

Model answer
 Class: B.Pharm V Semester
 Subject: Pharmaceutical Chemistry-V (Medicinal Chemistry-I)
 Paper Code: **AS-2520**

1 i) Medicinal chemistry and pharmaceutical chemistry are disciplines at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, where they are involved with design, chemical synthesis and development for market of pharmaceutical agents, or bio-active molecules (drugs). Example of any drugs like Aspirin, Propranolol

ii) SAR: Structure activity relationship

ACE: Angiotensin converting enzyme

iii) Due to protein binding available concentration of drug in circulation is less hence reduced therapeutic effect.

iv) A: 2, 6-dimethylaniline

B: Tocainide/ tonocard

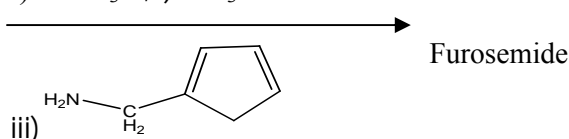
v) 5 α -glucosidase inhibitor

vi) 1-(*iso*-propylamino)-3-(1-naphthoxy)-2-propanol

vii)

2, 4-dichlorobenzoic acid

i) ClSO₃H, ii) NH₃



viii) A hydrogen bond is the electromagnetic attractive interaction between polar molecules in which hydrogen (H) is bound to a highly electronegative atom, such as nitrogen (N), oxygen (O) or fluorine (F).

ix) Angina – is chest pain due to ischemia of the heart muscle

Arrhythmia is any of a group of conditions in which the electrical activity of the heart is irregular or is faster or slower than normal

x) Mechanism of action of nitrates:

Nitrates \rightarrow release of free radical nitric oxide (NO) \rightarrow activation of cytoplasmic guanylyl cyclase \rightarrow increased cGMP \rightarrow dephosphorilation of myosin light chain kinase (MLCK) \rightarrow Fail to interact with actin \rightarrow Relaxation

xi) A: chlorosulfonic acid and ammonia

B: furfurylamine

xii) Sulfonylurea's bind to an ATP-dependent K⁺(KATP) channel on the cell membrane of pancreatic beta cells. Cause depolarization by reducing the conductance of ATP sensitive K⁺ channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of (pro) insulin.

2. Basic Principle of medicinal chemistry includes exploration and exploitation of existing information either from synthetic source or natural source in order to get therapeutically active molecules for different targets.

Role of pH and pKa on biological action:

- Definition of pH and pKa.
- Influence of both pH and pKa on biological action especially ionization of drug depends on pH of the media.
- Relationship between pH and pKa.
- Illustration of the points with some examples like weakly acidic drug aspirin, and weakly basic drug chloroquine phosphate

Similar points for hydrogen bonding.

3. Write notes on (any two):

- Receptors: points to be included
Definition, types of receptors, forces involved.
- Ca²⁺ channel blockers: points to be included
Definition, usefulness, classification, synthesis, metabolism and uses of some agents.
- Vasodilators: points to be included
Definition, usefulness, classification, synthesis, metabolism and uses of some drugs.
- Antihyperlipidemic agents: Definition, usefulness, classification chemically, synthesis, metabolism and uses of some class of compounds.

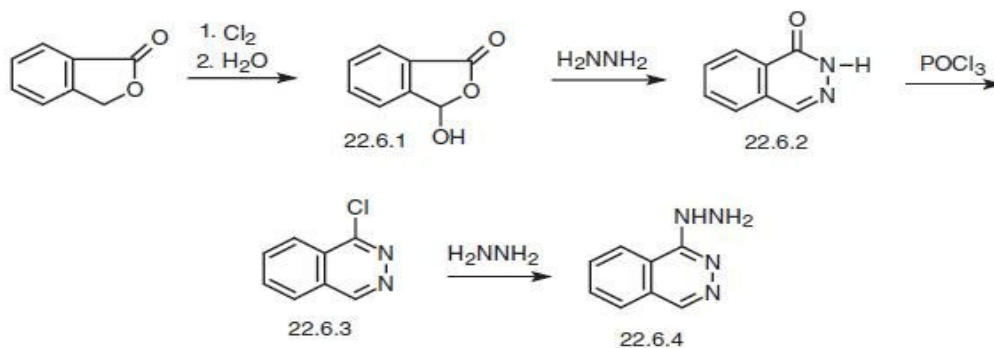
4.

