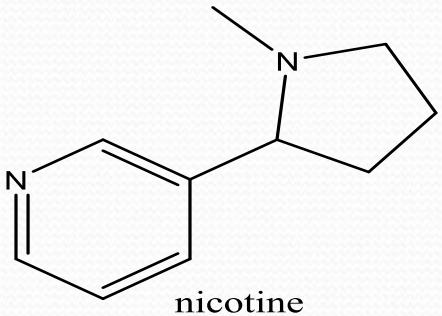
SAM (S-adenosylmethionine)



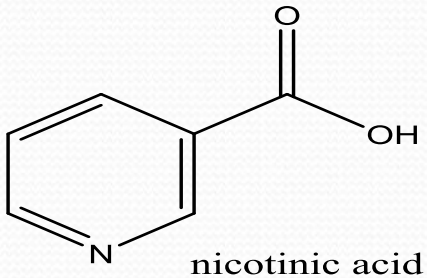
norepinephine



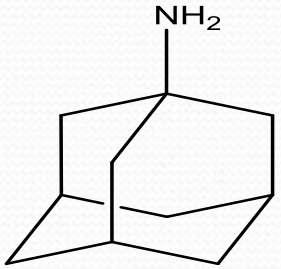
morphine



nicotine

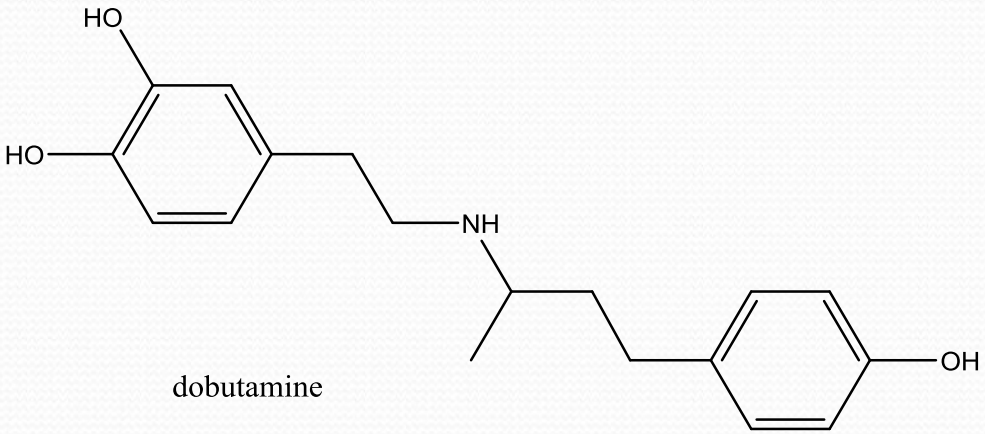


nicotinic acid

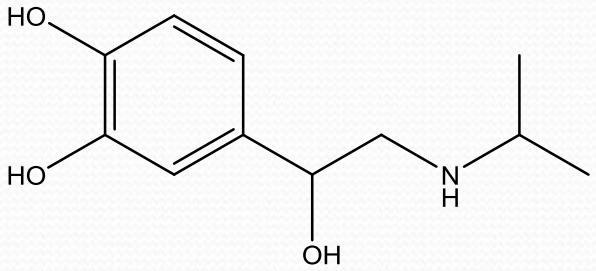


amantadine

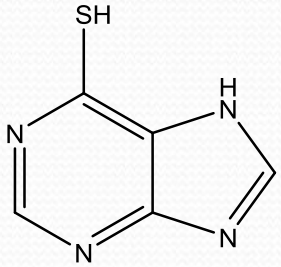
Some Substrates of Methylation



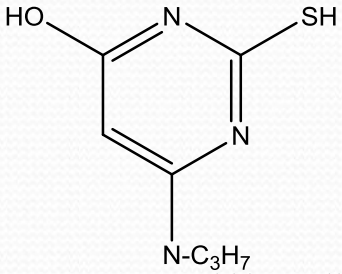
dobutamine



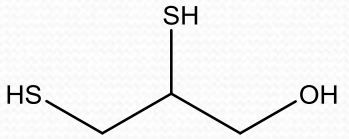
isoproterenol



6-mercaptopurine



propylthiouracil



2,3-dimetcapto-1-propanol

Methylation Transferases

Various cytoplasmic and microsomal enzymes, methyltransferases are involved in the transfer of the methyl group from SAM to the substrates.

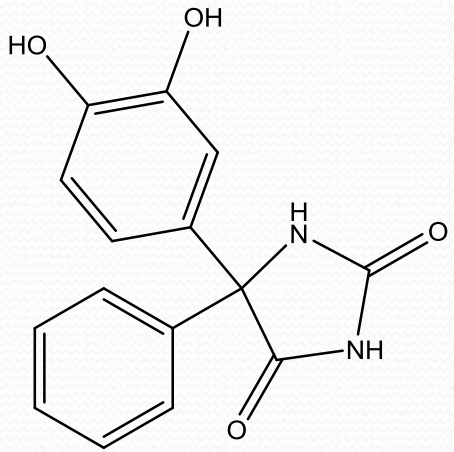
Methyltransferases for xenobiotecs include;

Catechol O-methyltransferase (COMT), Phenyl O-transferase, N-methyltransferase and S-methyltransferase.

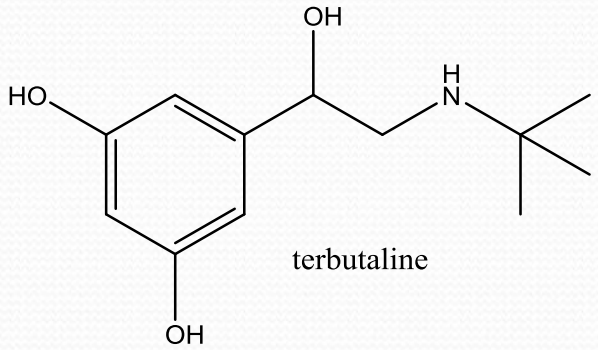
COMT is the most important methyl transfererase because it carries out O-methylation of important neurotransmitters as norephidrene and dopamine and thus terminates their activities.

COMT is distributed widely in the liver and kidneys in addition to central and peripheral nerves.

Resorcenol(1,3-dihydroxybenzene) or p-hydroxyquinone derivatives are not substrates for COMT. This explains the difference between terbutaline and resorcinol.



catechol metabolite of phenytoin



terbutaline

END OF LECTURE 9 .....GOOD LUCK