ANTIANGINAL DRUGS

- Antianginal drugs prevent, abort or terminate attacks of angina pectoris.
- Angina Pectoris is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium.

***The risk factors for the development of angina pectoris and CHD are genetic predisposition, age, male sex, and a series of reversible risk factors. The most important factors include high-fat and cholesterol-rich diets, lack of exercise, inability to retain normal cardiac function under increased exercise tolerance, tobacco and smoking (because nicotine is a vasoconstrictor), excessive alcohol drinking, carbohydrate and fat metabolic disorders, diabetes, hypertension, obesity, and the use of drugs that produce vasoconstriction or enhanced oxygen demand.

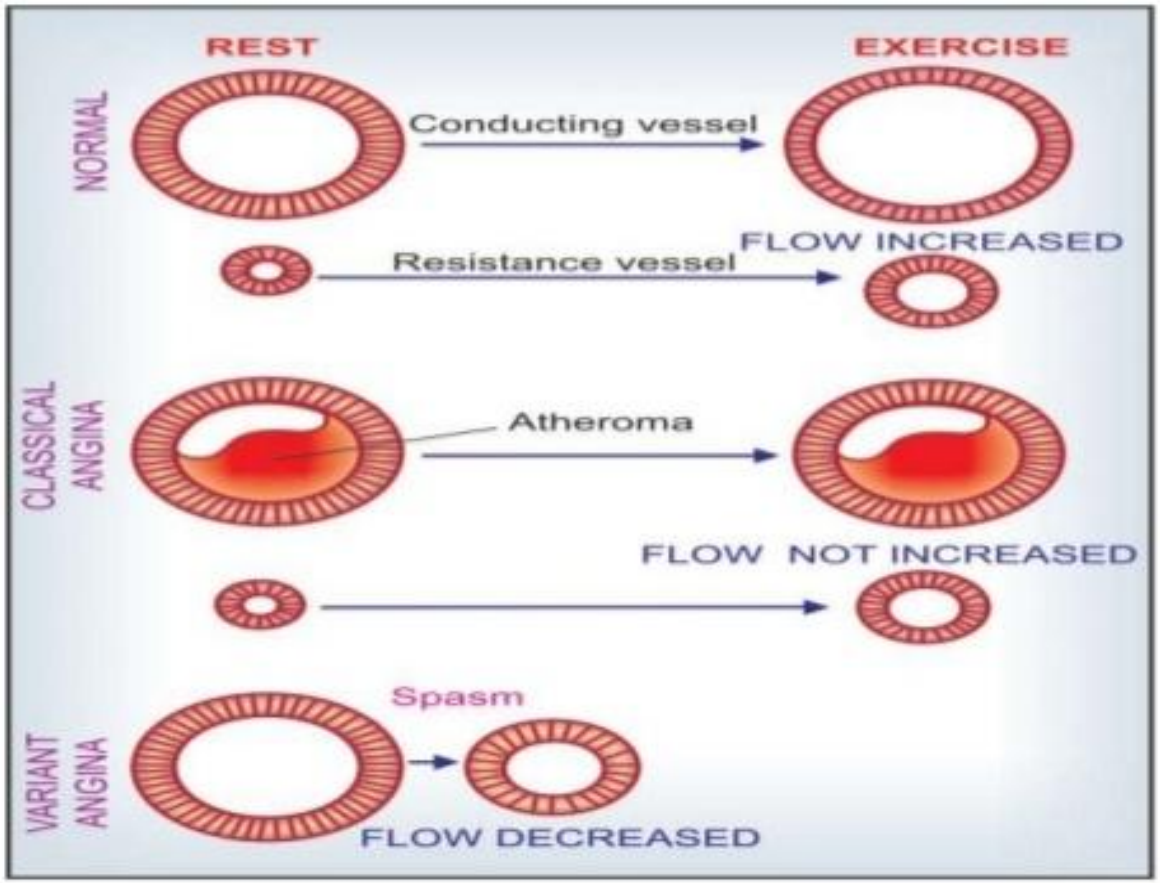


Fig. Diagrammatic representation of coronary artery caliber changes in classical and variant angina

Classification of Antianginal Drugs

1. Nitrates:

(a) Short acting: *Glyceryl trinitrate* (GTN, Nitroglycerine)
(b) Long acting: *Isosorbide dinitrate* (short acting by sublingual route*), Isosorbide mononitrate*, *Erythrityl tetranitrate, Pentaerythritol tetranitrate*.