a) Briefly discuss about ACE inhibitors: points to be included
Define ACE and ACE Inhibitors, Illustration of mechanism of action, Classification of ACE inhibitors, Route of synthesis of prototype drugs, Metabolism and uses of some drugs.

b) Thiazide diuretics: points to be included
Definition of diuretics and thiazide diuretics, Illustration about their chemical class, Mechanism of action, Route of synthesis of some prototype drugs, SAR and Uses

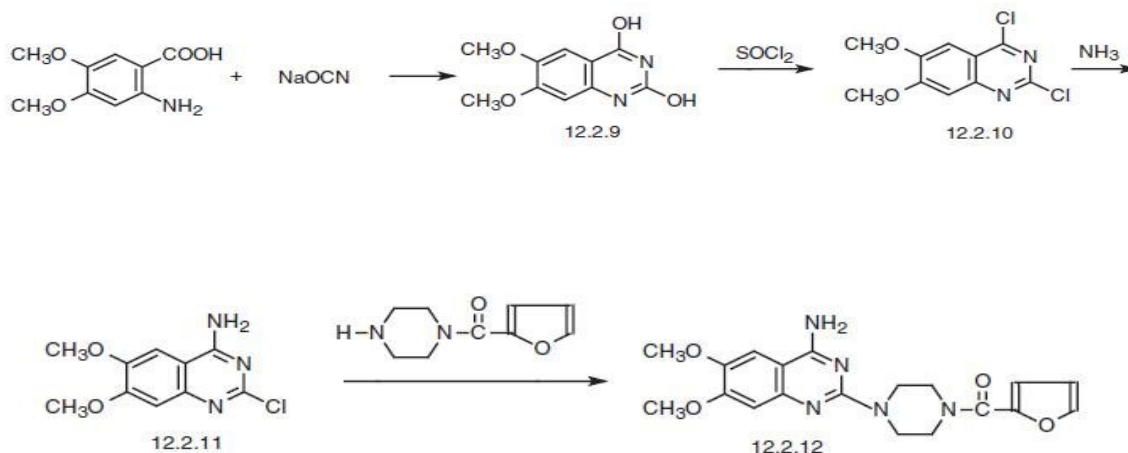
5. Write down the synthesis of (any three):

i) **Hydralazine:**



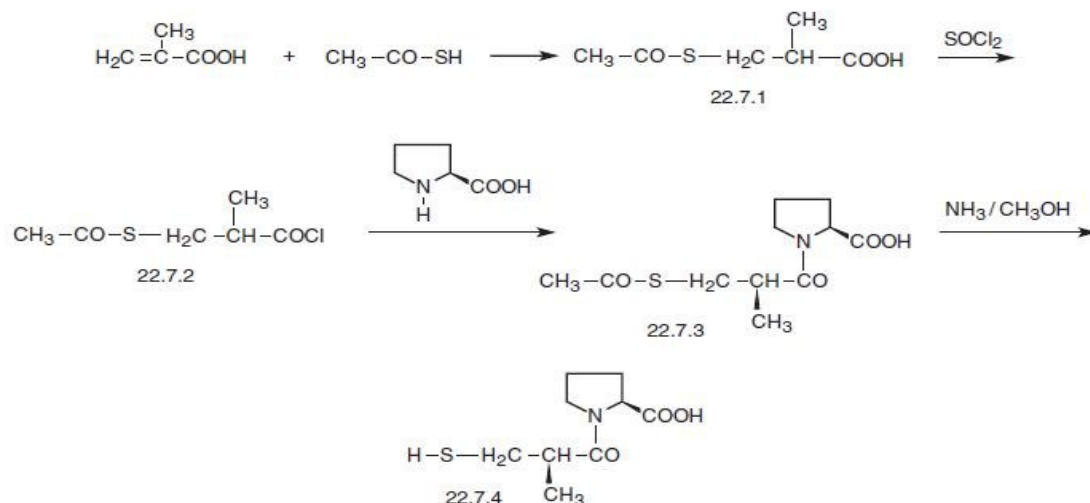
, Hydralazine, 1-hydrazinonaphthalazine (22.6.4), is synthesized by the oxidative chlorination of phthalide with simultaneous hydrolysis of product, which results in hydroxyphthalide (22.6.1), which upon reaction with hydrazine changes to phthalazone (22.6.2). This undergoes a reaction with phosphorous oxychloride forming 1-chlorophthalazine (22.6.3), in which substitution of the chlorine atom with hydrazine gives the desired hydralazine (22.6.4).

