Birla Institute of Technology & Science, Pilani, Rajasthan 333031

1st Semester 2022-23 **COMPREHENSIVE EXAM**

Course Number: CHEM F335 **Course Title: Org. Chem. and Drug Design (OCDD)** **Time: 90 min**

CLOSED BOOK **Max marks: 40**

Part-I: There are 18 MCQs (each of 1.5M); **there is a negative marking of -0.5 for each incorrect answer.** The last four questions (Q19-22) are short answer type without any negative mark.

Q1. Identify the peptide sequence with highest pain killer activity.

a. H-Val-Gly-Gly-Phe-Met-OH
b. H-Leu-Gly-Gly-Phe-Met-OH
c. H-Tyr-Gly-Gly-Phe-Met-OH
d. H-Met-Gly-Gly-Tyr-Phe-OH

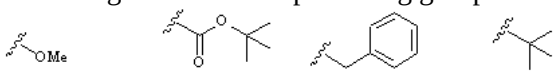
Q2. μ-receptor is related to:

a. K^+ ion channel.
b. Ca^+ ion channel.
c. Na^+ ion channel.
d. G-protein.

Q3. Which of the following statements is untrue about protein tertiary structure?

a. Proteins fold up into a tertiary structure such that most amino acids with hydrophobic residues are exposed to the aqueous surroundings.
b. Proteins fold up into a tertiary structure such that most amino acids with hydrophilic residues are exposed to the aqueous surroundings.
c. Proteins fold up into a tertiary structure such that most amino acids with hydrophobic residues are in the centre and hidden from the aqueous surroundings.
d. Interactions between amino acid residues are important in protein tertiary structure.

Q4. The following structures are protecting groups used in peptide synthesis.



A B C D

Which of these would you use to protect an amino group?

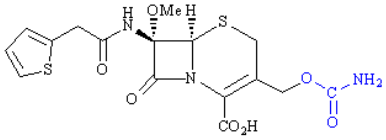
a. Structure A. b. Structure B. c. Structure C. d. Structure D.

Q5. What is meant by the term sequential blocking?

a. Administering two different drugs.
b. The inhibition of two different enzymes in the same biosynthetic pathway.
c. The order in which different binding regions of a binding site are occupied by a drug structure.
d. The protection of vulnerable functional groups in a drug.

Q6. The following structure is an example of a cephamycin. What is the significance of the urethane group

a. It acts as a steric shield leading to longer activity.
b. It is resistant to hydrolysis by esterases leading to longer activity.
c. It acts as a steric shield for the β-lactam ring leading to lower activity.
d. It acts as a polar group resulting in better water solubility.



Q7. How is π measured in QSAR studies?

a. It is measured by calculating molecular dimensions using relevant molecular modelling software.
b. It is measured by comparing the dissociation constants of two weak acids.
c. It is measured by subtracting the log *P* value of an analogue bearing the substituent from the log *P* value of the parent compound lacking the substituent.
d. It is measured by subtracting the log *P* value of the parent compound lacking the substituent from the log *P* value of an analogue bearing the substituent.

Q8. The σ_m value for a phenol substituent (OH) is 0.12, whereas the σ_p value is -0.37. Why are σ_m and σ_p so different?
a. The *meta* substituent is closer to the rest of the molecule than the *para* substituent and has a greater electron withdrawing effect.
b. The *meta* substituent is closer to the rest of the molecule than the *para* substituent and has a greater steric effect.
c. The *meta* substituent is closer to the rest of the molecule than the *para* substituent and has a greater hydrophobic effect.
d. The *meta* substituent has an inductive effect which makes it electron withdrawing, whereas the *para* substituent has a resonance effect which makes it electron donating.

Q9. The QSAR equation relating the insecticidal activity of a series of diethyl arylphosphonates versus σ is shown below.

$$\log\left(\frac{1}{C}\right) = 2.282\sigma - 0.348.(r^2\ 0.952,\ r\ 0.976,\ s\ 0.286)$$

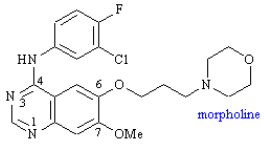
What physicochemical property is beneficial for activity?

a. An electron donating substituent.
b. An electron withdrawing substituent.
c. A hydrophobic substituent.
d. A small substituent.

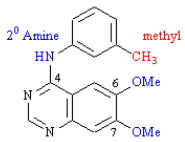
Q10. Which of the following statements is untrue when comparing 3D QSAR with conventional QSAR?
a. Drugs of the different structural classes can be studied by 3D QSAR but not by QSAR.
b. 3D-QSAR has a predictive quality which QSAR does not.
c. Experimental parameters are required by 3D-QSAR and QSAR.
d. Results can be shown graphically in 3D-QSAR, but not by QSAR.

Q11. What pharmacophore is shared by the opioid analgesics?
a. A charged nitrogen, a phenol, and an aromatic ring.
b. A charged nitrogen, an alcohol, and an aromatic ring.
c. A charged nitrogen, a phenol, an aromatic ring, and an ethylene hydrocarbon bridge.
d. A charged nitrogen, a phenol, an aromatic ring, and an *N*-methyl substituent.

