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Study synthesis and spectral identification of derivatives of Pyrone, Pyridones , and aliphatic diketo acids derivatives

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Abstract-
A synthetic approach to study various Pyrones , Pyridones and diketo acids has been proposed to study. Various substitution would be tried and spectral data will be studied to establish the structures. This study covers general introduction to Pyrone , Pyridone , and aliphatic diketo acids , their synthetic methods ,derivatives using Mannich reaction scheme and products are interpreted using IR , NMR, Mass spectral analysis. These studies demonstrate that substituted derivatives of pyrones ,pyridones have excellent biological activity as a new class of antifungal,antibacterial, anticancer agents..

Key words : *Pyrone , Pyridone , Aliphatic diketo acids , antifungal, antibacterial, anticancer*

1.Introduction -

More than sixty percent molecules of modern science drugs are heterocycles , natural amino acids , cellulose and related natural derivatives in nature. Heterocycles have very good applications in human life. The pyrone moiety is a structural feature found in a huge variety of biologically active metabolities. In recent times new insights into additional biosynthetic chemistry yielding in such six-membered unsaturated ester ring residues have been obtained. The purpose of this research is to explore chemistry of pyrones and their derivatives formed through Mannich reaction.We propose to study few commercially important pyrones and pyrimidones derivatives chemistry.

Pyrone and pyridon derivatives are able to exert remakeble range of biological ativity suchcompounds are validated as being capable of binding to specific protein domains and able to exert a remarkable range of biological effects.The biological activities exhibited by pyrone and pyridone are immense, including antimicrobial [2], antitumor [3,4], and antifungal activities [5].Aflatoxins, produced by several Aspergillus species, are known to cause food poisoning due to their cytotoxic activity. Any drug efficacyreduces after some years. Then needs to develop next version of building block molecules derivatives. Many substituted pyrone and pyridone derivatives are key building blocks in pharmaceutical products. We propose to synthesis different substitutions in pyrone and pyridone to achive next version of drugs.

They can regularly be found in improperly stored food, hence, entering the food supply chain [6]. Further coumarin derivatives, e.g., umbelliferone (4), esculetin (5), and scopoletin (6), are subject of investigation due to their pharmacological properties, i.e., anticancer effects [7]. α-Pyrones have also been shown to be HIV protease [8-10] and selective COX-2 inhibitors [11,12].The different biosynthetic routes towards an α-pyrone ring have commercial importance like the statin drug lovastatin, which has application in lowering cholesterol.

The product 4 – Hydroxy -6 –methyl-2-pyrone is also refered as Triacetic acid Lactone (TAL) , is a precursor in many chemical synthesis(Hansen) . TAL is reported to be made from Glucos by

using enzyme 2-pyrone synthase from Gerbera Hybrida , E Coli and Saccharomyces cerevisiae. (10,13,14)

1.1 Pyridone Derivatives:-

Owing to the versatile applications in different areas including biology, natural compounds, dyes, and fluorescent materials, the synthesis of 2-pyridone compounds is an important research field and has attracted a great deal of attention. The clinical success of paclitaxel (PTX) and docetaxel in the treatment of cancer has prompted a worldwide search for compounds with a similar mechanism of action but improved characteristics. The low aqueous solubility of PTX and the development of clinical drug resistance, mediated by both the overexpression of P-glycoprotein (P-pg) and the presence of L-tubulin mutations [15] are factors that hamper its applicability. The discovery [16] and recognition of the epothilones as potent tubulin polymerizing agents [17] propelled them into the forefront of chemical and biological research (for review see [18] and references therein 2-Pyridone derivatives are especially interesting because the 2-pyridone structure is present in many compounds of natural origin [1], many of which possess biological activity. Most of these compounds possess antibacterial [2,3], antifungal [4], anti-inflammatory [5], antiviral [6,7], antitumor [8] and antiplatelet [9,10] properties. 2-Pyridone derivatives are used in the manufacturing of paints [11], pigments, additives for fuels and lubricants, acid-base indicators, stabilizers for polymers and coatings [12]. Due to a variety of pharmacological properties, the 2-pyridone structure is important in the pharmaceutical industry [13]. Many medications contain 2-pyridone structure: cardiotonics (milrinone (Figure 1a) and amrinone (Figure 1b) used for the treatment of heart failure [14,15]