ii) Prazosin



Prazosin, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine (12.2.12), is synthesized from 2-amino-4,5-dimethoxybenzoic acid, which upon reaction with sodium cyanate undergoes heterocyclation into 2,4-dihydroxy-6,7-dimethoxyquinazoline (12.2.9). Substituting hydroxyl groups of this compound with chlorine atoms by reaction with thionyl chloride, or a mixture of phosphorous oxychloride with phosphorous pentachloride gives 2,4-dichloro-6,7-dimethoxyquinazoline (12.2.10). Upon subsequent reaction with ammonia, the chlorine atom at C4 of the pyrimidine ring is replaced with an amino group, which leads to the formation of 4-amino-2-chloro-6,7-dimethoxyquinazoline (12.2.11). Introducing this into a reaction with 1-(2-furoyl) piperazine gives prazosin (12.2.12).

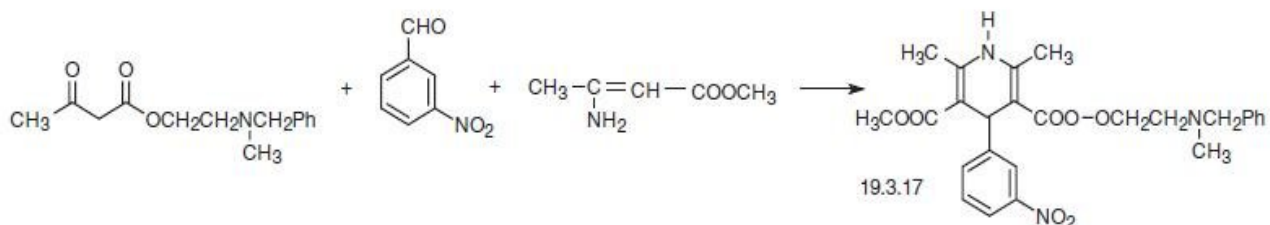
iii) Captopril



Captopril, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline (22.7.4), is synthesized by direct acylation of L-proline with 3-acetylthio-2-methylpropionic acid chloride (22.7.2), which is synthesized