2. Calcium Channel Blockers:

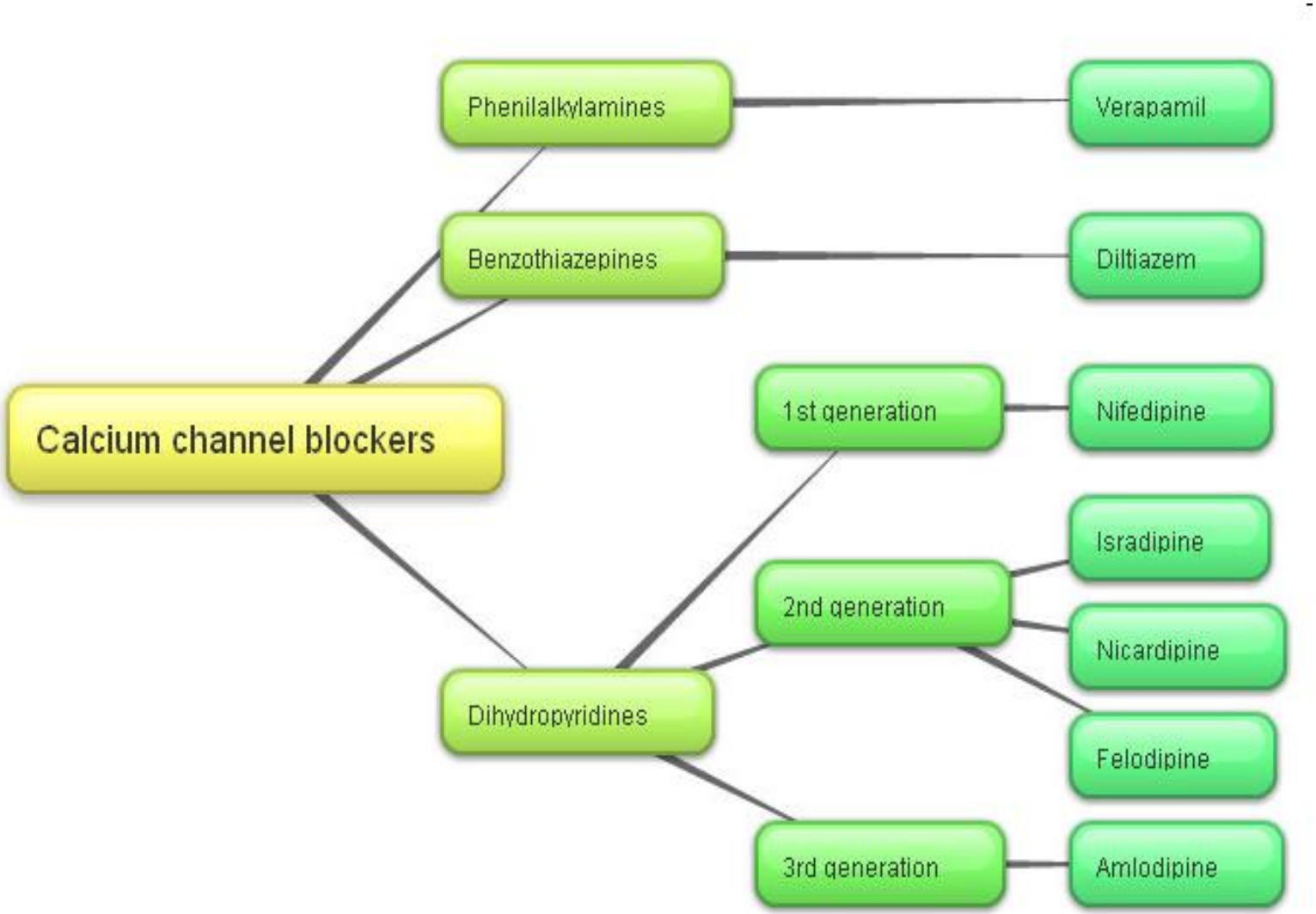
(a) Phenyl alkylamines: *Verapamil, Gallopamil*
(b) Benzothiazepine: *Diltiazem*
(c) Dihydropyridines: *Nifedipine, Felodipine, Amlodipine, Isradipine, Nitrendipine, Nimodipine, Lacidipine*, and others.

3. β Blockers:

*Propranolol, Metoprolol, Atenolo*l and others.

4. Others: Nonspesific Coronary Dilators

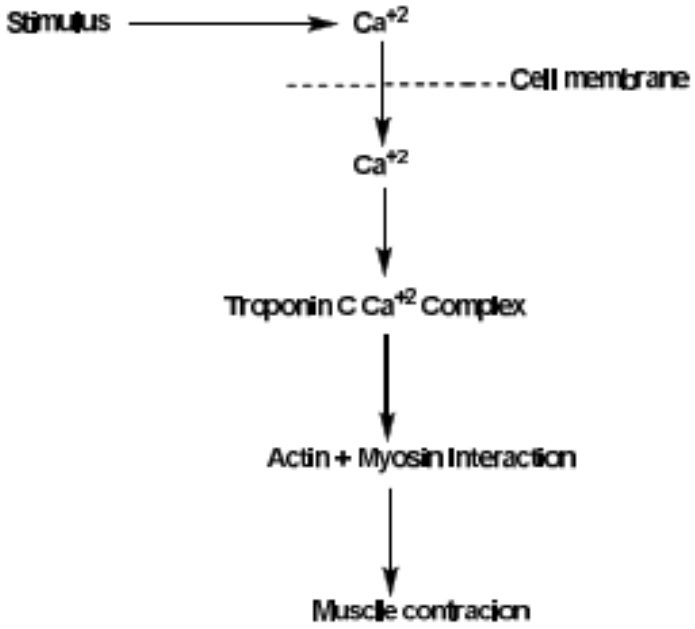
Calcium Channel Blockers - Classification



Calcium Channel Blockers

Calcium ions are known to play a critical role in many physiological functions. Inhibition of calcium ion influx into the myocardial cell may be advantageous in preventing angina.