1.2 Di-Keto Acids derivatives:-

1.1a Alpha Keto Leucine:- Alpha keto Leucine is an important pharmaceutical-chemical intermediate , Alpha-keto-leucine is an essential in the biosynthetic precursor of leucine. This is an important source material in functional drinks, alpha-keto-leucine and salt thereof also are its important component. Alpha-keto-leucine-calcium is the important source material in the compound alpha-ketoacid preparation.Alpha-ketoacid is as one of eubolism species of human body, can also be directly used in some uremic treatment, at present, the treatment of compound alpha-ketoacid preparation associating low

protein diet is alleviating the symptom of uremic patient, and good effect has been brought into play in the renal function deterioration aspect that can improve patient's renal function, blood fat disorder and nutritional status, and provides clinical theoretical foundation for the early diagnosis chronic renal insufficiency.

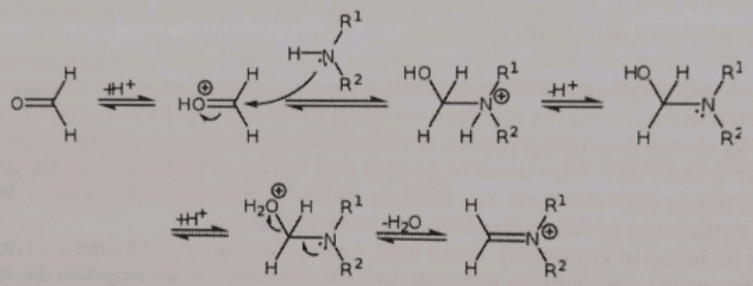
1.1b 3,3 Di methyl Oxo butyric acid:-3,3 Di methyl Oxo butyric acid is a ketoacid , a low melting solid , usually a semisolid , this is colourless and this is a precursor of Pantothenic acid. Pantothenic acid, also called vitamin B5 is a water soluble vitamin B and essential nutrient , it synthesizes Coenzyme A , which is essential for fatty acid metabolism and general metabolism. water-soluble B vitamin and therefore an essential nutrient.[7] All animals require pantothenic acid in order to synthesize coenzyme A (CoA) – essential for fatty acid metabolism – as well as to in general synthesize and metabolize proteins, carbohydrates, and fats.Vitamin B5 is a dietary supplement or animal feed ingredient the form commonly used is calcium pantothenate because of chemical stability, and hence long product shelf life, compared to sodium pantothenate or free pantothenic acid.[1]

Mannich Reaction mechanism

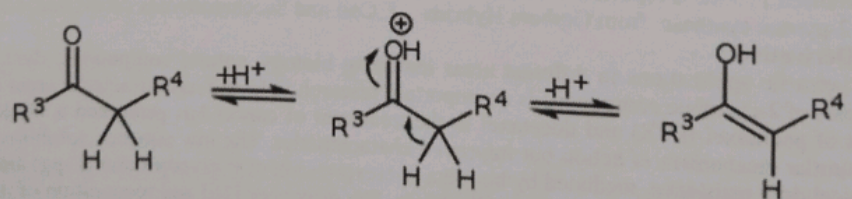
Mannich reaction is organic chemical coupling reaction which named by German chemist Carl Mannich. It is an organic Reaction in which an acidic H+ ion position next to carbonyl

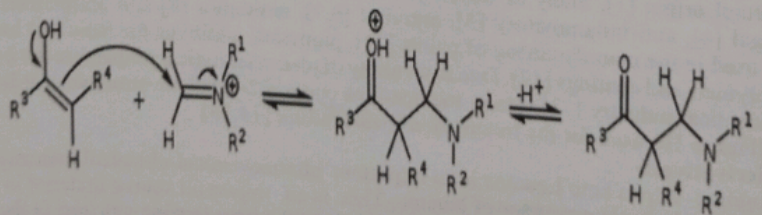
group undergo an amino alkylation with the help of formaldehyde and ammonia(primary, secondary). You can use amine instead of ammonia.Final product of this reaction is a beta amino carbonyl compound. Mannich reaction mechanism begins with formation of iminium ions from the reaction between formaldehyde and amine. Carbonyl compound functional group undergo toutomerisation to give enol form. This enol form attacks to iminium ion.Mannich reaction having two steps.