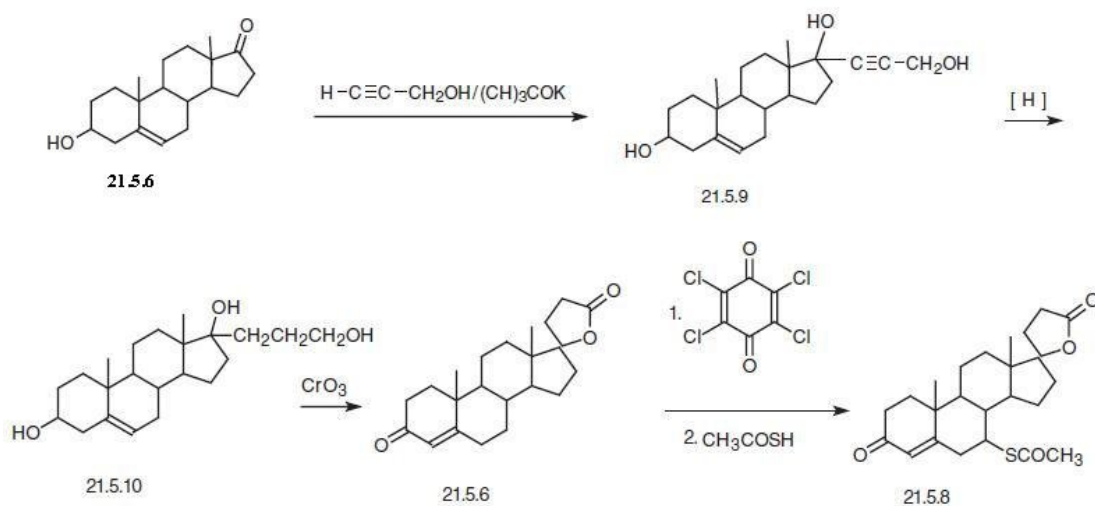
from 3-acetylthio-2-methylpropionic acid (22.7.1), which is in turn synthesized by reacting methacrylic and thioacetic acid. 1-(3-Acetylthio-2-Dmethylpropanoyl)- L-proline (22.7.3) is formed by reacting L-proline with 3-acetylthio-2- methylpropionic acid chloride, and it undergoes further ammonolysis with ammonia, to give the desired captopril (22.7.4).

iv) Nicardipine:



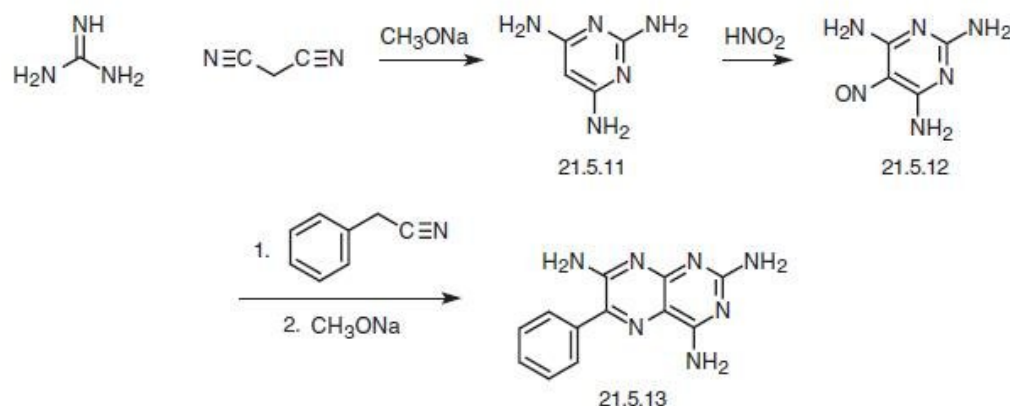
Nicardipine, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-methyl-2-[(methylphenylmethyl)- amino]ethyl ester 3,5-pyridinecarboxylic acid (19.3.7), is synthesized by heterocyclization reaction is accomplished by reacting, the methyl ester of β -aminocrotonic acid with the 2-methyl-2-benzylaminoethyl ester of acetoacetic acid [24–27].

v) Spironolactone



Spironolactone is from 4-androsten-3,17-dione (21.5.6), which undergoes ethynylation by propargyl alcohol in the presence of potassium *tert*-butoxide, forming 17 β -hydroxy- 17 α -(3-hydroxypropynyl)-4-androsten-3-one (21.5.9), the triple bond of which is completely reduced by hydrogen using as a catalyst a complex of triphenylphosphine and rhodium chloride, which forms 17 β -hydroxy-17 α -(3-hydroxypropyl)-4-androsten-3-one (21.5.10). Oxidation of this product with chromium (VI) oxide in pyridine gives lactone (21.5.6), which is oxidized in the manner described above by chloranyl to (21.5.9) and reacted further with thioacetic acid to the desired spironolactone (21.5.8).

vi) Triamterene:



Triamterene, 2,4,7-triamino-6-phenylpteridine (21.5.13), is synthesized in by Reacting guanidine with malonodinitrile gives 2,4,6-triaminopyrimidine (21.5.11). This undergoes nitrosation by reacting it with nitric acid, which results in the formation of 5-nitroso-2,4,6-triaminopyrimidine (21.5.12), which upon condensation with benzyl cyanide in the presence of sodium methoxide cyclizes into triamterene (21.5.13).