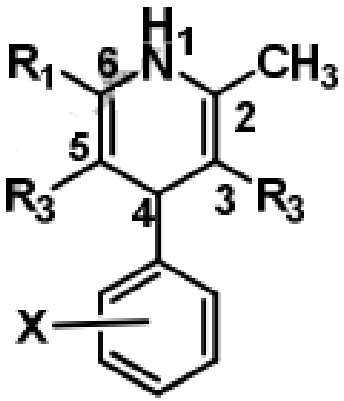
Because of the dependency of myocardium contraction on calcium ions, these drugs have a negative inotropic effect on the heart. Vascular smooth muscles also depend on calcium influx for contraction. The use of calcium channel blockers results in decreased heart work load and after load. The pre-load is not affected because of the lesser sensitivity of the venous bed to calcium channel blockers.



Sequence of events showing excitation contraction coupling in cardiac muscle

a)Dihydropyridine derivatives

The General SAR for 1,4-DHP drvs.



General structure

- 1,4-dihydropyridine ring is essential for the activity.
- Position 2,6 are substituted with alkyl gp that play a role in the drug duration of action
- Substituted Phenyl ring at C_4-position optimizes the activity [heteroaromatic rings (e.g. pyridine) show similar therapeutic activity but not used due to toxicity].
- substitution at C_4-position with a small nonplanar alkyl or cycloalkyl gp decrease activity.

Phenyl ring substitution (X):

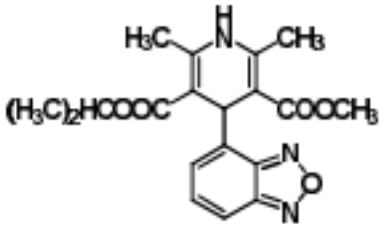
- compounds with *O*- or *m*- substitutions possess optimal activity, while those which are unsubstituted or contain *p*- substitution show a significant decrease in activity

Despite the fact that all commercially avaialable 1,4 DHPs have electron withdrawing O- & or *m*- substituents ,compounds with electron donating groups show good activity.

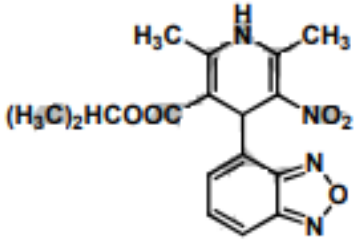
- The importance of *o*- & *m*- substituent is to provide sufficient bulk to "lock" the conformation of the 1,4DHP such that C_4 aromatic ring is perpendicular to the 1,4DHP.

This perpendicular conformation is essential for activity

- Substitution at N_1 or the use of oxidized (piperidine) or reduced (pyridine) ring systems greatly decreases or abolishes activity.
- Ester gp at C_3 and C_5 positions optimizes activity, other electron withdrawing gp show decreased antagonist activity and may show agonist activity



