AS-2162

M.Sc. (THIRD SEMSTER) EXAMINATION, 2013

CHEMISTRY

(ELECTIVE SUBJECT)

PAPER : CMT-307

(MEDICINAL CHEMISTRY)

SECTION A

Q1 i) WHAT IS THE BASIC PRINCIPLE OF ANCHOR/LINKER CONCPT ? WHAT IS PROTECTING GROUP STRATEGY ?

Ans i) ANCHOR/LINKER : IT IS A MOLECULAR UNIT COVALENTLY ATTACHED TO THE POLYMER CHAIN MAKING UP THE SOLID SUPPORT.

DIFFERENT LINKERS ARE USED DEPENDING UPON

a) THE FUNCTIONAL GROUP THAT WILL BE PRESENT ON THE STARTING MATERIAL.

b) THE FUNCTIONAL GROUP THAT IS DESIRED ON THE FINAL PRODUCT ONCE IT IS RELEASED

PROTECTING GROUPS AND SYNTHETIC STRATEGY: WHEN A MOLECULE IS BEING CONSTRUCTED BY SOLID PHASE SYNTHESIS, IT IS IMPORTANT TO PROTECT ANY REACTIVE FUNCTIONAL GROUPS THAT ARE NOT MEANT TO REACT DURING A REACTION SEQUENCE, TO PREVENT SIDE REACTIONS, THE PROTECTING GROUPS SHOULD BE STABLE TO THE REACTION CONDITIONS BUT BE CAPABLE OF BEING REMOVED IN HIGH YIELD UNDER MILD CONDITIONS ONCE SYNTHESIS IS COMPLETE.

ii) DIFFERENTIATE BETWEEN A NEUROTRANSMITTER, HORMONE AND A DRUG.

Ans ii) NEUROTRANSMITTER AND HORMONE CAN BE DISTINGUISHED

a) BY THE ROUTE THEY TRAVEL

b) THE WAY THEY ARE RELEASED

★ BUT THEIR ACTION WHEN THEY REACH THE CELL IS THE SAME

NEUROTRANSMITTER ACT AS A CHEMICAL MESSENGER THAT BIND TO RECEPTORS. EXAMPLE ACETYL CHOLINE, NORDRENALINE.

HORMONES — BLOOD SUPPLY (EPINEPHRINE, GLUCAGON).

NEUROTRANSMITTERS — NERVES.

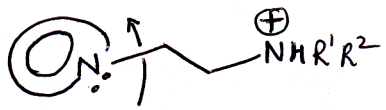
DRUGS — SYNTHETIC ANALOGS THAT WILL BIND TO THE RECEPTOR TO BRING ABOUT ANTAGONIST/AGONIST TYPE RESPONCE.

SECTION A

Q1 iii) BASED ON SAR EXPLAIN AGONISTS AT H_1 AND H_2 RECEPTOR?

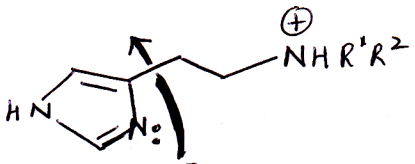
Ans iii) BASED ON SAR (STUCTURE ACTIVITY RELATIONSHIP).

AGONISTS AT H_1 & H_2 RECEPTOR NEED TO HAVE THE FOLLOWING STRUCTURAL MOTIFS.



FLEXIBLE CHAIN

AGONIST AT H_1 RECEPTOR



FLEXIBLE CHAIN

AGONISTS AT H_2 RECEPTOR.

THE FOLLOWING EXPLAINS THE STRUCTURAL REQUIREMENTS.

a) THE SIDE CHAIN HAD TO HAVE A POSITIVELY CHARGED NITROGEN ATOM WITH AT LEAST 1 ATTACHED PROTON FOR EXAMPLE QUATERNARY AMMONIUM SALTS THA CACKED SUCH A PROTON WERE VERY LOW IN ACTIVITY (AGONIST)

b) THERE HAD TO BE A FLEXIBLE CHAIN BETWEEN THE ABOVE MENTIONED CATION AND A HETERO AROMATIC RING. (H_1 RECEPTOR)

c) THE HETEROAROMATIC RING DID NOT HAVE TO BE IMIDAZOLE BUT IT DID HAVE TO CONTAIN A NITROGEN ATOM WITH A LONE PAIR OF ELECTRON; ORTHO TO THE SIDE CHAIN. (H_1 RECEPTOR)

