Technical University of Mombasa

Faculty of Applied and Health Sciences

DEPARTMENT OF PURE AND APPLIED SCIENCES

UNIVERSITY EXAMINATION FOR THE DEGREE OF BACHELOR OF TECHNOLOGY IN APPLIED CHEMISTRY

BTAC 11M$_2$

ACH 4402 : MEDICINAL CHEMISTRY II

SEMESTER EXAMINATION

DECEMBER 2013 SERIES 2 HOURS

Instructions to candidates:

This paper consist of FIVE questions
Answer question ONE (compulsory) and any other TWO questions

QUESTION ONE

a) Cimetidine (1) was developed by carrying out SARS of burimamide (2) and metiamide (3) amongst other molecules.

(i) Why is burimamide (2) inactive at physiological pH? What modifications were carried out to stabalise burimamide? **(3marks)**

(ii) Metiamide (3) was found to be ten times more potent than burimamide (2) but had the limitation of causing agranuloccytosis.

I. Which functional group in metiamide was responsible for the side effect?

II. Provide the structures of TWO compounds which were evalutated in the attempt to come up with more potent molecules than metiamide (3)

(2marks)

III. Why was the cyano group included on the side chain of cimetidine

(1mark)

b) Proton pump inhibitors (PPTs) have largely susperseded the H_2 antagonists in the management of ulcers. The PPIs undergo activation when they are protonated in acidic environment as per the following scheme. Make use of curly arrows to provide for the mechanism leading to formation of the intermediates 4 – 7 and the attachment of the intermediate 4 to the proton pump. **(5marks)**

c) Resonance effects do play a predominant role in explaining specifically the influence of various substituents of aromatic portion of local anaesthetic molcecules upon the local anaethetic actions as in the case of tetracaine (8)

(i) Provide the resonance structures of tetracaine (8) clearly indicating how the structures are achieved by making use of curly arrows **(2marks)**

(ii) Provide the structure of protonated form of tetracaine (8) **(1mark)**

d) (i) Methohexital sodium (9) is a general anaesthetic which can be synthesized from N-methyl urea (10) and diethyl ester of malonic acid.

(ii) Provide a synthetic scheme of methohexital sodium (9) based on the two molecules dearly indicating other required reagents and intermediates involved. **(5marks)**

QUESTION TWO

a) Define the following terms as applied in medicinal chemistry.

(i) Competitive antagonist
(ii) Non-competitive antagonist

(2marks)

b) Salbutamol (II) is a B_2-agonist and was developed from adrenaline (12). The drug was widely used in the management of asthma before the discovery of more potent analogues

(i) Trace the structure of salbutamol (11) and identify four functional groups in the molecule. **(2marks)**
(ii) Give an account of the development of the drug from the neutron-transmitter adrenaline (12) indicating the analogues developed based on SARS and limitations encountered in the development process. **(10marks)**

c) Salbutamol (11) can be synthesized as per the scheme outlined below. Use the scheme to answer the following questions.

(i) Provide reagents required in the interconvening processes 1 -3 **(3marks)**
(ii) Give the structure of the intermediate A **(1mark)**
(iii) Make use of curly arrows to provide a plausible reaction mechanism leading to the formation of the amino-side chain in Salbutamol (11) from the epoxide intermediate. **(2marks)**

QUESTION THREE

a) Cimetidine (13) is a histamine H_2 –receptor antagonist which was developed based on SAR studies of the neutrotransmitter histamine (14)

(i) Other than imidazole ring system, name four other functional groups on the structure of cimetidine (13) **(2marks)**

(ii) Imadazole ring in cimetidine has two equivalent tautomeric forms. Provide the structures of the two tautomers and indicate the active tautomers. **(3marks)**

(iii) Provide the structure of ether analogue of cimetidine (13) and account for its limitation as H_2-receptor antagonist **(3marks)**

b) Acid catalysed hydrolysis of cimetidine (13) results into formation of guanylurea. Provide the structure of guanylurea and make use of curly arrows to provide the mechanism leading to its formation **(4marks)**

c) Roxatidine HCl (16) is a histamine H_2 – receptor antagonist with an expressed antiulcer activity, and can be synthesized as per the following scheme

(i) Provide the structure of the reagents labelled A and C, and the structure of the intermediate B. **(4marks)**

(ii) Make use of curly arrows to provide the mechanism of the reaction leading to the formation of intermediates 15 and B. **(4marks)**

QUESTION FOUR

a) What are general anaesthetics? Other than inhalation anaesthetics name two other classes of this group of anaesthetics. **(3marks)**
b) Outline the general physical and chemical properties of inhaled anaesthetics **(4marks)**
c) Thiopental (17) is short-acting barbiturate which is administered as a sodium salt.

(i) Provide the structure of the sodium salt. **(1mark)**
(ii) Provide the structures of any two metabolic product of thiopental (17). **(2marks)**
(iii) Outline the synthesis of thiopental starting from sodium malonic ester (18) indicating all the intermediates and reagents required for the proposed synthetic scheme. **(6marks)**

d) Describe how each of the following theories account for the observed activities of general anaesthetics.

(i) Lipid theory **(2marks)**
(ii) Physical theory **(2marks)**

QUESTION FIVE

a) What are antipyretic analgesics? **(1mark)**
b) Antipyretic analgesics may be classified on the basis of their chemical structures. Name THREE classes of the drugs. **(3marks)**
c) (i) Paracetamol (19) enjoys still world-wide recognition for its abundant utility in controlling fever in most non – inflammatory conditions. Outline the synthesis of paracetamol starting from phenol. **(5marks)**

(ii) Paracetamol is metabolized primarily in the liver, into two non-tox products. Provide the structures of the metabolic product formed through glucoronidation and sulphation. **(3marks)**

d) Salicylamide (20) can be used in patients who are sensitive to asprin.

(i) Outline the synthesis of salicylamide (20) starting from salicyclic acid (21)
(ii) Make use of curly arrows to provide for the mechanism leading to the formation of the amide functional group in salicylamide (20) **(3marks)**

e) Benorilate is a drug molecule which possesses antipyretic analgesic and anti-inflilammatory properties. The drug molecule may be prepared by esterification reaction of acetyl salicyclic acid (asprin) and paracetamol(19).

(i) Provide the structure of benorilate **(1mark)**
(ii) Give the structure of two metabolic products of benorilate emanating from the aspirin entity. **(2marks)**