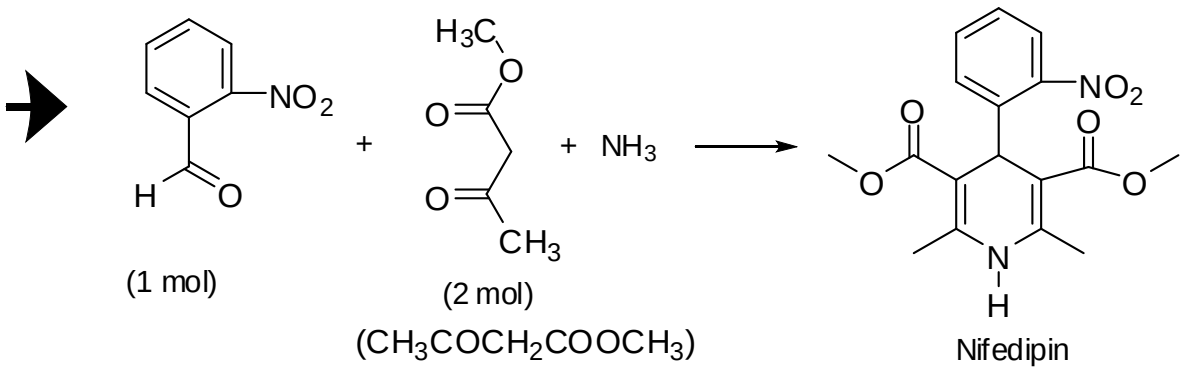
Isradipine
Calcium channel blocker

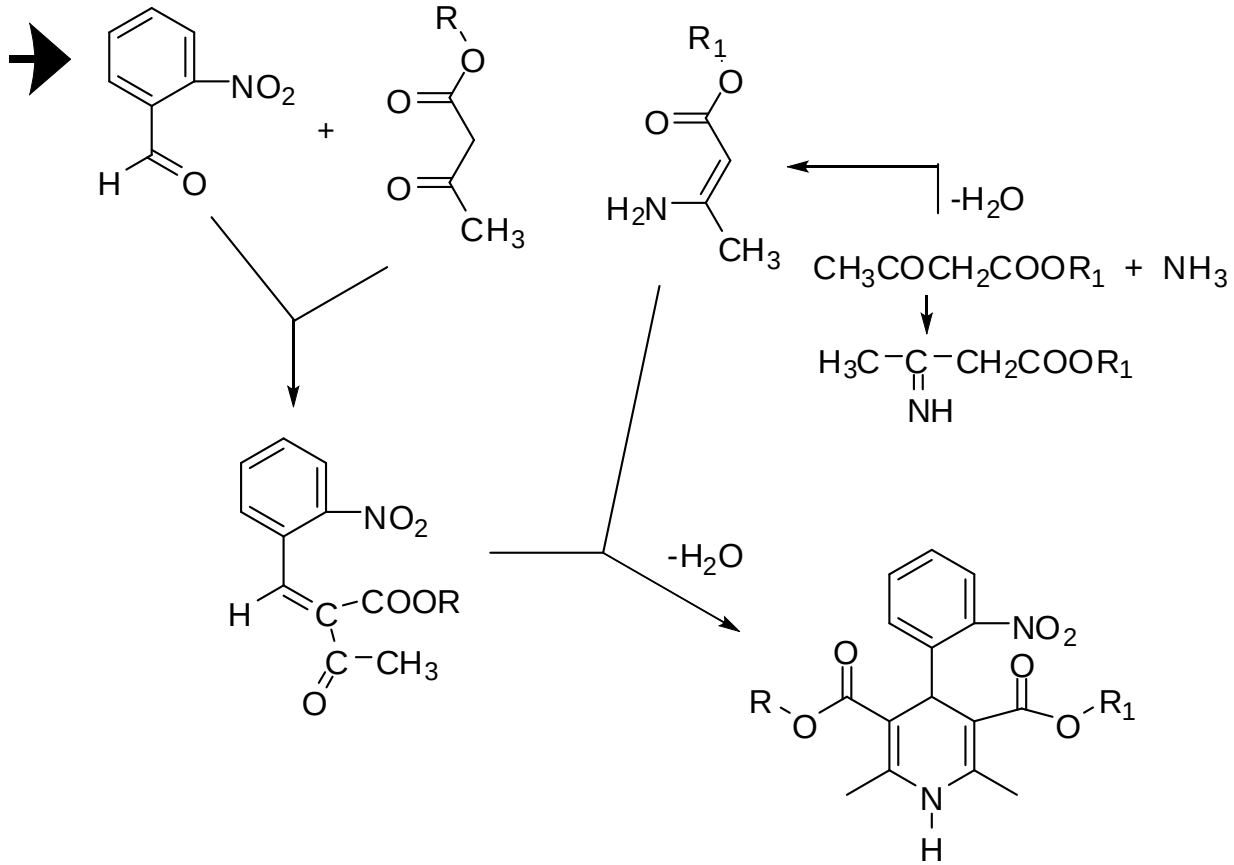


Calcium channel activator

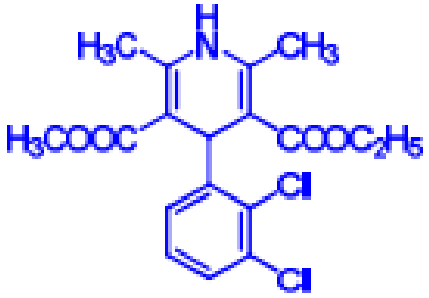
Nonidentical esters at C3 and C5 result in C4 chiral carbon (asymmetrical compounds enhance selectivity)

Hantzsch Dihydropyridine (Pyridine) Synthesis

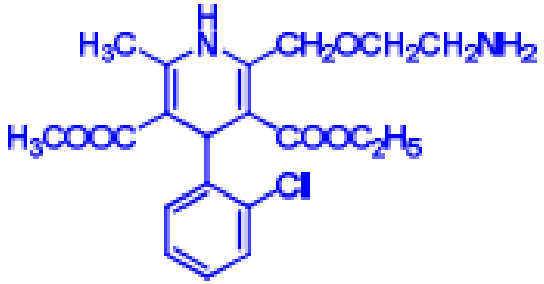




These are examples of 2 nd generation Ca^{+2} channel blockers , which are more selective for vascular smooth muscle than for cardiac tissue



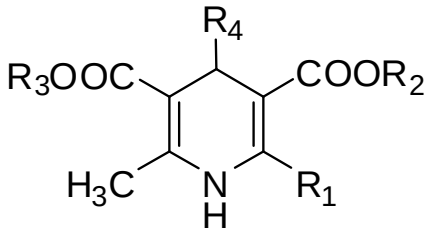
Felodipine
(Plendil)

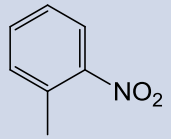
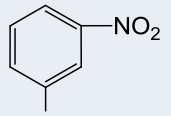
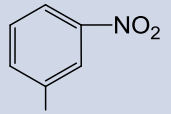
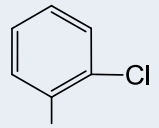


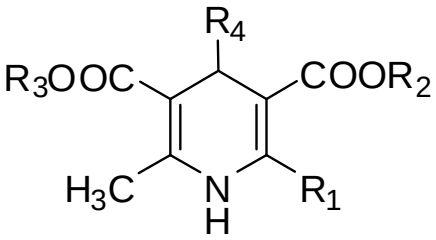
Amlodipine
(Norvasc)