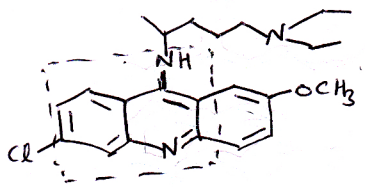
FOR H_2 RECEPTOR SAR REQUIREMENT INCLUDED

d) THE HETERO AROMATIC RING NEEDED TO CONTAIN AMIDINE UNIT

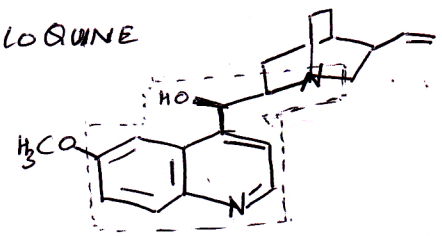
(HN—CH—N:)

viii) DRAW THE STRUCTUCTURE FOR QUINACRINE, QUININE AND COMPARE THEIR STRUCTRURE TO MEFLOQUINE

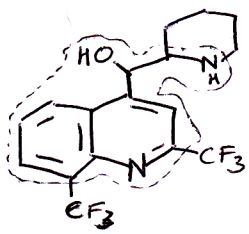
Ans viii)



QUINACRINE



QUININE



MEFLOQUINE

DOTTED LINES INDICATE THE STRUCTURALLY SIMILLAR PARTS OF THE THREE DRUGS.

SECTION A

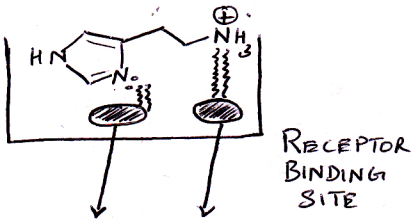
Q1 ix) HOW IS DICLOFENAC DIFFERENT FROM OTHER NSAIDS? [ONLY GIVE KEY POINTS]

ANS ix) DICLOFENAC SODIUM BELONGS TO THE ARYLALKANOIC ACID CLASS OF ANTI INFLAMMATORY DRUG AND IT DISPLAYS ANTI INFLAMMATORY ANALGESIC AND ANTIPYRETIC PROPERTIES.
THERE ARE THREE MECHANISMS OF ACTION:

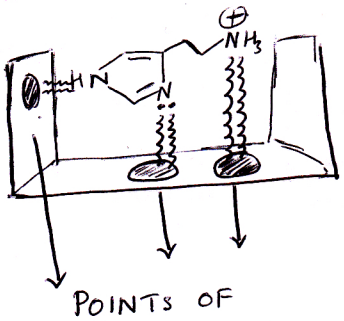
a) INHIBITION OF ARACHIDONIC ACID COX SYSTEM (WHERE POTENCY IS 3 TO 1000 TIMES MORE POTENT THAN OTHER NSAIDS ON A MOLAR BASIS) RESULTING IN DECREASED PRODUCTION OF PROSTAGLANDINS AND THROMBOXANES
b) INHIBITION OF THE LIPOXYGENASE PATHWAY RESULTING IN DECREASED PRODUCTION LEUKOTRIENES. PARTICULARLY THE PROINFLAMMATORY LKB_4
c) INHIBITION OF ARACHIDONIC ACID RELEASE AND STIMULATION OF ITS REUPTAKE, RESULTING IN A REDUCTION OF ARACHIDONIC ACID AVAILABILITY.

x) WHAT ESSENTIAL SUBSTITUTIONS AND INTERACTIONS ARE NECESSARY FOR ANTHISTAMINIC ACTIVITY?

ANS X) CONSIDERING THE FOLLOWING BINDING SCHEMES.



H_1 RECEPTOR BINDING SITE



H_2 RECEPTOR BINDING SITE

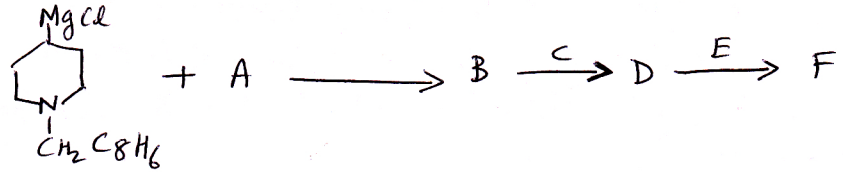
★ ESSENTIAL

THE TWO DIAGRAMS SHOW THE INTERACTIONS NECESSARY FOR ANTIHISTAMMINIC ACTIVITY; THE ESSENTIAL SUBSTITUTIONS ARE

a) HETEROAROMATIC RING (HN—CH—N:)
b) IMIDAZOLE RING TO CONTAIN A NITROGEN ATOM WITHA LONE PAIR OF ELECTRON, ORTHO TO THE SIDE CHAIN.

