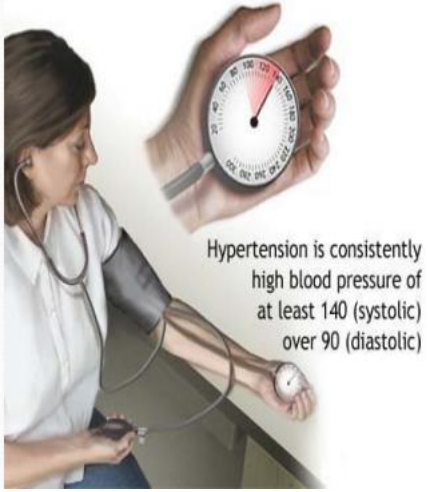
Antihypertensive Drugs

Treatment of Hypertension: 7 classification

Categories

BP	Systolic	Diastolic
Normal	>120	<80
Prehypertension	120-139	80-89
Stage1	149-159	90-99
Stage2	>160	>100



Risk factors

1. Age above 55 and 65 in Men and Woman respectively
2. Family History
3. Smoking
4. DM and Dyslipidemia
5. Hypertension
6. Obesity
7. Microalbuminuria

Antihypertensive Drugs

- Diuretics:
  - Thiazides: Hydrochlorothiazide, chlorthalidone
  - High ceiling: Furosemide
  - K+ sparing: Spironolactone, triamterene and amiloride

MOA: Acts on Kidneys to increase excretion of Na and H_2O – decrease in blood volume – decreased BP

- Angiotensin-converting Enzyme (ACE) inhibitors:
  - Captopril, lisinopril., enalapril, ramipril and fosinopril

MOA: Inhibit synthesis of Angiotensin II – decrease in peripheral resistance and blood volume

- Angiotensin (AT1) receptor blockers:
  - Losartan, candesartan, valsartan and telmisartan

MOA: Blocks binding of Angiotensin II to its receptors

Antihypertensive Drugs

- Centrally acting:
  - Clonidine, methyldopa

MOA: Act on central α2A receptors to decrease sympathetic outflow – fall in BP

- ß-adrenergic blockers:
  - **Non selective:** Propranolol (others: nadolol, timolol, pindolol, labetolol)
  - **Cardioselective:** Metoprolol (others: atenolol, esmolol, betaxolol)

MOA: Bind to beta adrenergic receptors and blocks the activity

- ß and α – adrenergic blockers:
  - Labetolol and carvedilol
- α – adrenergic blockers:
  - Prazosin, terazosin, doxazosin, phenoxybenzamine and phentolamine

MOA: Blocking of alpha adrenergic receptors in smooth muscles - vasodilatation

Antihypertensive Drugs –

- Calcium Channel Blockers (CCB):
  - Verapamil, diltiazem, nifedipine, felodipine, amlodipine, nimodipine etc.

MOA: Blocks influx of Ca++ in smooth muscle cells – relaxation of SMCs – decrease BP

- K+ Channel activators:
  - Diazoxide, minoxidil, pinacidil and nicorandil

MOA: Leaking of K+ due to opening – hyper polarization of SMCs – relaxation of SMCs

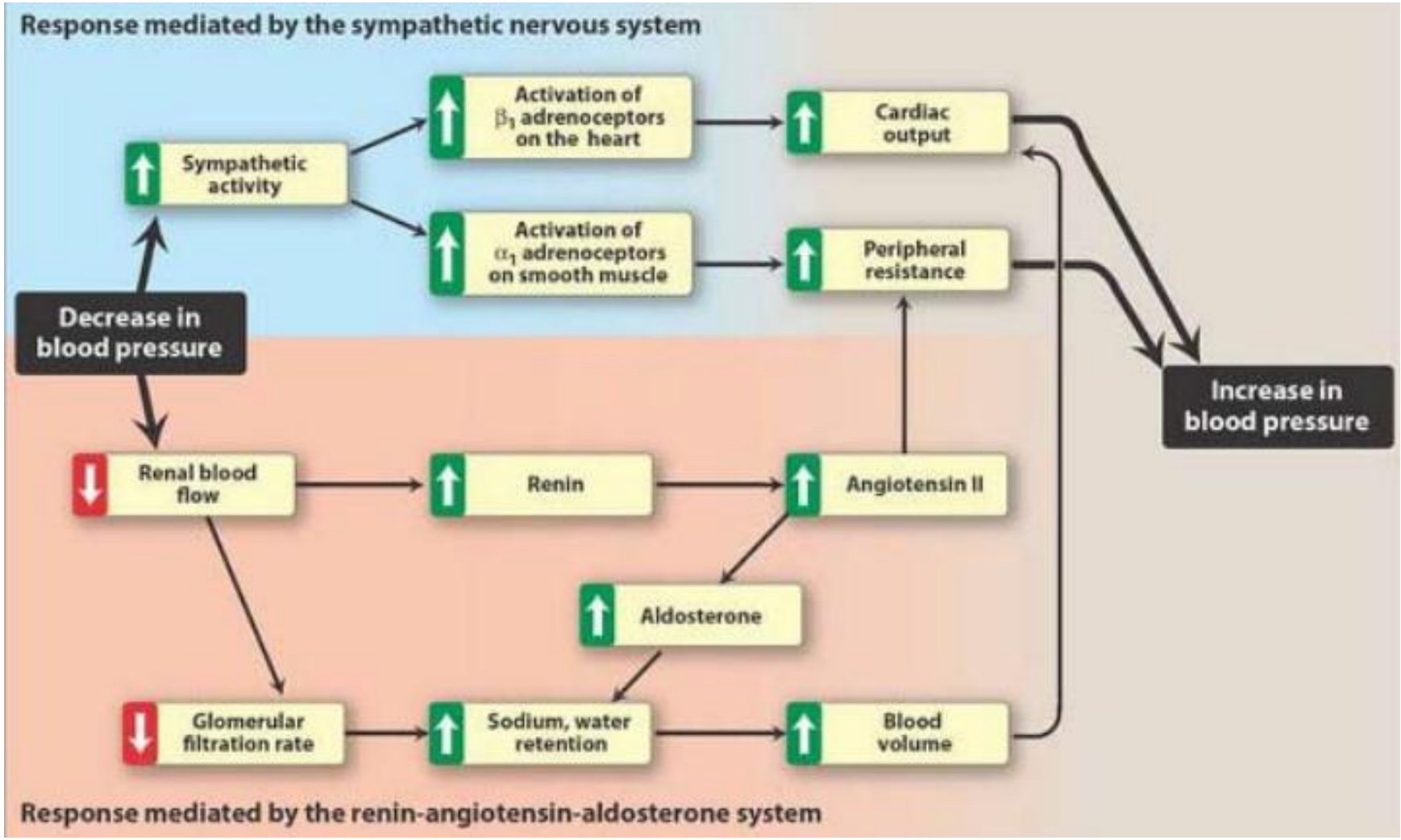
- Vasodilators:
  - Arteriolar – Hydralazine (also CCBs and K+ channel activators)
  - Arterio-venular: Sodium Nitroprusside