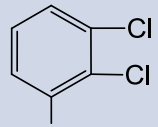
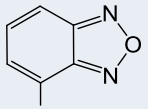
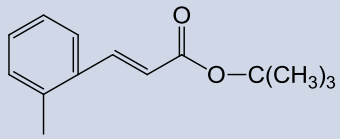
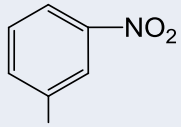
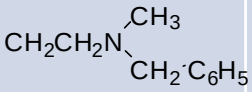
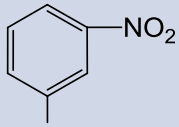
Duration 34 hours

With the exception of amlodipine, all 1,4 DHP have C_2&C_6 methyl groups. The enhanced potency of amlodipine (vs. nefidipine) suggests that 1,4 DHP receptor can tolerate larger substituents at this position and enhanced activity can be obtained by altering these groups

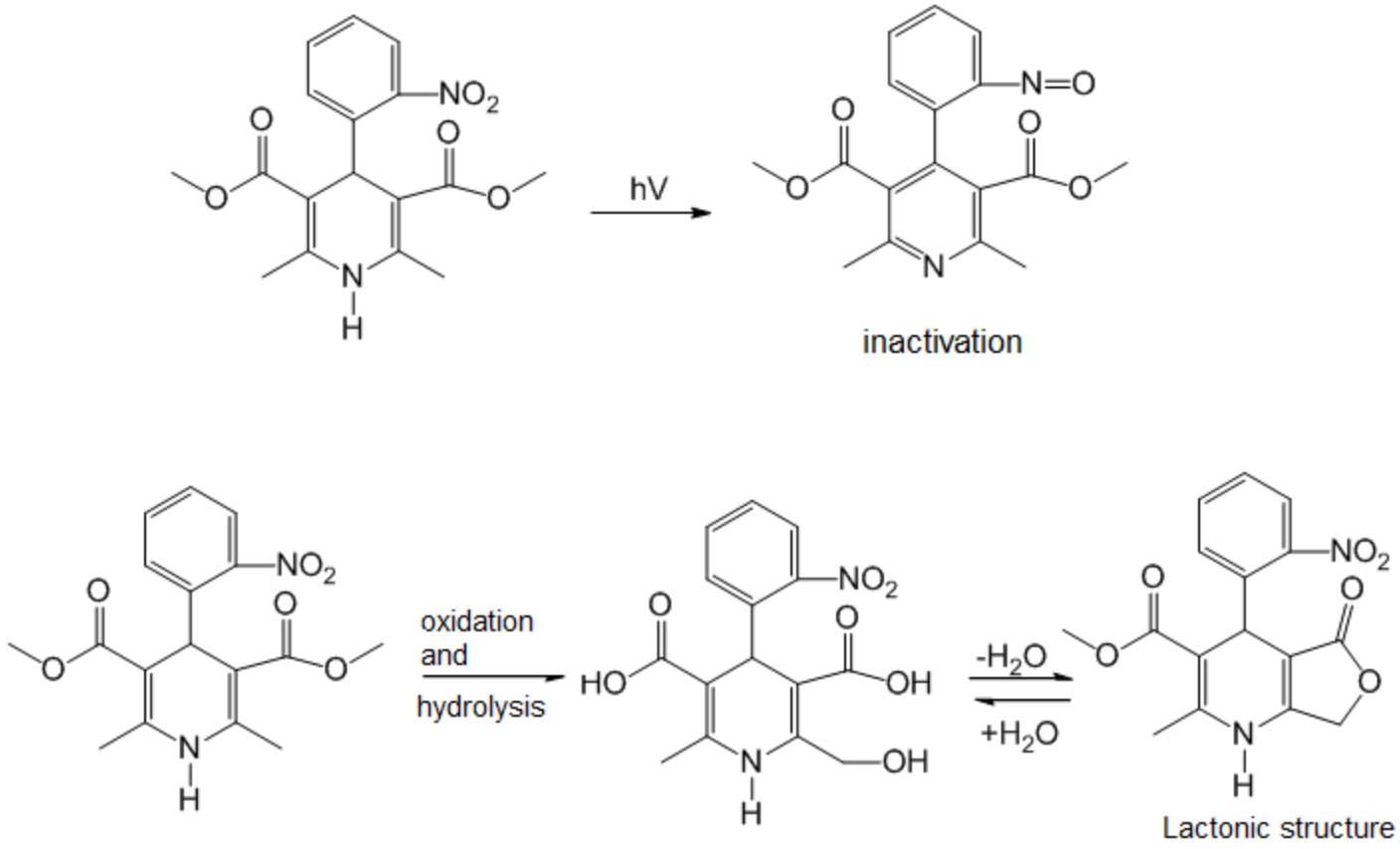


Compound	R1	R2	R3	R4
Nifedipine - ADALAT®, KARDILAT®, NIDILAT® dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	CH_3	CH_3	
Nitrendipidine-BAYPRES® 3-ethyl 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	CH_3	C_2H_5	
Nimodipine-NIMOTOP® 3-isopropyl 5-(2-methoxyethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	$-(CH_2)_2OCH_3$	$-CH(CH_3)_2$	
Amlodipine-NORVASC®, NIPIDOL® 3-ethyl 5-methyl 2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate	$-CH_2OCH_2CH_2NH_2$	C_2H_5	CH_3	