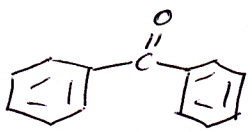
SECTION B

Q2. a) IDENTIFY THE REACTANTS AND REAGENTS IN THE FOLLOWING SYNTHESIS OF TERFENADINE; EXPLAIN THE SIGNIFICANCE OF REAGENTS IN EACH STEP.



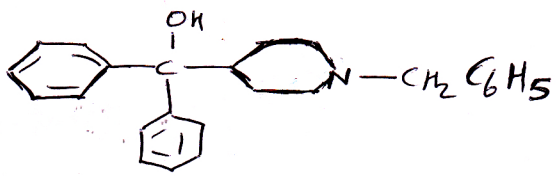
b) WHAT IS THE PRIMARY MODE OF ACTION FOR TEFENADINE? WHAT ARE THE POINTS OF MODIFICATIONS FOR THIS DRUG TO INCREASE ITS POTENCY.?

ANS 2 a)

A= 

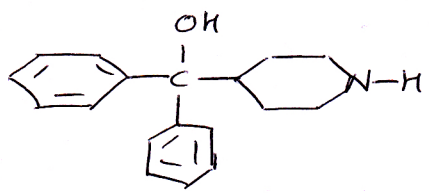
BENZOPHENONE

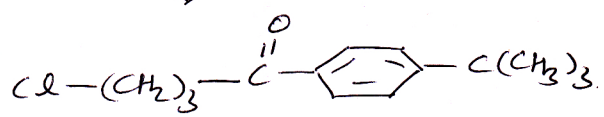
GRIGNARD REACTION
NUCLEOPHILLIC ADDITION

B= 

C= H_2 / Pd-C

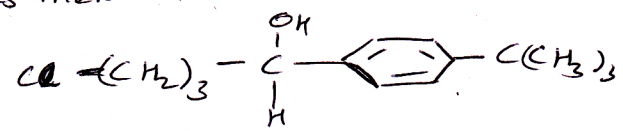
DEBENZYLATION, REDUCTION
DEPROTECTION

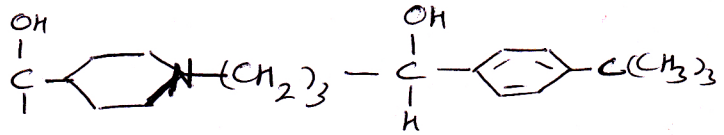
D = 

E = 

[IF THIS REACTANT IS USED. WE NEED TO PERFORM A REDUCTION TO OBTAIN THE PRODUCT

THE CORRECT COMPOUND IS THEREFORE

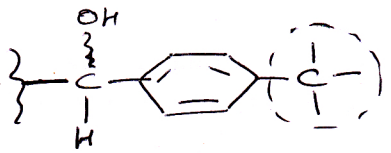


F = 

SECTION B

Q2 ANS 2 CONTINUED

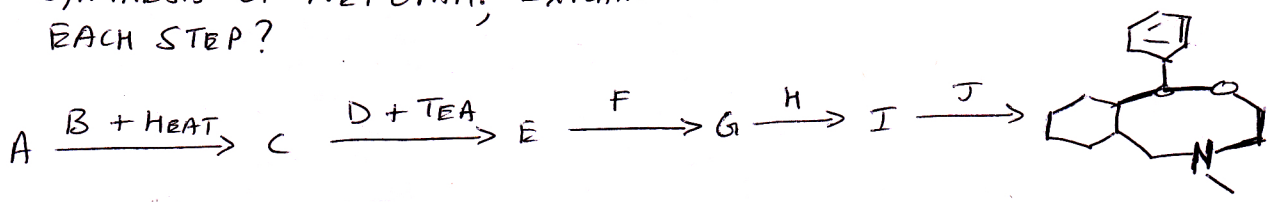
b) PRIMARY MODE OF ACTION FOR TERFENADINE; IT COMPETES WITH HISTAMINE FOR BINDING H_1 RECEPTOR SITES IN GI-TRACT UTERUS, LARGE BLOOD VESSELS, BRONCHIAL MUSCLE AND MEDIATES CONTRACTION O SMOOTH MUSCLES AND INCREASES CAPILLARY PERMEABILITY.



= R CAN BE H, ME, n-BUTYL, ISOBUTYL

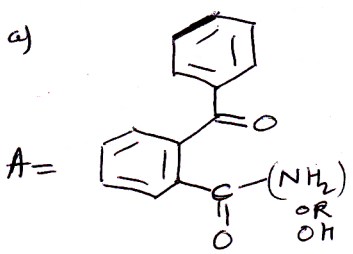
VARIATION IN STRUCTURE PROVIDING ACTIVITY HAS BEEN HIGHLIGHTED ABOVE

Q3 a) IDENTIFY THE REACTANTS AND REAGENTS IN THE FOLLOWING SYNTHESIS OF NEFOPAM, EXPLAIN THE SIGNIFICANCE OF REAGENTS IN EACH STEP?