Q12. Gefitinib (I) has been used for the treatment of refractory lung cancers. Structure II was the lead compound for structure I. Why was the methyl group replaced with a chloro group?



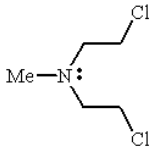
I



II

a. To replace an inductive electron-donating group with an inductive electron-withdrawing group.
b. To replace the methyl group with a smaller chloro group.
c. To replace a lipophilic methyl group with a more polar chloro group.
d. To replace a metabolically susceptible methyl group with a metabolically stable chloro group.

Q13. The following agent is used for the treatment of Hodgkin's lymphoma as part of a multi-drug regime.

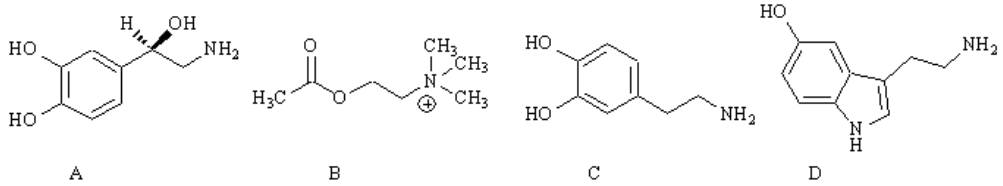


What is the name of the activated species which is formed from the above structure and which acts as the actual alkylating agent?
a. A quaternary ammonium ion.
b. An iminium ion.
c. A cyclopropylamine ion.
d. An aziridinium ion.

Q14. The nerve gases are irreversible inhibitors of the acetylcholinesterase enzyme and react with a serine residue in the active site. What kind of reaction takes place on the serine residue?

a. Reduction b. Oxidation c. Phosphorylation d. Esterification

Q15. Which of the following is a natural chemical messenger for the adrenergic receptor?

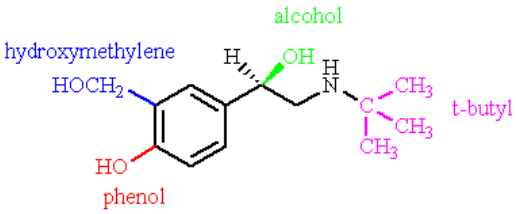


a. Structure A. b. Structure B. c. Structure C. d. Structure D.

Q16. Which of the following descriptions best describes an allosteric inhibitor?
a. A drug that binds to an active site and undergoes a reaction.
b. A drug that binds to an active site and inhibits the enzyme, but which is displaced by increasing the concentration of substrate.
c. A drug that binds to an active site and inhibits the enzyme, but which is not displaced by increasing the concentration of substrate.
d. A drug that binds to a different binding site from the active site and affects the activity of the enzyme.

Q17. Which of the following statements about adrenaline is false?
a. It acts like a hormone. b. It is rapidly metabolised.
c. It shows poor selectivity between different types of adrenoreceptor. d. It is a useful medicine

Q18. The following structure is the anti-asthmatic agent salbutamol. Which of the colored groups interacts with a hydrophobic binding region in the adrenergic binding site?



a. The hydroxymethylene group. b. The phenol.
c. The alcohol. d. The *tertiary* butyl group.

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Q19. What type of agents are the following? Answer in two to three words each. **[1M each]**

a. Nitrogen mustards =

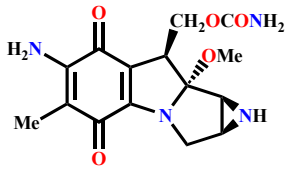
b. Cisplatin =

c. Morphine =

Q20. Draw the correct structure of Morphine and identify how many stereocenters are there. **[2+1=3]**

Q21. Why κ-agonist is preferred as target for analgesic development (Write in 1-2 lines within the provided space). **[2]**

Q22. How Mytomycin C acts as a DNA alkylator? (Draw the molecular mechanism of action) **[5]**



Mytomycin C

….. END of PART-I …..

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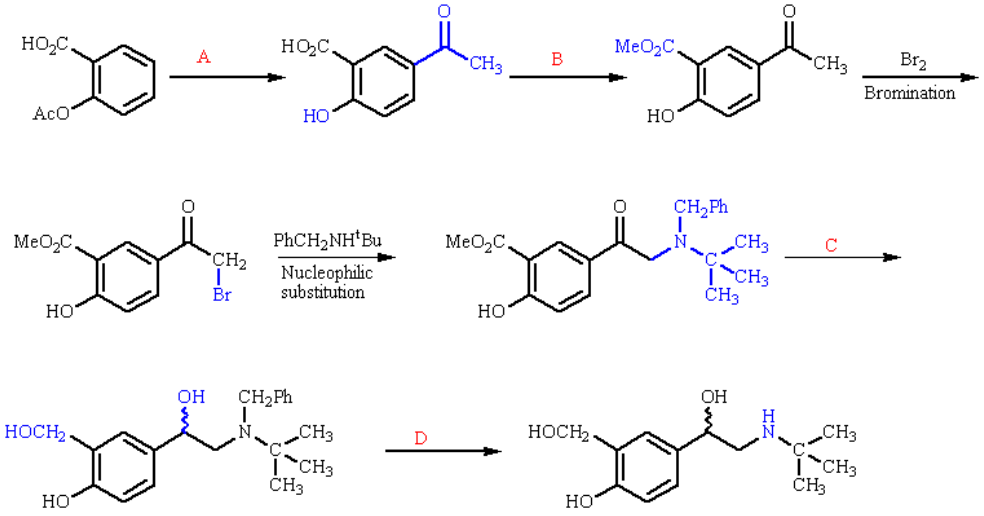
Time: 90 min **OPEN BOOK** **Max marks: 40**