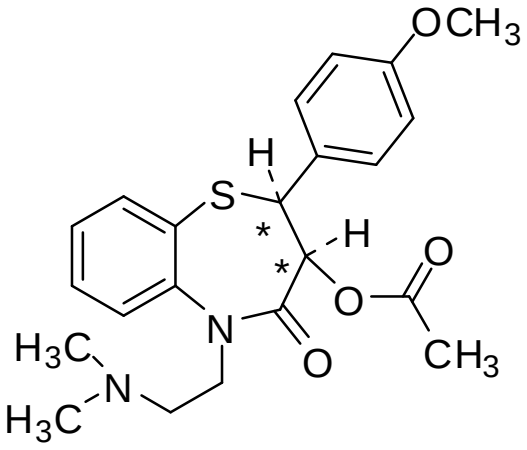
Compound	R1	R2	R3	R4
Felodipine-PLENDIL® 3-ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	C_2H_5	CH_3	
Isradipine- DynaCirc®, Prescal® 3-isopropyl 5-methyl 4-(benzo[c][1,2,5]oxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	$-CH(CH_3)_2$	CH_3	
Lacidipine-LACIPIL®, MOTENS® (E)-diethyl 4-(2-(3-tert-butoxy-3-oxoprop-1-enyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	C_2H_5	$-C_2H_5$	
Nilvadipine -NILVADIS® 5-isopropyl 3-methyl 2-cyano-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	-CN	CH_3	$-CH(CH_3)_2$	
Nicardipine-CARDENE® 3-(2-(benzyl(methyl)amino)ethyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	CH_3	CH_3		

Metabolism CYP3A4



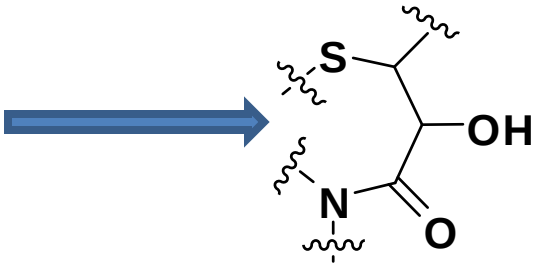
b) Benzothiazepine drvs.

Diltiazem



(2S,3S)-5-(2-(dimethylamino)ethyl)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl acetate