Angiotensin Converting Enzyme (ACE) Inhibitors

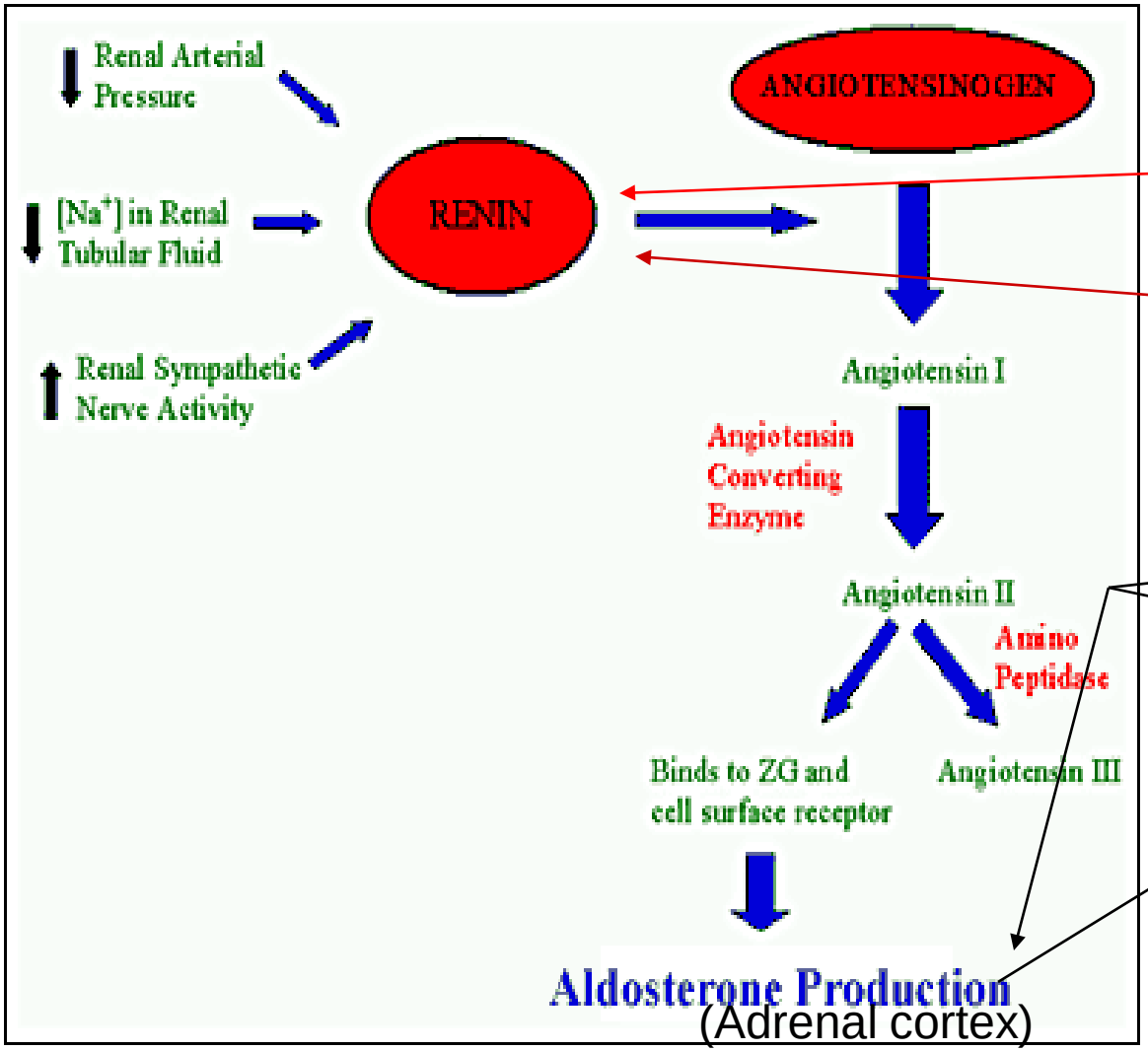
What is Renin - Angiotensin?

(Physiological Background)

Response of the autonomic nervous system and the reninangiotensin-aldosterone system to a decrease in blood pressure



RAS - Physiology



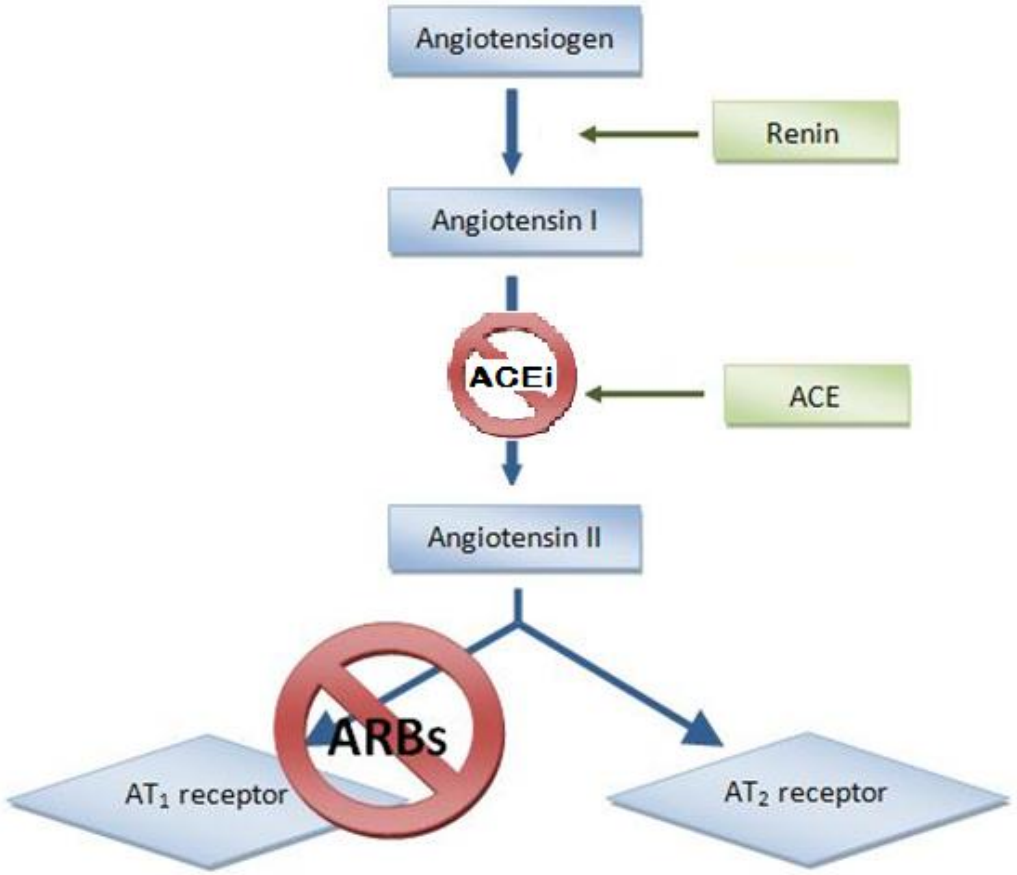
Angiotensin-II

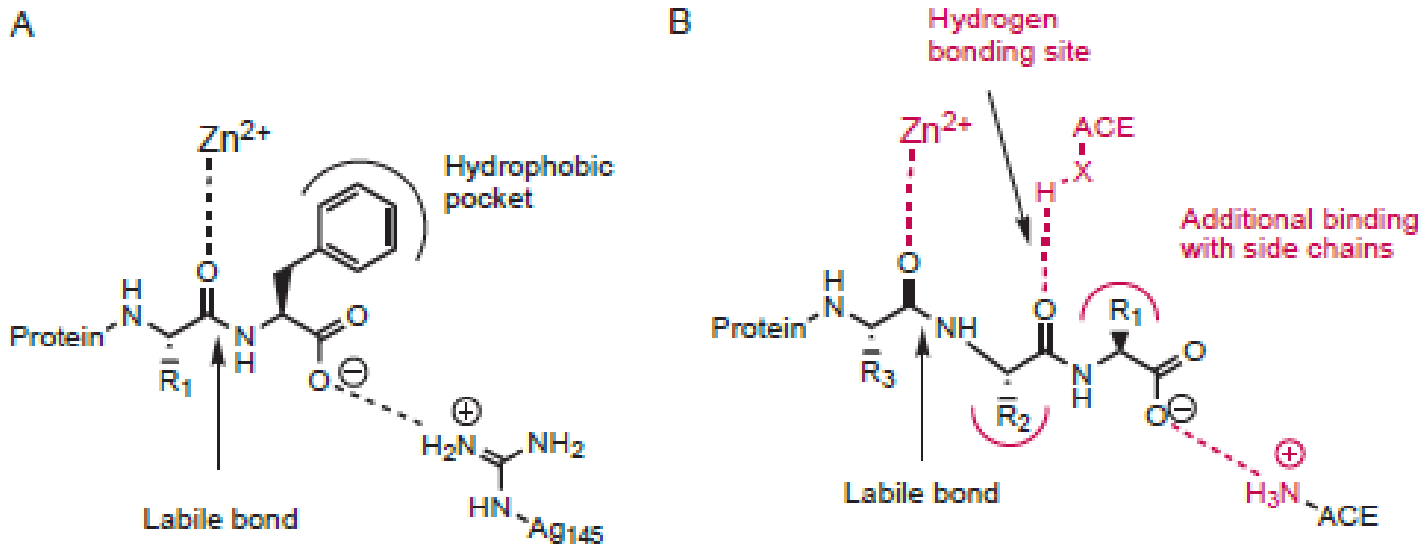
- What are the ill effects on chronic ?
  - Volume overload
    - Cardiac hypertrophy and remodeling
    - Coronary vascular damage and remodeling
  - Hypertension – long standing will cause ventricular hypertrophy
  - Myocardial infarction – hypertrophy of non-infarcted area of ventricles
  - Renal damage
  - Risk of increased CVS related morbidity and mortality
- ACE inhibitors reverse cardiac and vascular hypertrophy and remodeling