6 Write exhaustive notes on cardio selective β blockers.

Definition, Usefulness, Classification, Synthesis, SAR, metabolism and uses

7. Drugs that are being used for the treatment of arrhythmia are known as antiarrhythmic drugs. Classification of drugs covers

Class I and subclass drugs

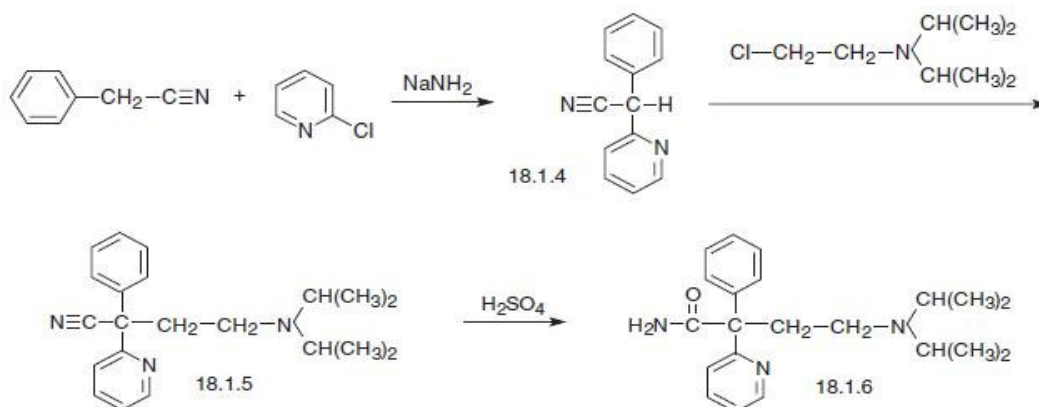
Class II drugs

Class III drugs

Class IV drugs

Others drugs

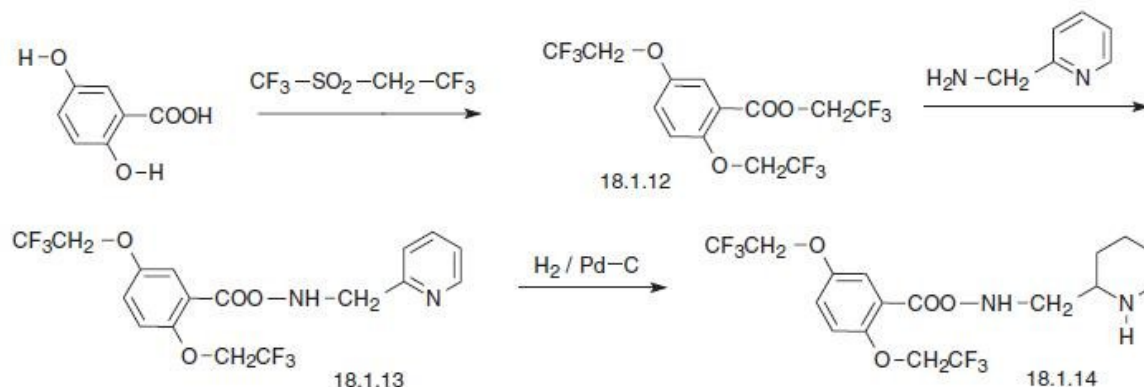
Disopyramide:



Disopyramide, α -(2-diisopropylaminoethyl)- α -phenyl-2-pyridineacetamide (18.1.6), is synthesized by arylating benzylcyanide with 2-chloropyridine in the presence of sodium amide and subsequent alkylation of the resulting α -phenyl- α -(2-pyridyl) acetonitrile (18.1.4) with 2-diisopropylaminoethylchloride using sodium amide. Sulfuric acid hydrolysis of the resulting nitrile

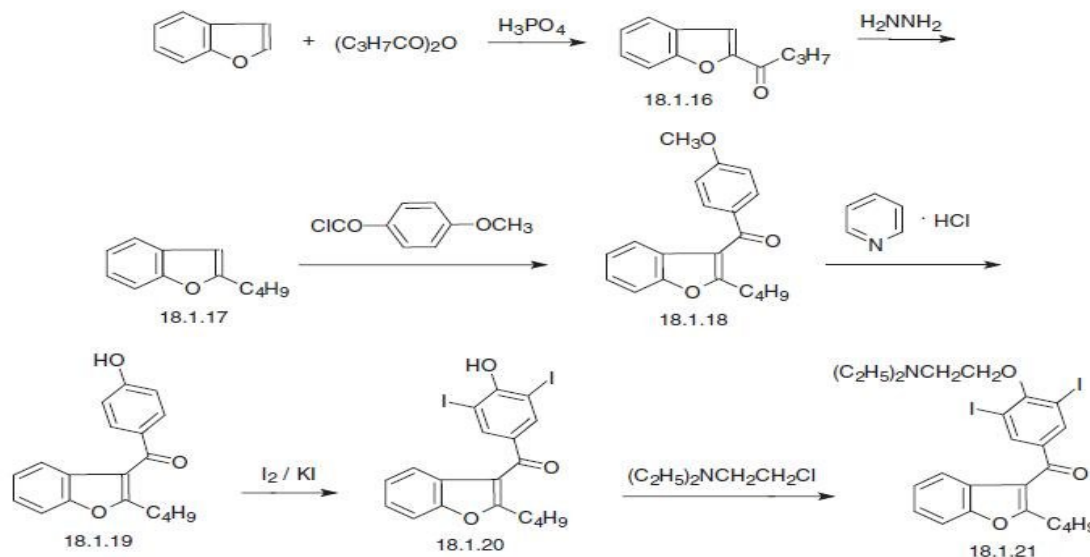
(18.1.5) leads to the formation of α -(2-diisopropylaminoethyl)- α -phenyl-2-pyridineacetamide, disopyramide.

Flecainide:



Flecainide, *N*-(2-piperidylmethyl)-2,5-bis-(2,2,2-trifluoroethoxy)benzamide (18.1.14), is synthesized from 2,5-dihydroxybenzoic acid. Reacting this with trifluoroethylfluoromethylsulfonate gives 2,2,2-trifluoroethoxylation of all three hydroxyl groups, to produce 2,2,2-trifluoroethyl ester of 2,5-bis-(2,2,2-trifluoroethoxy)benzoic acid (18.1.12). Reacting this with 2-aminomethylpyridine gives the corresponding amide (18.1.13), which upon reduction of the pyridine ring with hydrogen gives flecainide (18.1.14).

Amiodarone:



Amiodarone, 2-butyl-3-benzofuran-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone (18.1.21), is synthesized in the following manner. Benzofuran is acylated by butyric acid anhydride in the presence of phosphorous acid, forming 2-butylbenzofuranone (18.1.16). Reduction of the carbonyl group in a Wolff-Kishner reaction using hydrazine hydrate gives 2-butylbenzofuran (18.1.17). This is acylated with 4-methoxybenzoic acid chloride, giving 2-butyl-3-(4-methoxybenzoyl)benzofuran (18.1.18), which undergoes demethylation by pyridine hydrochloride, forming 2-butyl-3-(4-hydroxybenzoyl)benzofuran (18.1.19). The resulting product is iodized in the presence of potassium iodide, forming 2-butyl-3-benzofuran-4-(2-hydroxy-3,5-diiodophenyl) ketone (18.1.20), which is reacted further with 2-diethylaminoethylchloride, giving desired amiodarone (18.1.21).