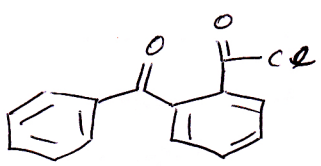


b) WHAT IS THE PRIMARY MODE OF ACTION FOR NEFOPAM? WHAT ARE THE POINTS OF MODIFICATION FOR THIS DRUG TO INCREASE TTS POTENCY?

ANS 3 a)



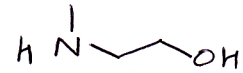
; B = $SOCl_2$; C =



THIONYL CHLORIDE

[ACTIVATION OF THE ACYL GROUP]

D =

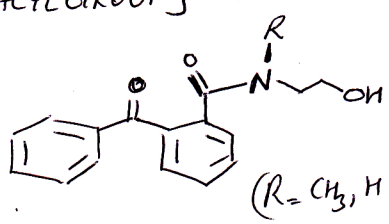


N-METHYL-2-AMINO ETHANOL

H_2N OH ETHANOLAMINE

MORE ACCURATE

E =



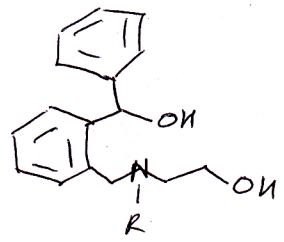
(R = CH_3, H)

F = $LiAlH_4$

REDUCTION OF KETO TO ALCOHOL

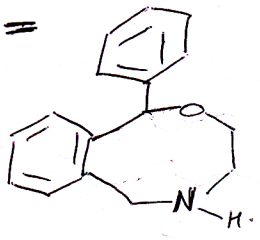
ANS 3 a) CONTINUED

G =



(R = CH_3, H).

I =



NEFOPAM.

N-METHYLATED

H = p-TsA
PhH, Δ

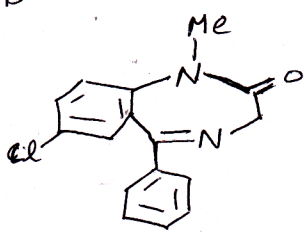
CYCLIZATION

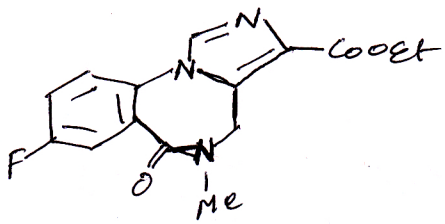
J = SO_4Me_2 OR CH_2O

CYCLIZATION
METHYLATION.

b) IT IS A POTENT NON-OPIOID ANALGESIC USED TO IMPROVE POSTOPERATIVE OPIOD ANALGESIA IN PATIENTS.

MODIFICATIONS ARE PRIMARILY RELATED TO RING EXPANSION AND SUBSTITUTIONS OF THE FOLLOWING TYPE





SHOWS ENHANCED ACTIVITY

Q 7. WHAT ARE THE ESSENTIAL DIFFERENCES BETWEEN THE BONDING FORCES RESPONSIBLE FOR DRUG BINDING? EXPLAIN THE ROLE OF EACH CLEARLY ?

ANS 7. INTERMOLECULAR BONDING FORCES.

A) ELECTROSTATIC OR IONIC BONDS
B) HYDROGEN BONDS (HBD) DONOR
(HBA) ACCEPTOR
C) VAN DER WAALS INTERACTIONS
D) DIPOLE-DIPOLE AND ION-DIPOLE INTERACTIONS.
E) REPULSIVE INTERACTIONS
F) THE ROLE OF WATER AND HYDROPHOBIC INTERACTIONS

EXPLAIN WITH STRUCTURALLY DEFINING THE COMPONENTS IN EACH OF BONDING FORCES.

SECTION A

Q8. WHAT ARE THE ESSENTIAL STEPS INVOLVED IN DRUG DESIGN?

Ans 8. THE FOLLOWING ARE BASIC STRATEGIES.

1. SCREENING OF NATURAL COMPOUNDS FOR BIOLOGICAL ACTIVITY
2. ISOLATION AND PURIFICATION OF THE ACTIVE PRINCIPLE
3. DETERMINATION OF STRUCTURE.
4. STRUCTURE - ACTIVITY RELATIONSHIP (SAR'S).
5. SYNTHESIS OF ANALOGUES.
6. DESIGN AND SYNTHESIS OF NOVEL DRUG STUCTURES.

EXPLAIN THE STEPS WITH REFERENCE TO DRUG CLASSIFICATION