ACE inhibitors

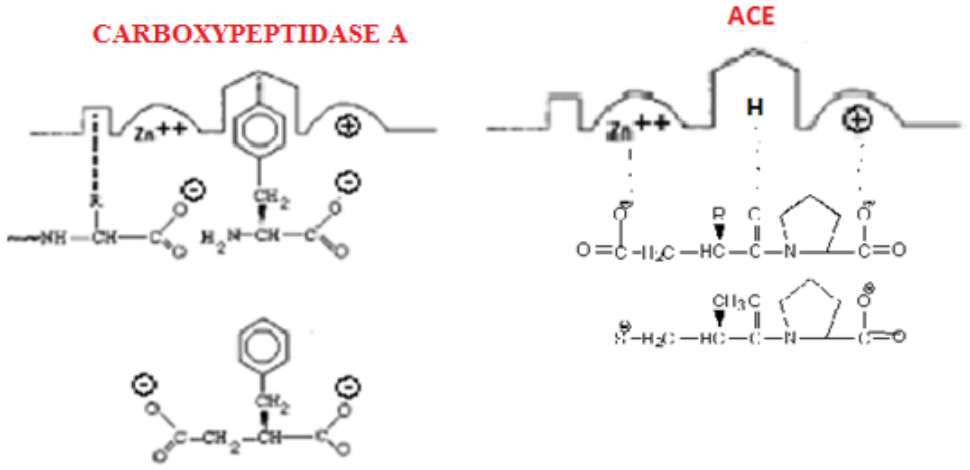
- ACE Inhibitors block the angiotensin-converting enzyme, thus preventing the formation of angiotensin II.
- Also prevent the breakdown of the vasodilating substance, bradykinin

Result: decreased systemic vascular resistance (afterload), vasodilation, and therefore, decreased blood pressure



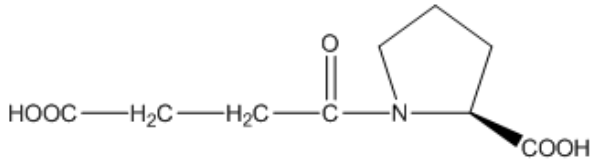


A model of substrate binding to carboxypeptidase A (A) and ACE (B). ACE substrate binding sites are highlighted in red.

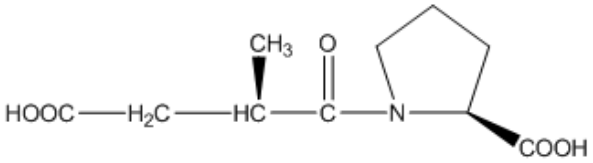


(R)-2-benzyl succinic acid

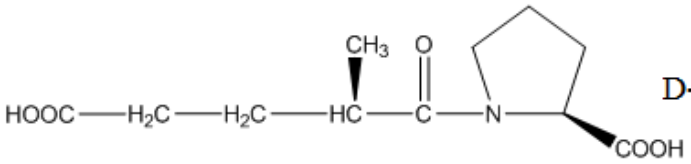
Development of ACE Inhibitors



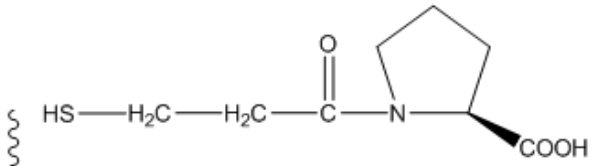
N-Succinyl-L-proline



SQ 13,297
D-2-Methylsuccinyl-L-proline

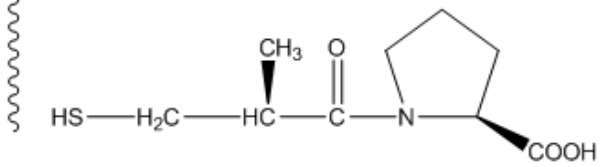


D-2-Methylglutaryl-L-proline



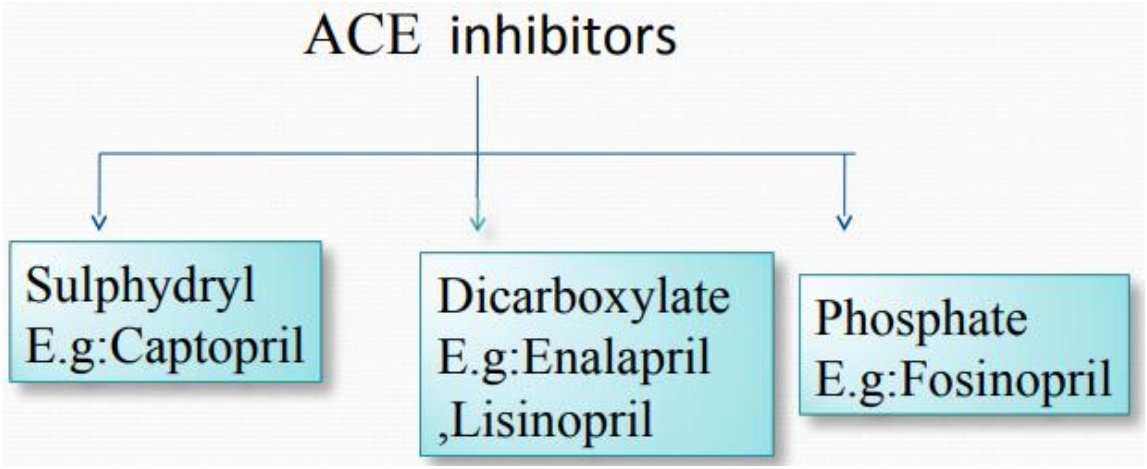
SQ 13,863
3-Mercapto propanoyl-L-proline

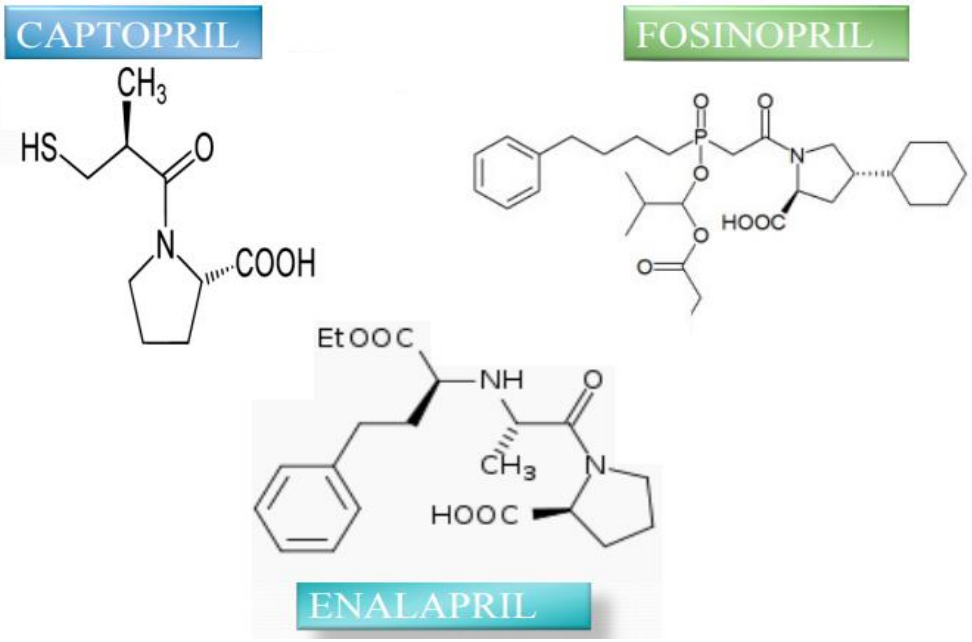
more active than
SQ 20,881
(teprotide)