***Active metabolite is desacetyl diltiazem**



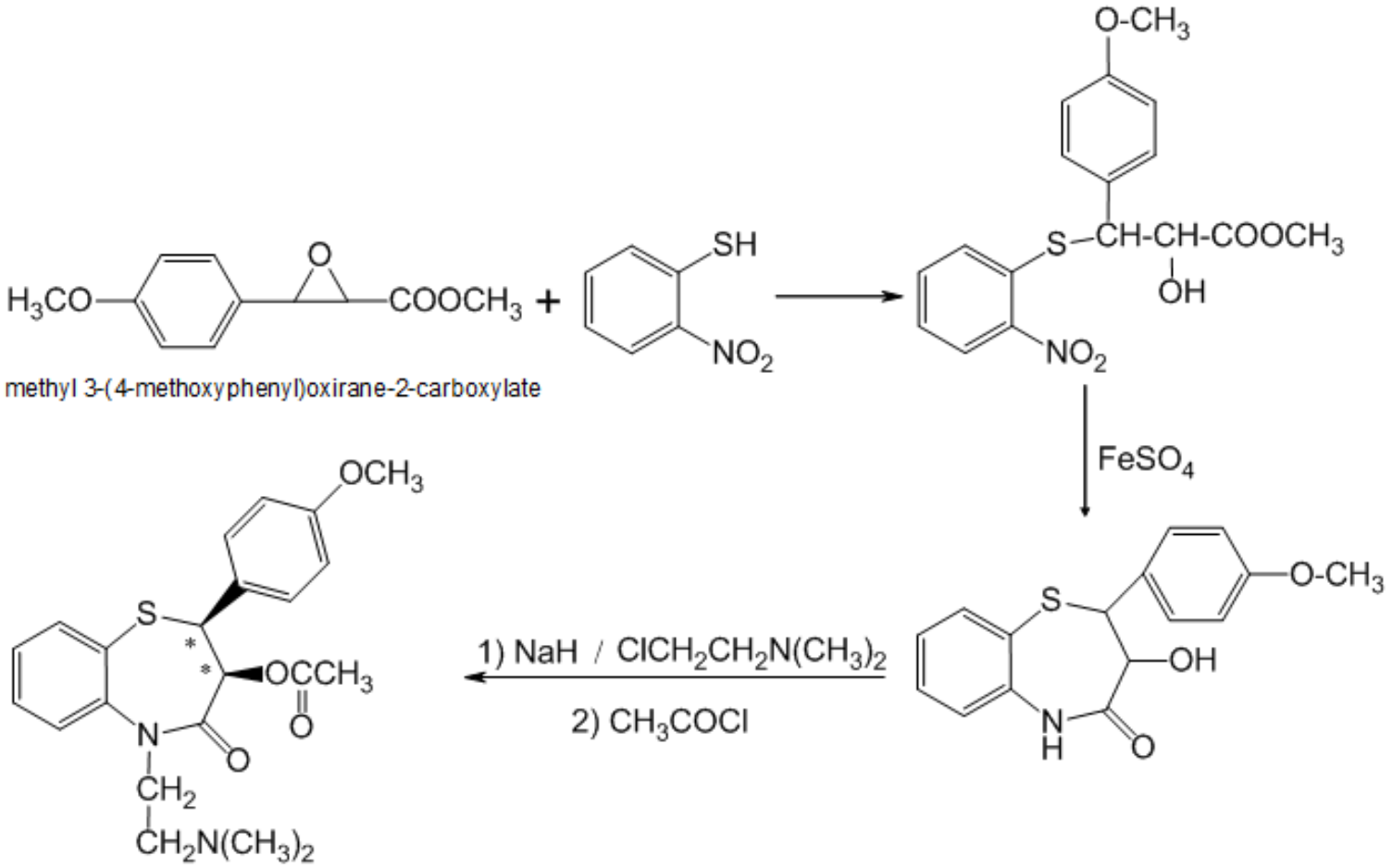
40-50% activity

***N-Demethylation -$NHCH_3$**

***O-Demethylation (congutaion via phenol)**

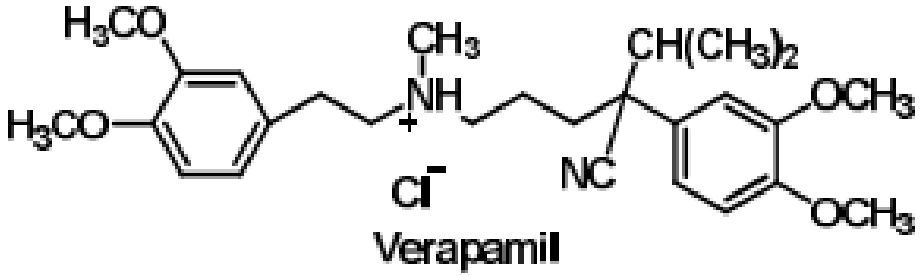
The drug is used in patients with variant angina and is used also as antiarrhythmic agent.

Synthesis of Diltiazem



c)Phenyl alkylamine drvs

Verapamil (Isoptin)