Step-1 :- Reaction between formaldehyde and amine leads to formation of iminium ion. It is example of nucleophilic addition of an amine to a carbonyl group. R1 , R2,R3 ,R4 = alkane, alkene, alkyne, phenyl groups.



Step-2 :- The compound containing carbonyl group (ketone) undergoes toutomerisation to give enol form. This enol form of carbonyl functional group attacks on iminium ion and yield beta amino carbonyl compound. Also called Manich base.





This reaction is useful for preparation of alkyl amine , antibiotics (tetracycline) , catalyst , polymer , pharmaceutical drug (fluoxetic) , soap and detergents.

2. Synthesis of derivatives:-

2.1 Synthesis of Pyrone Derivatives:- Pyrone rings are found in natural products as well a lot many drugs are designed based on pyrone chemistry. Pyrone chemistry1 is used in Antimicrobials , Anticancers3 , Insecticides , Herbicides.There are two pyrone derivatives – 1) 2- pyrone and 2) 4- pyrone These are very valuable products from pharmaceutical application point of view. These are useful as anticfungal,antibacterial, antanticancer , anti HIV as ,[1] anti convulsant , Insecticide etc. A synthetic2 and Spectral interpretation as well application approach of these products have been attempted here.[2,3]A scheme of synthesis has been proposed to synthesise various substituted Pyrones

2.1a. Starting from simple alkyl carboxylic acids like Butanoic acid , isobutanoic , pentanoic , isopentanoic , heptanoic , ocatnoic , phenyl acetic , nicotynyl ,adamantly, phenyl alkyl acids will be explored to convert to ketone and further condensed with dicarboxylic acid to get keto acid to get desired product. [23]

2.1b. Alkyl carboxylic acid esters are reacted with dimethyl sulphoxide or it's derivative , which further reacted with chloro propionic ester , which is further cyclised to get 6 substituted pyrone. Different substiturions like Butanoic acid , isobutanoic , pentanoic , isopentanoic , heptanoic , ocatnoic , phenyl acetic , nicotynyl ,adamantly, phenyl alkyl acids will be explored to get different 6 substituted pyrone.[24]

2.1c. Fused Benzopyrone will be explored by treating various substituted homopthalic acid , various substituted and 3 – substituted fused pyrones or isocoumarines will be explored.

2.1d. Short chain fatty acids will be explored to get 6 – substituted pyrone by treating with carboxylic acid chlorides , various acid chlorides will be explored such as aliphatic , aromatic , heterocyclic.

2.2. Pyrone derivatives using Mannich reaction to make β-amino-carbonyl compound

Multicomponent reactions are important from the point of expanding molecules , while doing molecule , or drug design , which requires complexity. Mannich reaction offers such opportunity to explore chemistry of keto group of Pyrone and that yields multiple products of biological importance , while reacted with an aldehyde and an amine. Such exploration provides an opportunity to shorten the reaction time , path , less waste , lower cost and one pot , irreversible reaction.Various aldehydes , amines , reaction conditions will be explored.

Mannich reaction provides this opportunity and this generates Mannich base , substituted amino carbonyl compound. Solvent system used for this reaction varies from water to alcohol , acetonitrile , toluene , ionic liquids. Various solvents , reaction conditions , and amines and aldehydes will be explored to get different Mannich base. Cyclic amines , aliphatic , aromatic amines , substituted aldehydes will be explored. [Reference - 33 to 39] In recent years various such components are explored as antiviral , insecticidal , antimalerial properties.(reference 31,32)

2.3. Synthesis of Pyridone Drivative:- A scheme of synthesis has been proposed to synthesise various substituted Pyridones as stated above and further these pyrone are converted to respective Pyridone by doing exchange of Oxygen by Nitrogen.