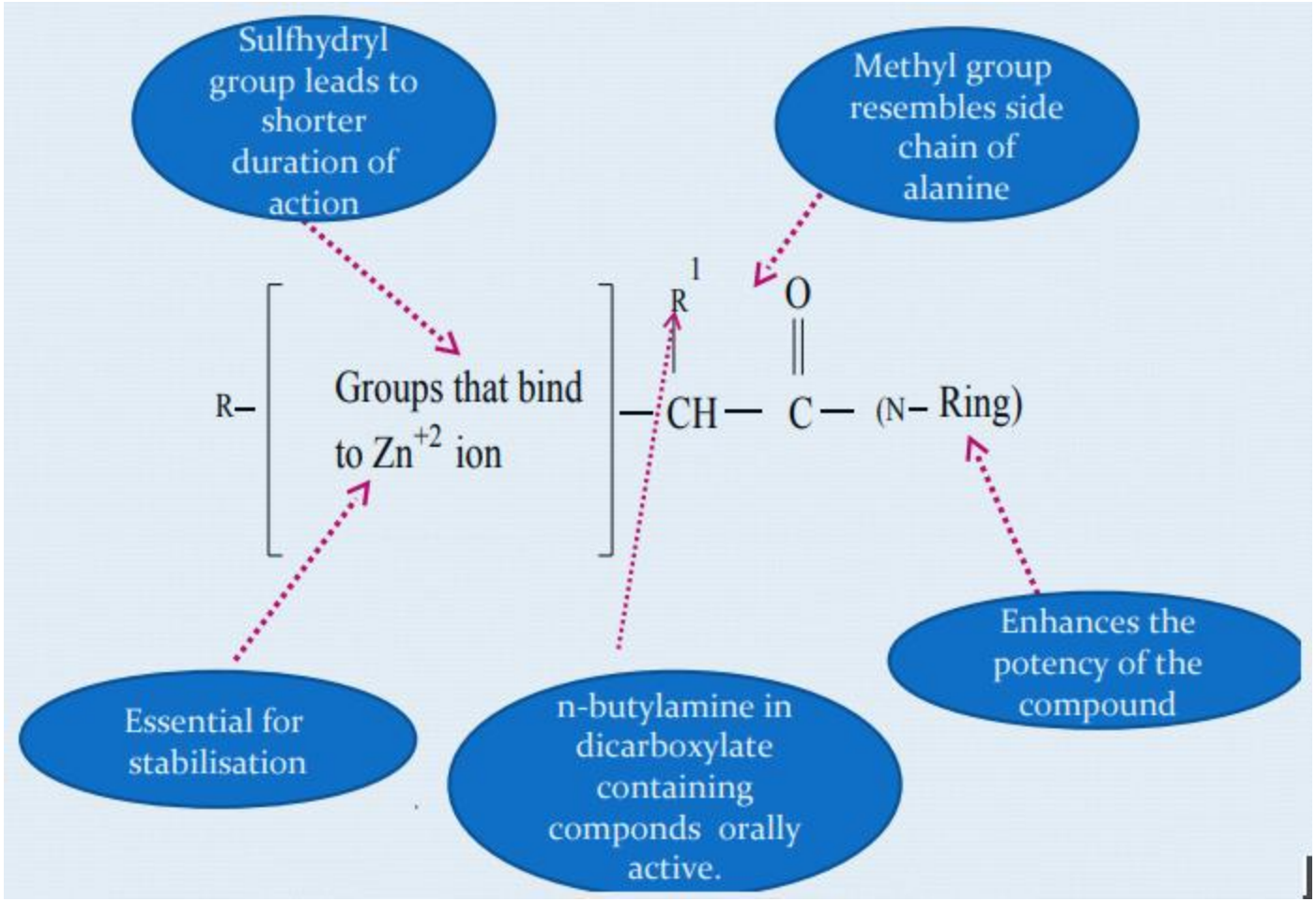
SQ 14,225
D-2-Methyl-3-Mercapto propanoyl-L-proline

Depending on chemical classification



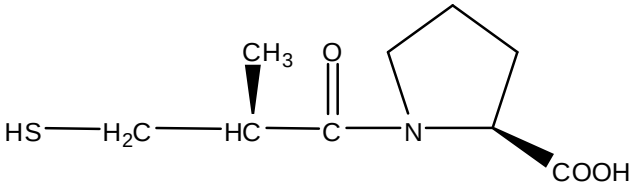


Structure Activity Relationship (SAR)



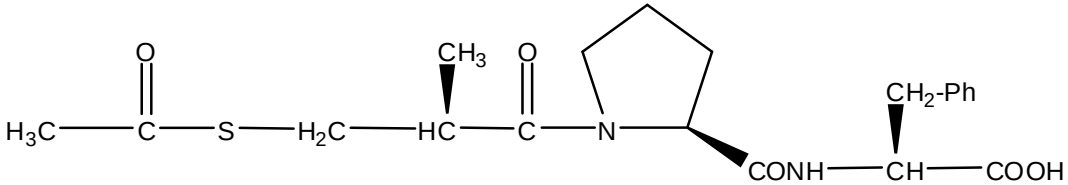
1- Sulfhydryl-Containing ACE inhibitors

KAPTOPRIL (KAPTORIL, CAPTOPRIL)



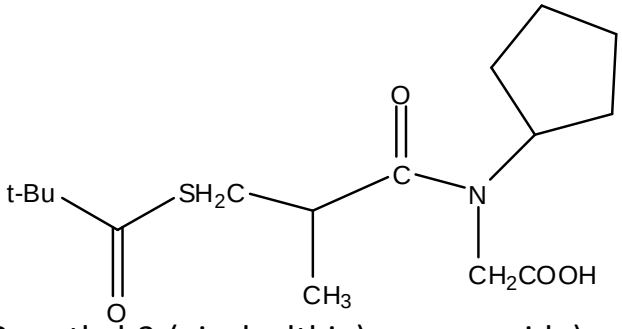
(*S*)-1-((*S)*-3-mercapto-2-methylpropanoyl)pyrrolidine-2-carboxylic acid

ALACEPRIL (LACIPIL)