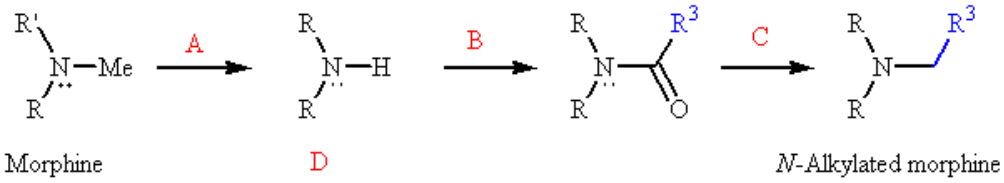
Part-II: Answer all questions. Answer all parts of a question together.

Part-II Descriptive

Q1.a. The following synthetic route has been used to prepare SALBUTAMOL. What are the reagents A – D? **[4]**



b. The following synthetic route can be used to prepare *N*-alkylated analogues of morphine. **[4]**

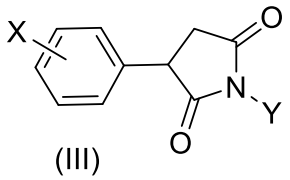


What reagents are used in step A , step B, and step C, and what is structure D?

c. A QSAR equation for the anticonvulsant drug (III) was derived as follows: **[2]**

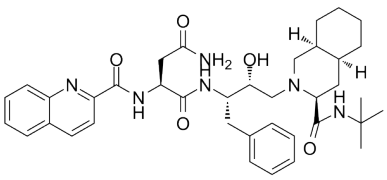
$\log(1/C) = 0.92\ \pi_x - 0.34\ \pi_x^2 + 3.18$ $(n=15, r^2=0.902, s=0.09, \pi_o=1.35)$

What conclusions can you draw from this equation? Would you expect the activity to be greater if X = CF_3 rather than H or CH_3?

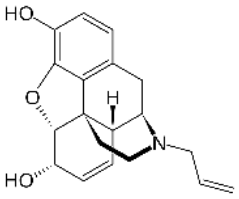


(III)

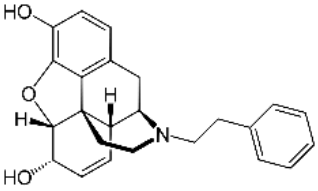
Q2.a. Point out the important fragments of Saquinavir to show the anti-HIV protease activity. Justify your answer in three to four lines. **[4]**



b. Based on the model proposed by Snyder group explain why Nalorphine (a) can act as antagonist for a specific opioid receptor whereas N-Phenethylnormorphine (b) acts as an agonist for the same? **[4]**

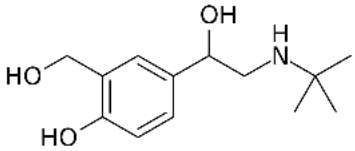


a



b

c. Identify the important structural units within Salbutamol to show its adrenergic agonist activity. **[2]**



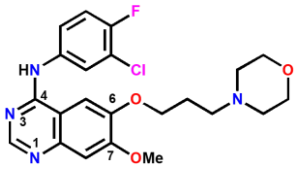
Q3.a. Write the mechanism of proteolytic (peptide) cleavage by Chemotrypsin. The active site contains three major amino acids Ser, His, Asp which are involved into the catalytic triad. **[3]**

b. How many (major) different types of inhibitors are possible in terms of their mechanism of action? **[1]**

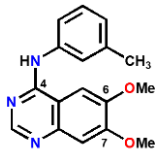
c. Derive Michaelis Menten equation and show the Lineweaver Burk expression. **[4]**

d. Draw the Lineweaver Burk plots with proper labelling for the (main) different types of inhibition processes. **[2]**

Q4.a. Compare the structure of the Gefitinib (Iressa) with corresponding lead molecule to show the Tyrosine Kinase inhibition. Comment on the necessity of each modification on the lead to obtain better drug action. **[4]**

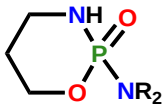


Gefitinib



Lead molecule

b. Describe the molecular mechanism of cyclophosphamide to show the anti-cancer activity? What type of inhibitor is it? **[3+1=4]**



Cyclophosphamide

c. Name an Organometallic drug with anticancer activity. Also mention the target biomolecule of the drug. **[1+1=2]**

……. END OF PART-II …….