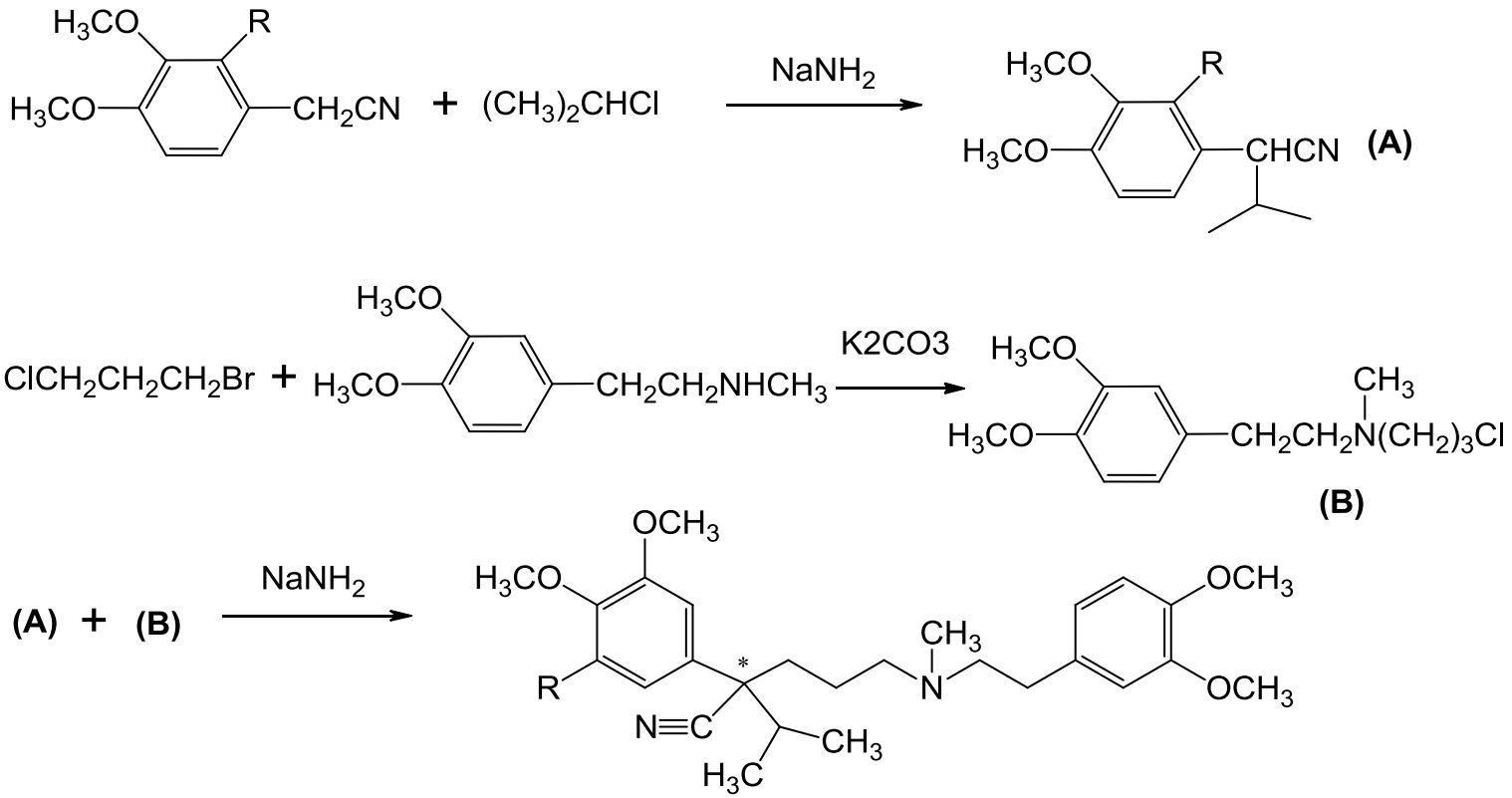


Verapamil

5-[(3,4-Dimethoxyphenethyl)-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile

Active metabolite : nor verapamil

Synthesis of Verapamil and Gallopamil



R= H ➡ Verapamil: 5-((3,4-dimethoxyphenethyl)(methyl)amino)-2-(3,4-dimethoxyphenyl)-2-isopropylpentanenitrile (ISOPTIN®, VERAMIL®)(Class IV antiarrhythmic)

R= OCH_3 ➡ Gallopamil : 5-((3,4-dimethoxyphenethyl)(methyl)amino)-2-isopropyl-2-(3,4,5-trimethoxyphenyl)pentanenitrile (PROCORUM®)

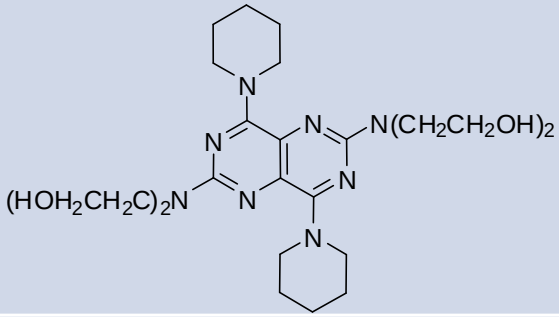
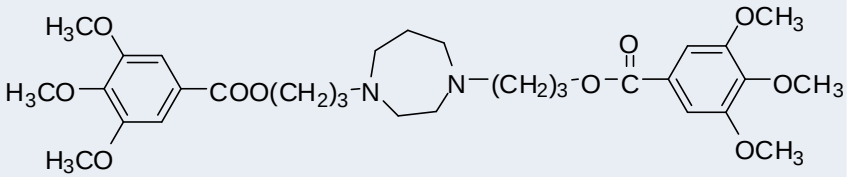
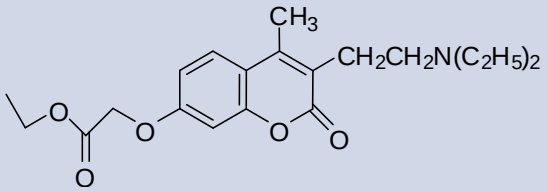
ADVERSE EFFECTS

Ca^{2+} Blockers: The adverse effects of Ca^{2+} blockers in general include: edema, flushing, hypotension, nasal congestion, palpitations, chest pain, tachycardia, headache, fatigue, dizziness, rash, nausea, abdominal pain, constipation, diarrhea, vomiting, shortness of breath, weakness, bradycardia, and AV block. Serious adverse effects of verapamil are uncommon although some patients may experience CHF and pulmonary edema. Verapamil has been reported to cause constipation. Patients on diltiazem usually will experience mild adverse effects.

DRUG–DRUG AND DRUG–FOOD INTERACTIONS

In addition to the drug–drug interactions, an interesting drug–food interaction occurs with the 1,4-DHPs and grapefruit juice. Coadministration of 1,4-DHPs with grapefruit juice produces an increase in systemic concentration of the 1,4-DHPs.

Others: Nonspesific Coronary Dilators

Compound	Formula
Dipyridamole-PERSANTIN® 2,6-Bis[diethanolamino]-4,8-dipiperidinopyrimido[5,4-d] pyrimidine 2,2',2'',2'''-(4,8-di(piperidin-1-yl)pyrimido[5,4-d]pyrimidine-2,6-diyl)bis(azanetriyl)tetraethanol	
Dilazep-CORMELIAN® 3,3'-(1,4-diazepane-1,4-diyl)bis(propane-3,1-diyl) bis(3,4,5-trimethoxybenzoate)	
Carbocromen-INTENSAIN® ethyl 2-(3-(2-(diethylamino)ethyl)-4-methyl-2-oxo-2H-chromen-7-yloxy)acetate	
Khellin 4,9-dimethoxy-7-methyl-5H-furo[3,2-g]chromen-5-one