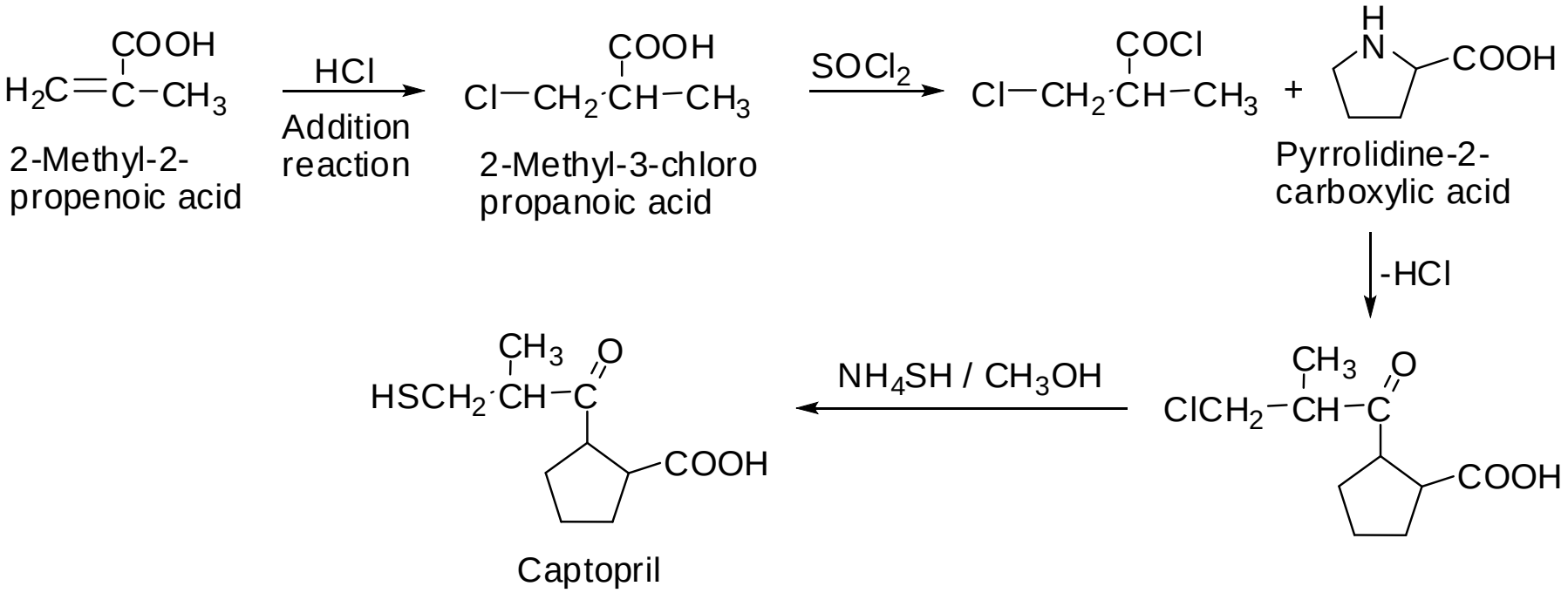
(*S*)-2-((*S*)-1-((S)-3-(acetylthio)-2-methylpropanoyl)pyrrolidine-2-carboxamido)-3-phenylpropanoic acid

PIVOPRIL



2-(*N*-cyclopentyl-2-methyl-3-(pivaloylthio)propanamido)acetic acid

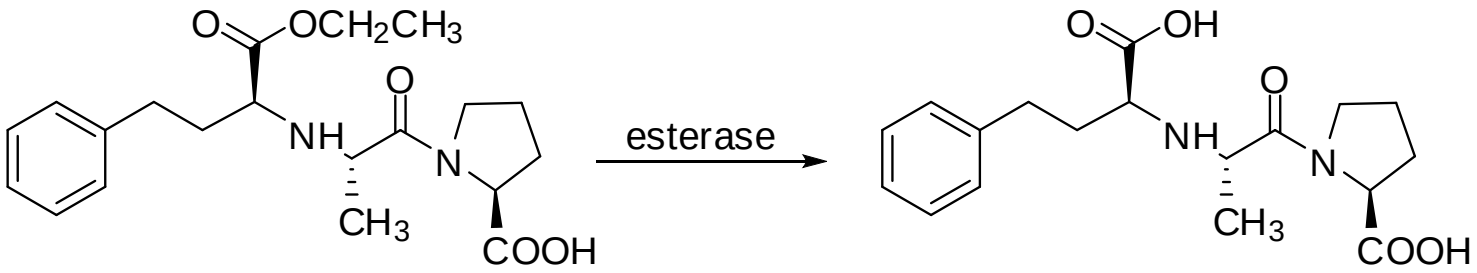
Synthesis


COOH
H2C=C−CH3
2-Methyl-2-propenoic acid
HCl
Addition reaction
COOH
Cl−CH2·CH−CH3
2-Methyl-3-chloro propanoic acid
SOCl2
COCl
Cl−CH2·CH−CH3
+
H
N
COOH
Pyrrolidine-2-carboxylic acid
-HCl
CH3
O
ClCH2−CH−C
COOH
NH4SH / CH3OH
CH3
O
HSCH2·CH−C
COOH
Captopril

2-Dicarboxylate-Containing Inhibitors

ENALAPRIL (ENALAP, ENAPRIL,CONVERIL)

Pro-drug;



Enalapril

Enalaprilat

*17 times better activity than Captopril

*The only ACE inhibitor available in oral and parenteral forms

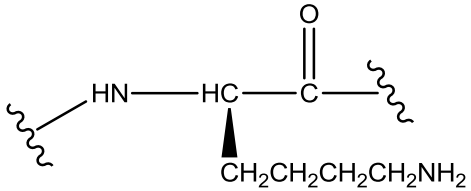
ENALAPRIL maleate + HCTZ → Co-Renitec

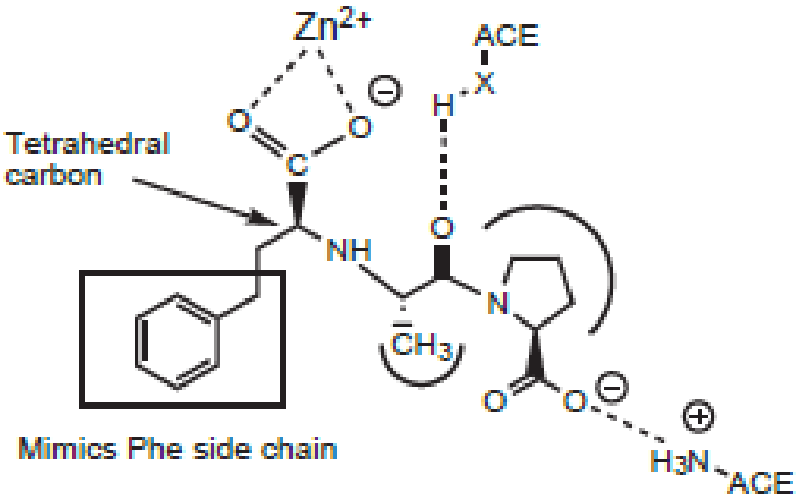
Vaseretic

Longer half-life than kaptopril

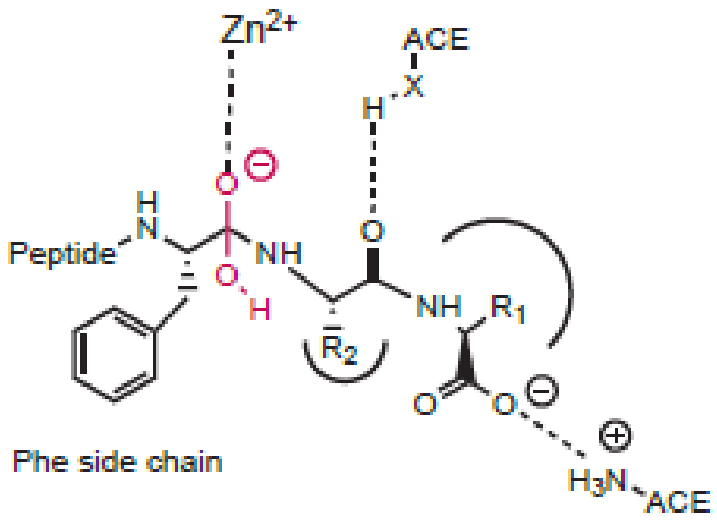
LISINOPRIL

lysine analog of Enalapril maleate (RILACE, SINOPRYL)