2.3a. Starting from simple Alkyl carboxylic acids like Butanoic acid , isobutanoic , pentanoic , isopentanoic , heptanoic , ocatnoic , phenyl acetic , nicotynyl ,adamantly, phenyl alkyl acids will be explored to convert to ketone and further condensed with dicarboxylic acid to get keto acid to get pyrones , which are further converted to pyridine , desired product

2.3b. Alkyl Carboxylic acid esters are reacted with dimethyl sulphoxide or it's derivative , which further reacted with chloro propionic ester , which is further cyclised to get 6 substituted Pyrone. Different substiturions like Butanoic acid , isobutanoic , pentanoic , isopentanoic , heptanoic , ocatnoic , phenyl acetic , nicotynyl ,adamantly, phenyl alkyl acids will be explored to get different 6 substituted pyrone., which are further converted to pyridine.Fused Benzopyrone will be explored by treating various substituted homopthalic acid , various substituted and 3 – substituted fused pyrones or isocoumarines will be explored. Further these will be converted to fused pyridines.

2.3c. Short chain fatty acids will be explored to get 6 – substituted pyrone to further convert to pyridine , by treating with carboxylic acid chlorides , various acid chlorides will be explored such as aliphatic , aromatic , heterocyclic.

2.4a. Diketo acid Derivatives:- This is an approach to study Synthesis and application of diketo acids. These are found in Human body as , incomplete break dawn of amino acids. Here we have tried to study synthesis and application of these products. Different aliphatic substitutions would be studied in this approach.

2.4b. Alpha Keto Leucine:-Acetone cyanohydrine will be converted to hydantoin , which will be further converted to imidazolidine dion to convert further to Alpha keto Leucine , various aldehyde will be explored to get different acids.

2.4c. 3,3 Di methyl Oxo butyric acid:-3,3 Methyl Oxo butyric acid – These are also found as , incomplete break dawn of amino acids. This is one more example to study synthesis and application of similar products. Different aliphatic substitutions would be studied in this approach.

2.4 d. Synthesis of various alpha keto acids , interpretation:-

Isopropyle chloride will be treated with coppercyanide and that will be further hydrolysed to get a dimethyl oxo butyric acid . Such different diketo acids will be explored and their chemistry will be studied with IR , NMR and Mass spectral interpretation

3. Objective of Research

3a.To explore the chemistry of the different substitution of pyrone,pyridone,and diketo acid.molecules.3b. To study reaction behaviour of pyrone,pyridone,and diketo acids in solvent and aqueous activity.3c.To study the effect of concentration of synthesis compound on spectral characteristics.3d.To evaluate the microbial activity of pyron,pyridone,and diketo acid

derivative moity with other compound.

4. Experimental design

Appropriate substitution derivative will be prepared using latest literature review.The synthesized substituted derivative of pyron,pyridone,and diketo acids will be used to study spectral identification using UV-viseible ,IR,NMR ,mass , spectrometric methods. Further use for biological activity test such as antimicrobial, antifungal, anticancer, insectisidle, Herbicidle,etc.

5. Expected result

5a. Substitution of pyron,pyridone and diketo acids in aqueous and non aqueous solution will be studied.5b.Develop substituted product purifay as per standard lab procedur and use for spectral analysis.5c.The effect of concentration on spectral characteristics will be studid.5d.Te data of spectral identification will be analysed.in every substitution seperatly.5e. The effects due to concentration on biological activity will be studied.5f.To evaluate antimircobial activity of the newly synthesized compounds by broth dilution method and to study the structure activity relationship to optimize the structure

6. Conclusion

Any drug efficacy reducesafter some years. Then needs to develop next veivirsion of building block molecules derivatives. Many substituted pyrone and pyridone derivatives are key building blocks in pharmaceticle products. We propose to synthesize different dfferent substitutions in pyrone and pyridone to achive next version drugs.Appropriate substitution derivative will be prepared using latest literature review.The synthesized substituted derivative of pyron,pyridone,and diketo acids will be used to study spectral identification using UV-viseible ,IR,NMR ,mass , spectrometric methods. Further use for biological activity test such as antimicrobial,antiungal, anticancer, insectisidle,Herbicidle,etc.We propose to synthesis different substitutions in pyrone and pyridone to achive next version drugs.Biological activity evaluate by Agar and broth dilution method.

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