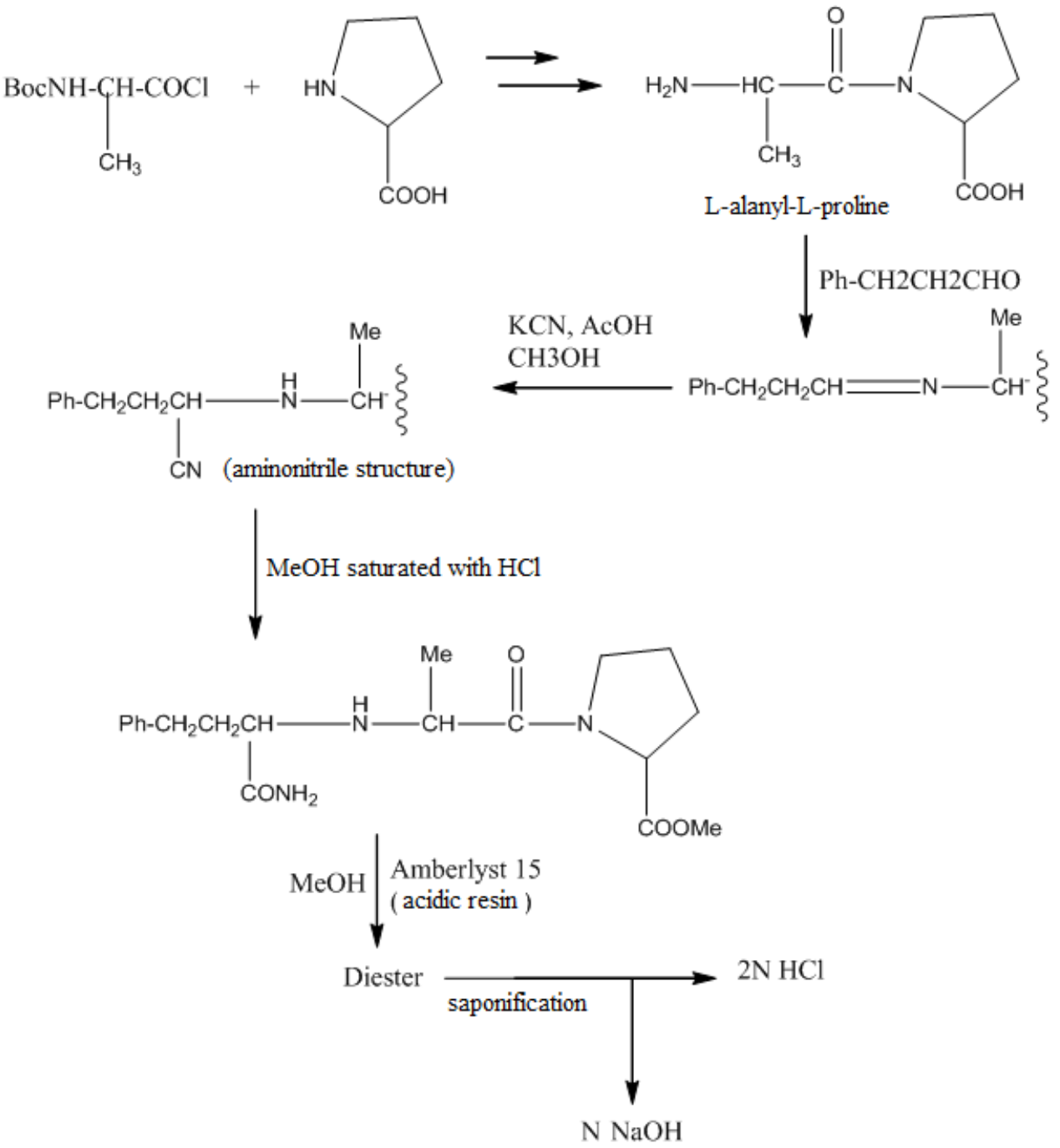
Enalaprilat

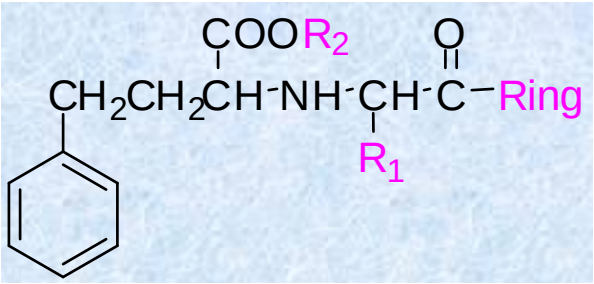


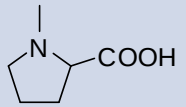
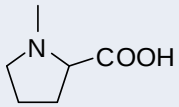
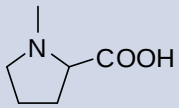
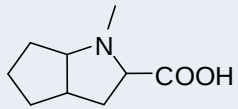
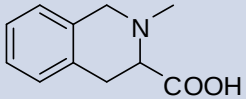
Transition state (in red) of angiotensin I hydrolysisby ACE (R_1 and R_2 = side chains of Lys and His, respectively).

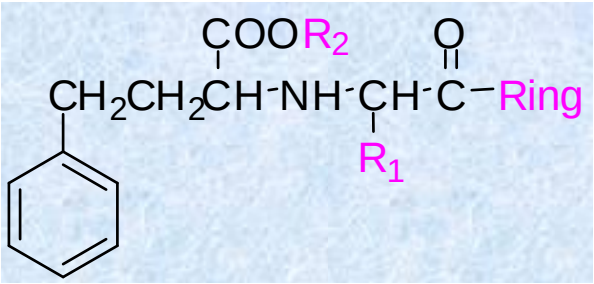
A comparison of enalaprilat and the transition state of angiotensin I hydrolysis by ACE.

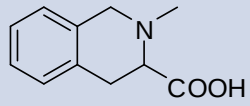
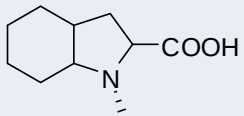
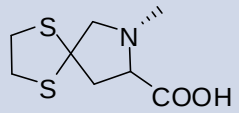
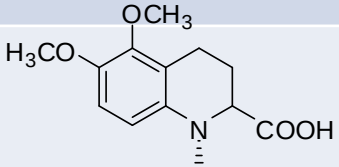
ENALAPRIL:


BocNH-CH-COCl
CH3
+
HN
COOH
H2N—HC—C—N
O
CH3
COOH
L-alanyl-L-proline
Ph-CH2CH2CHO
KCN, AcOH
CH3OH
Ph-CH2CH2CH
N
CH
Me
CN
(aminonitrile structure)
MeOH saturated with HCl
Ph-CH2CH2CH—N—CH—C—N
CONH2
COOMe
MeOH
Amberlyst 15
(acidic resin)
Diester
saponification
2N HCl
N NaOH



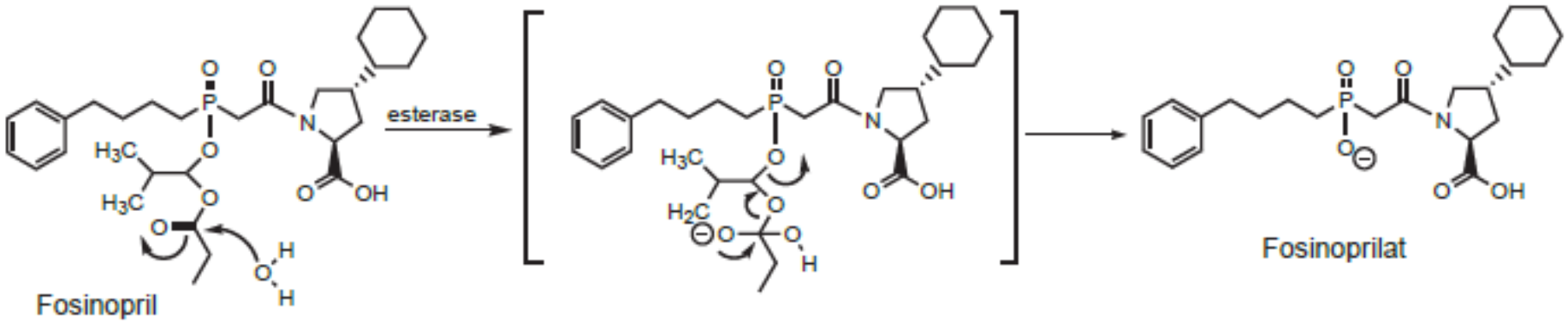
COMPOUND	R1	R2	Ring
Enalapril 1-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)pyrrolidine-2-carboxylic acid	CH_3	C_2H_5	
Enalaprilat 1-(2-(1-carboxy-3-phenylpropylamino)propanoyl)pyrrolidine-2-carboxylic acid	CH_3	H	
Lisinopril 1-(6-amino-2-(1-carboxy-3-phenylpropylamino)hexanoyl)pyrrolidine-2-carboxylic acid	$(CH_2)_4NH_2$	H	
Ramipril 1-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid	CH_3	C_2H_5	
Quinapril 2-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	CH_3	C_2H_5	



COMPOUND	R1	R2	Ring
Quinapril 2-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	CH_3	C_2H_5	
Trandolapril 1-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)octahydro-1H-indole-2-carboxylic acid	CH_3	C_2H_5	
Sprapril 7-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid	CH_3	C_2H_5	
Moexipril 1-(2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanoyl)-5,6-dimethoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid	CH_3	C_2H_5	

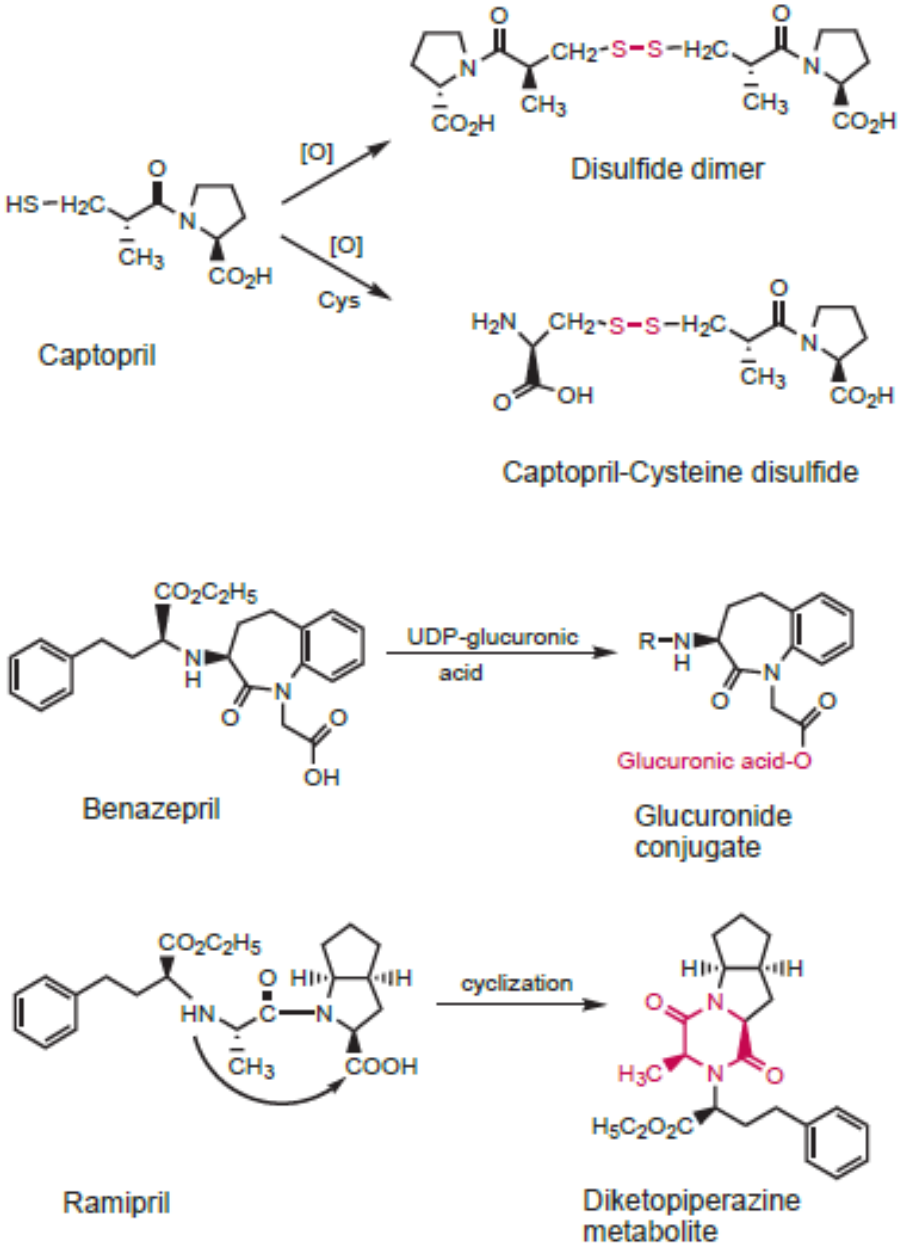
3-Phosphonate-Containing Inhibitors

FOSINOPRIL (Monopril) (2S,4S)-4-cyclohexyl-1-(2-((2-methyl-1-(propionyloxy)propoxy)(4-phenylbutyl)phosphoryl)acetyl)pyrrolidine-2-carboxylic acid



Bioactivation of fosinopril.

Metabolism



Metabolic routes of ACE inhibitors.

ADVERSE EFFECTS OF ACE INHIBITORS

Hypotension, hyperkalemia, cough, rash, taste disturbances, headache, dizziness, fatigue, nausea, vomiting, diarrhea, acute renal failure, neutropenia, proteinuria, and angioedema

reverses when therapy is stopped

NOTE: first-dose hypotensive effect may occur!!

UNLABELED USES

Hypertensive crises, renovascular hypertension, neonatal and childhood hypertension, stroke prevention, migraine prophylaxis, nondiabetic nephropathy, chronic kidney disease, scleroderma renal crisis, Raynaud phenomenon, and Bartter syndrome

Angiotensin Receptor Blockers (ARBs)

Angiotensin Receptors:

- Specific angiotensin receptors have been discovered, grouped and abbreviated as – AT1 and AT2
- They are present on the surface of the target cells

Angiotensin II Receptor Blockers (ARBs)

- Newer class
- Well-tolerated
- Do not cause coughing

Mechanism of Action Angiotensin II Receptor Blockers

- Allow angiotensin I to be converted to angiotensin II, but block the receptors that receive angiotensin II
- Block vasoconstriction and release of aldosterone

Therapeutic Uses

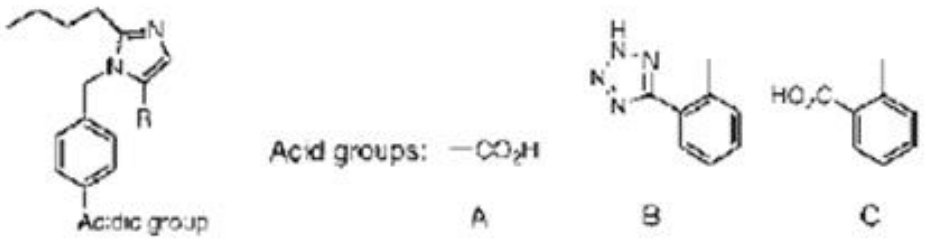
- Hypertension
- Adjunctive agents for the treatment of CHF
- May be used alone or with other agents such as diuretics

Side Effects

• Upper respiratory infections • Headache • May cause occasional dizziness, inability to sleep, diarrhea, dyspnea, heartburn, nasal congestion, back pain, fatigue

Structure–Activity Relationships

All commercially available ARBs are analogs of the following general structure:



1. The "acidic group" is thought to mimic either the Tyr[4] phenol or the Asp[1] carboxylate of angiotensin II. Groups capable of such a role include the carboxylic acid (A), a phenyl tetrazole or isostere (B), or a phenyl carboxylate (C).
2. In the biphenyl series, the tetrazole and carboxylate groups must be in the ortho position for optimal activity (the tetrazole group is superior in terms of metabolic stability, lipophilicity, and oral bioavailability).
3. The n-butyl group of the model compound provides hydrophobic binding and, most likely, mimics the side chain of Ile[5] of angiotensin II. As seen with azilsartan, candesartan, telmisartan, and olmesartan, this n-butyl group can be replaced with either an ethyl ether or an n-propyl group.

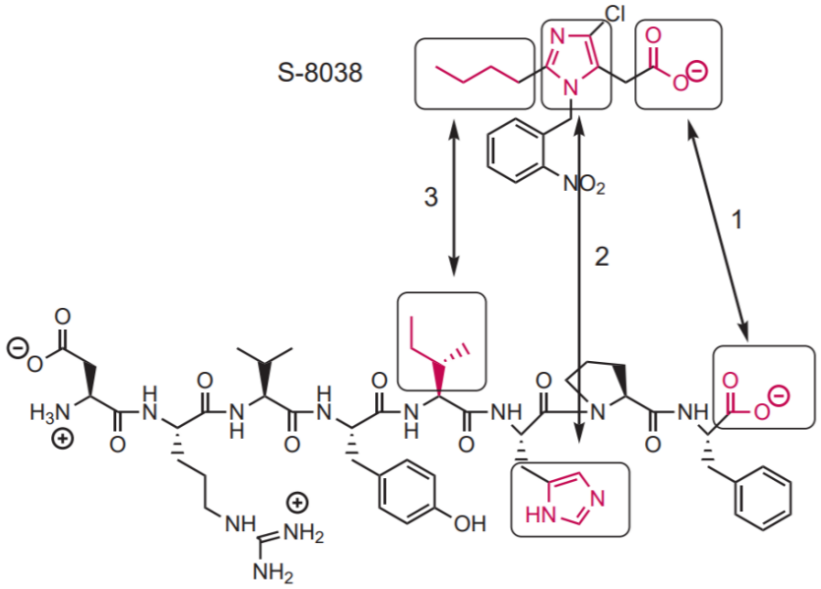
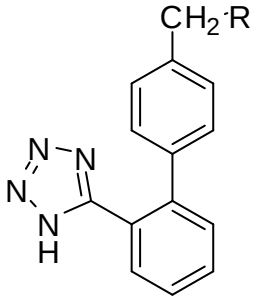
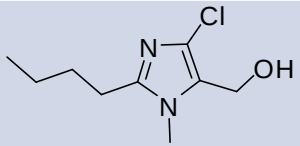
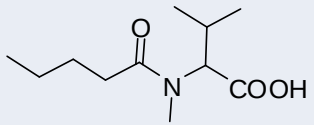
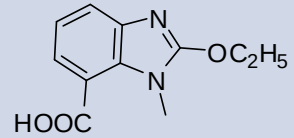
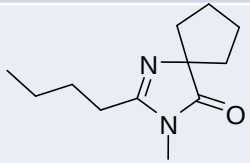
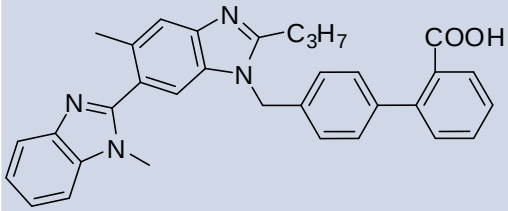
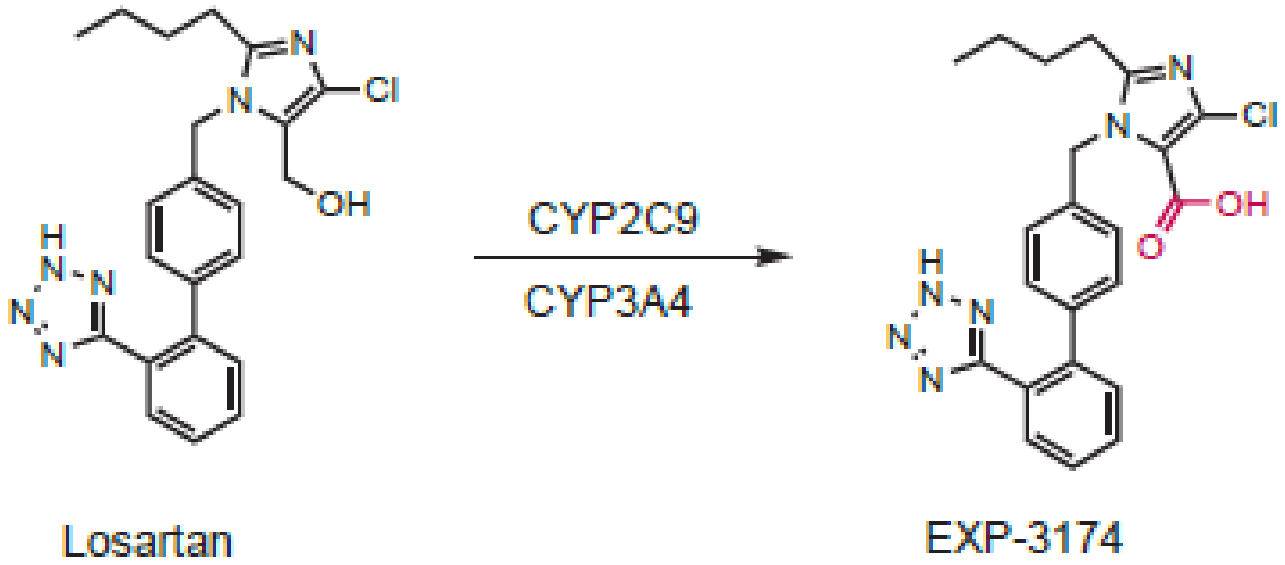


FIGURE Structural comparison of S-8308, an imidazole-5-acetic acid analog, with angiotensin II.

4. The imidazole ring or an isosteric equivalent is required to mimic the His[6] side chain of angiotensin II.
5. Substitution can vary at the "R" position. A variety of R groups, including a carboxylic acid, a hydroxymethyl group, a ketone, or a benzimidazole ring, are present in currently available ARBs and are thought to interact with the AT_1 receptor through either ionic, ion–dipole, or dipole–dipole bonds.



Compound	R
Losartan (1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methanol	
Valsartan 2-(N-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)pentanamido)-3-methylbutanoic acid	
Candesartan 1-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylic acid	
Irbesartan 3-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one	
Telmisartan 4'-((1,6'-dimethyl-2'-propyl-1H,3'H-2,5'-bibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carboxylic acid	



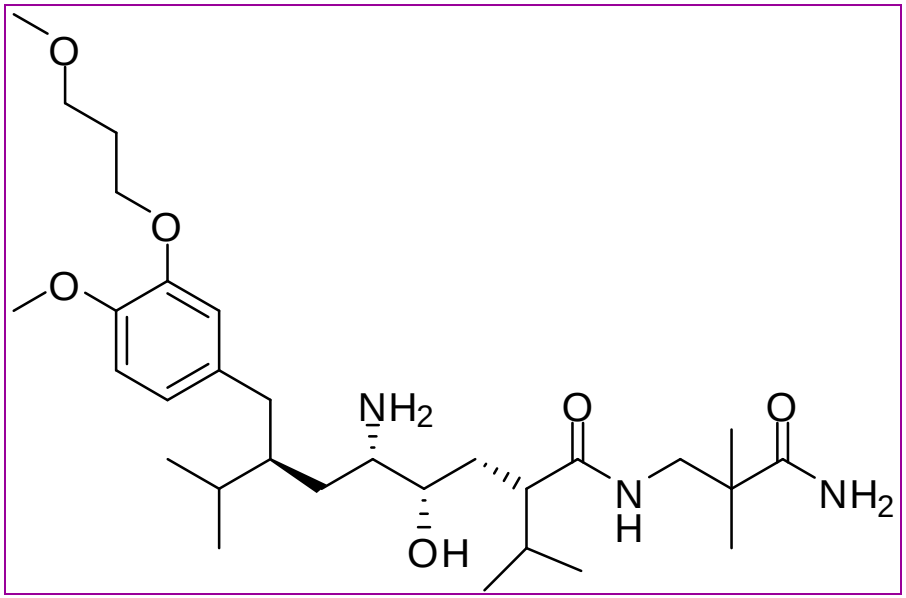
The metabolic conversion of losartan to EXP-3174 by cytochrome P450 isozymes.

ADVERSE EFFECTS OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

Headache, dizziness, fatigue, hypotension, hyperkalemia, dyspepsia, diarrhea, abdominal pain, upper respiratory tract infection, myalgia, back pain, pharyngitis, and rhinitis

Renin inhibitor

Aliskiren TEKTURNA, RASILEZ ®



(2S,4S,5S,7S)-5-amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide