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Comparative Study of Effect of Structural Modification on Antimicrobial Activity of Esters

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ABSTRACT

Esters are the chemical compound derived from the acids in which at least one hydroxyl group is replaced by an alkoxy group. The discovery of antimicrobials was an essential part. They stand as one of the most important weapons in fighting against various microbial infections. The objective of this research was to study comparatively that slight structural modification in the existing ester can change their antimicrobial activity against various microbes. In this research, we comparatively studied the five esters and their derivatives after structural modification. Different esters were subjected to various microbial strains for the determination of any change in their antimicrobial activity after structural modification. The results demonstrated that the increasing alkyl chain length or condensation of two esters are the most important factors influencing the antimicrobial activity of the various esters.

HIGHLIGHTS:

1. Phenolic Acid Alkyl Esters,

2. Esters of Polyhydric alcohols,

3. Lipophilic Tyrosyl Ester Derivatives,

4. Betaine Esters,

5. L-phenylalanine and L- tyrosine Esters.

INTRODUCTION:

- In our project, we are comparatively studying the effect of structural modification on the antimicrobial activity of various esters.

- In this, we studied how the various ester derivatives are synthesized by modifying the structure by increasing alkyl chain length, increasing fatty acid chain length, or by condensation of two esters.

- In this study, we compare the antimicrobial activity of the parent compound and the activity of derivatives and we found that the Derivatives compound shows more antimicrobial activity.

- This structural modification leads to enhancement of antimicrobial activity is determined by subjecting ester derivatives against various antimicrobial screening.

COMMON METHOD OF SYNTHESIS OF ESTER:

❖ Esters are formed from the esterification reaction of carboxylic acid and alcohol. In this reaction, the carboxylic acid is heated with alcohol in presence of catalysts like conc. Sulphuric acid (a dry form of hydrogen chloride gas can also be used in some cases).

❖ Simply this reaction converts the alcohol and acid to the ester by removing water (OH- from acid and H+ from alcohol). Therefore, this reaction does not work for the compound which has an OH group directly attached to the benzene ring.

❖ This is a reversible and slow reaction. Acid and alcohol can form back by hydrolysis of ester in presence of water. This reaction is also called as Fischer esterification reaction.

❖ The equation of the reaction between the alcohol ROH and the acid RCOOH is given below-

Figure No. 1: Equation of the reaction between carboxylic acid and alcohol.

COMMON SAR OF ESTERS:

Structural Activity relationship study of esters states that-

1) R1 functional group chain present is important for antimicrobial activity of the structure.

2) Also in Aromatic ester benzene ring is important for the antibacterial and antifungal activity against *C.albicans* and *E.coli*.

3) Substitution on the benzene ring with an electron-withdrawing group increases the antimicrobial activity.

Notes-

- Esters are rapidly undergone hydrolytic degradation in the presence of water therefore they have a very short duration of action. The R1 alkyl chain has initiated hydrolysis. It becomes difficult to hydrolyze when the alkyl chain increased. Therefore, due to the increase in alkyl chain length duration of action increases which leads to an increase in antimicrobial activity.

- Esters are more polar than the others but less polar than alcohol due to the presence of carbonyl moiety. They cannot act as a hydrogen donor therefore they are less soluble in water.

REACTION USED FOR STRUCTURAL MODIFICATION:

CLAISEN CONDENSATION

What is Claisen Condensation?

- In this reaction, two esters or one ester and another carbonyl group such as aldehyde fused by forming a carbon-carbon bond.
- This reaction occurs in the presence of a strong base such as sodium hydroxide (NaOH) or alkoxides. The product of the reaction will be beta keto ester or beta diketone.
- The mechanism of this reaction is divided into three steps.

Mechanism of Claisen Condensation:

Step 1

In this step, the first molecule of ester reacting with a strong base resulting in the formation of the enolate anion. Due to the attack of alkoxide alpha hydrogen gets removed from the ester and the bond between carbon and hydrogen shifts to the next carbon which leads to the formation of an enolate ion. The enolate anion is relatively stable due to the delocalization of the negative charge on carbonyl oxygen. Given below is the reaction that leads to the formation of an enolate anion.

Step 2

In this step, the second ester/carbonyl functional group comes into the picture. Carbonyl oxygen being more electronegative attracts the pair of the electron itself and becomes negatively charged leaving carbon electron deficient. Then the enolate ion as a nucleophile attack on the electron-deficient carbonyl carbon. This leads to the formation of a tetrahedral intermediate.

Step 3

The tetrahedral intermediate formed in the previous step is highly unstable therefore in this step carbonyl atom rearrange by giving negative chargeback and forming C=O bond and alkoxide ion leave the structure as a leaving group. This leads to the formation of beta diketone or beta keto ester.

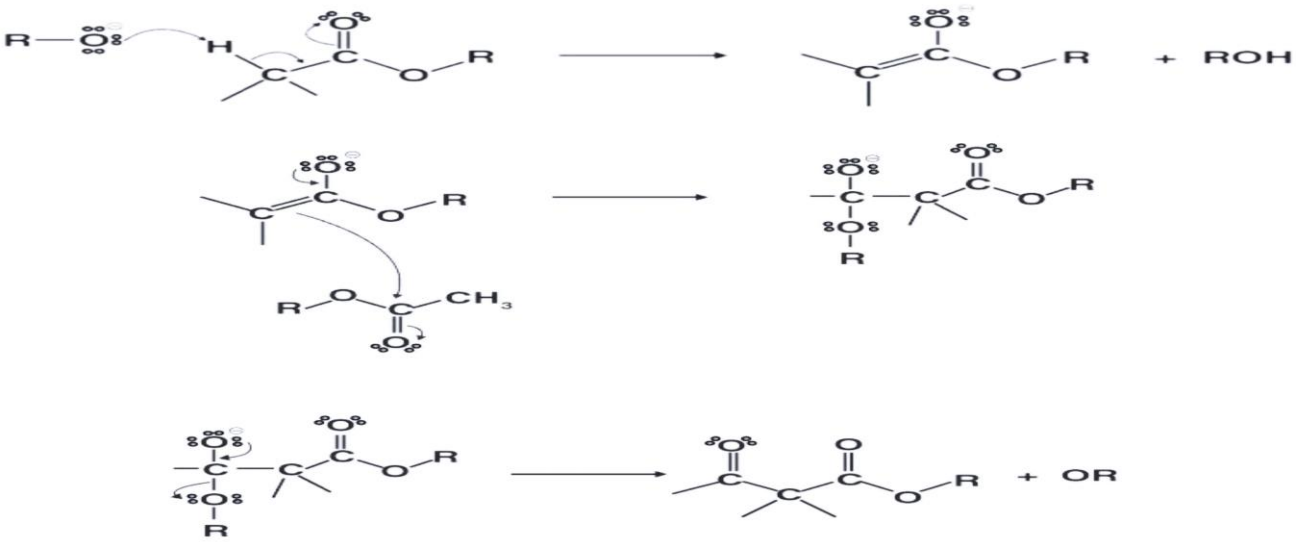

Figure No. 2: Claisen Condensation

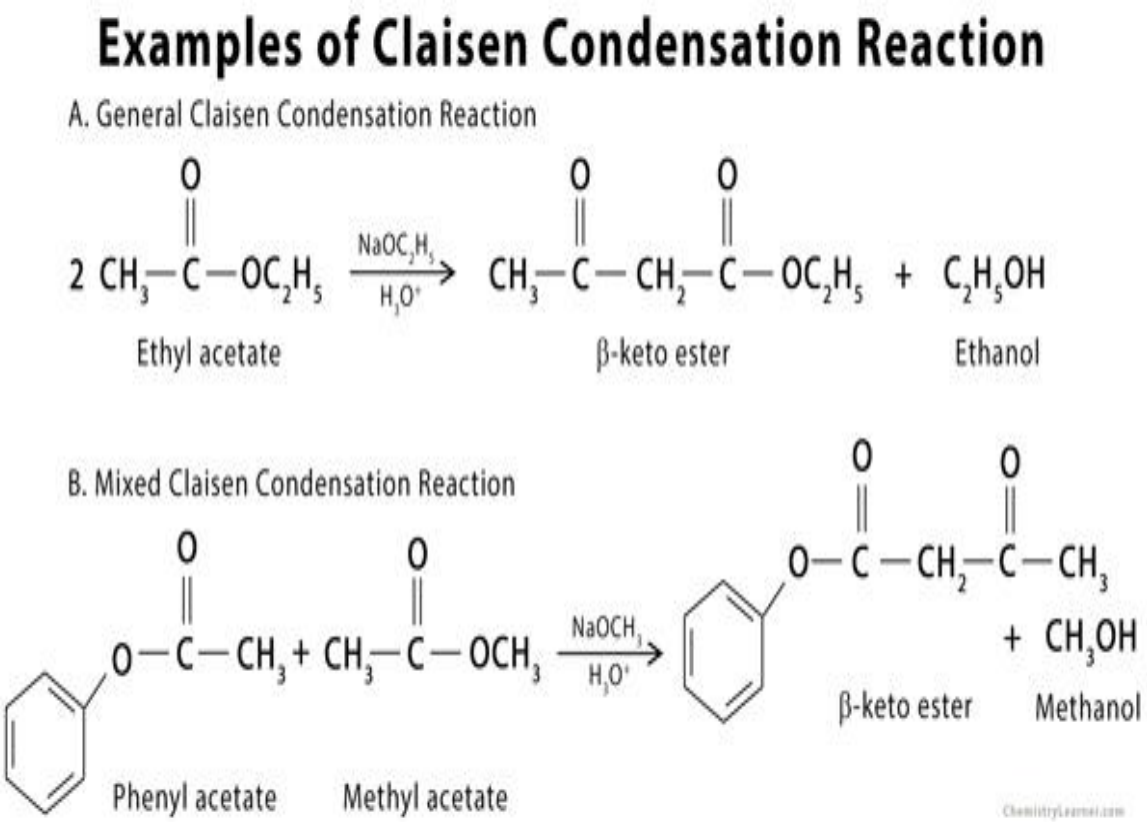

Figure No. 3: Examples of Claisen condensation

Beta keto esters form in this reaction are more active than the parent ester and have more antimicrobial activity.

EXAMPLE which shows the Beta keto ester formed by the condensation reaction enhances the antimicrobial activity:

SYNTHESIS OF BETAKETOESTERS FROM KETONES AND ETHYL CHLOROFORMATE AND ANTIMICROBIAL ACTIVITY OF THEIR DERIVATIVES:[1,8]

- Pyrazolones are Derivatives of beta Keto esters traditionally synthesized by the reaction of β-ketoesters with hydrazine and ethanol.

- The newly formed pyrazolones as per the above reaction subjected to antimicrobial screening against many microbes such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* bacterial strains by the disc diffusion method.

- In the disc diffusion method drug-containing disc place on the surface of the inoculated agar plate. Then invert the plate and incubation done at 35°c for 18-24 hours. The diameter of the inhibition zone is measured in mm.

- Results obtained were compared with the standard ciprofloxacin. Most of the synthesized compounds exhibited very good bacterial activity.

- The antifungal activity of pyrazolone was also determined against *A. flavus*, *A. fumigates*, *P. marneffei*, and *T. mentagrophytes* in DMSO by the serial plate dilution method. Most of the tested compounds exhibited good fungicidal activities.

- Therefore, pyrozolones as a derivative of beta Keto esters show promising antimicrobial activity.

COMPARATIVE STUDY:

In the comparative study, we compare the five esters for their Structural modification which enhances antimicrobial activity. Those five esters are as follows:

1. Phenolic Acid Alkyl Esters,

2. Esters of Polyhydric alcohols,

3. Lipophilic Tyrosyl Ester Derivatives,

4. Betaine Esters,

5. L-phenylalanine and L- tyrosine Esters.

1. Antimicrobial Activity of Phenolic acid alkyl esters:[2,9]

Introduction:

In this article, some phenolic acid alkyl esters like methyl, ethyl, butyl, hexyl esters were prepared and their antimicrobial activity was determined against various bacterial strains. Their minimum inhibitory concentration is determined. From the M.I.C observation, it is found that the inhibitory activity of phenolic acids butyl esters is much higher than that of methyl esters.

Antimicrobial activity study:

- Phenolic acid alkyl ester was obtained from the reaction of Phenolic acid with respective alcohol. For example, phenolic acid methyl ester formed from the reaction of Phenolic acid with methanol.

- The antimicrobial activity of this phenolic derivative against gram-negative, gram-positive bacteria, yeast, and fungi was measured by minimum inhibitory concentration determination.

- M.I.C means the lowest concentration of ester which would inhibit the visible growth of the microorganisms.

- In the detailed study, some phenolic acid esters (methyl, ethyl, butyl, hexyl) are compared for their M.I.C. against various microbial strains.

- Bacterial cultures were prepared freshly in nutrient broth, while yeast and fungi were prepared in malt extract. Prepared culture incubated as per following bacterial conditions:

Table No. 1: Incubation conditions for various microorganisms

Organisms	**Incubation Conditions**
E.coliDMF7503	37°Cinairfor20hours
BacilluscereusDMF2001	30°Cinairfor20hours
ListeriamonocytogenesDMF5776	37°Cinairfor20hours
SaccharomycescerevisiaeDMF1017	25°Cinairfor48hours
FusariumculmorumDMF0103	20-23°Cinairfor72-120hours

- After the incubation MIC values are determined and it is found that the MIC values of phenolic acids and alkyl esters determined for yeast and fungi were significantly different.

- Butyl esters show more microbial inhibition against all the tested strains (Escherichia coli DMF 7503, Bacillus cereus DMF 2001, Listeria monocytogenes DMF 5776, Fusarium culmorum DMF 0103, and Saccharomyces cerevisiae) than all other methyl, ethyl, propyl esters.

CONCLUSION:

From the above discussion, we conclude that the antimicrobial effect of phenolic acid derivatives increases with the increasing alkyl chain length. Therefore, we conclude that structural modification in phenolic acid alkyl ester enhances their antimicrobial activity.

2.Antimicrobial action of esters of polyhydric alcohols:[3,7,9,10,11,12]

INTRODUCTION:

In this article, we go through series of fatty acid esters of polyhydric alcohols and their antimicrobial activity against gram-negative & gram-positive organisms. In this article various ester derivatives with different fatty acids, carbon-chain lengths are compared, and by determining their M.I.C. values observed that the inhibitory activity increases for the esters as the fatty acid chain length increases.

Antimicrobial Activity study:

- In this case, the structural relationship involved with the antimicrobial activity of fatty acids and their derivatives is shown by subjecting several compounds against various microbes.

- M.I.C. values are a very important aspect for the determination of antimicrobial activity, so the Broth dilution method was used to determine the minimum inhibitory concentration of series of fatty acid esters of polyhydric alcohols against gram-positive & gram-negative organisms.

- We observed that the M.I.C. values of the ester derivatives containing 4-8 carbon chains are high and M.I.C. values of the ester derivatives containing 8-12 carbon chains are lower. (Lower M.I.C. values = Higher inhibition at low concentrations).

- So we found that the antimicrobial activity of polyglycerols esters is impressive. e.g. - Esters of polyglycerols (Tri, Hexa, deca-glycerol) were generally active when fatty acid had a chain length of 8-12 carbon atoms.

- Except decaglycerol gives inhibition even when fatty acid chain length decreased to six.

- All those screened derivatives esters of monohydric alcohols showed little or no inhibition, however mono glycerol esters like mono glycerol laureate were observed most active.

- C-18 mono glycerol is found to be slightly active than shorter fatty acid chain mono glycerol against all gram-positive organisms which were tested, it is found that S.pyrogenes was the most susceptible organisms.

CONCLUSION:

From this study, we understood that Polyhydric alcohol Esters show more antimicrobial activity when the fatty acid chain length is 8-12 carbon. Microbial Inhibition increases for the esters as the fatty acid chain length increases.

3. Antimicrobial Activity of Lipophilic Tyrosyl Esters Derivatives:[4]

INTRODUCTION:

In this comparative study, a large group of Tyrosyl esters was synthesized and evaluated for their minimum inhibitory concentration (M.I.C.) for the determination of antimicrobial activity. From the M.I.C. results, we understood that only tyrosyl ester-containing carbon chains of 8, 10, and 12 (TyC8, TyC10, and TyC12) exhibited antibacterial activity against all the tested strains.

Antimicrobial activity study:

- Tyrosyl esters Synthesized from Tyrosol via esterification of the primary hydroxyl group.
- Tyrosol and its Synthesize esters were investigated for their antimicrobial activity against several pathogenic bacteria spp.
- The result found that the Tyrosol showed no inhibition against all the bacteria tested in this study.
- Among all the esters tested, only medium-chain tyrosyl Derivatives that are TyC8, TyC10, TyC12 exhibits antimicrobial activity.
- TyC8 and TyC10 showed the highest inhibitory activity against *Staphylococcus aureus*, *Staphylococcus xylosus*, *Bacillus cereus*.

Table No. 2: M.I.C. values of Tyrosyl esters against tested microorganisms.

Compounds		MIC (microgram/mL)	
	S.aureus	*S.xylosus*	*B.cereus*
Ty	ND	ND	ND
TyC8	25	25	12.5
TyC10	12.5	12.5	3.1
TyC12	50	50	>100

ND*: Without effect up to 5 mg/ml.

- The above table of M.I.C. values shows that TyC10 has the most potent effect. 3.12 µg/ml against B. cereus, and 12.5 µg/ml against Staphylococcus strains. TyC8 was 12.5 µg/ml against B. cereus and 25 µg/ml against Staphylococcus strains. TyC12 was estimated to be more than 50 µg/ml against the three strains.

CONCLUSION:

So from this study, we conclude that by increasing the carbon chain length of Tyrosyl ester from 2-3 carbon atoms to 8-12 carbon atoms we can increase the antimicrobial activity of the tyrosyl esters. Also from decreasing the carbon chain length of Tyrosyl esters from 16-18 carbon atoms to 8-12 carbon atoms can increase the Antimicrobial Activity of the tyrosyl esters.

4. Antimicrobial Activity of Betaine Esters:[5,13]

INTRODUCTION:

In this comparative study antimicrobial activity of Quaternary ammonium compounds that are esters of betaine and fatty alcohols with hydrocarbon chain lengths of 10 to 18

carbon atoms studied. These ester derivatives were tested against various bacterial strains like *E.coli, S.typhi, B.megaterium, P.aeruginosa* and compared with stable quaternary ammonium compound CTAB that is cetyltrimethylammonium bromide.

Antimicrobial activity study:

- Firstly to find out the optimal chain length of Betaine enter for their antimicrobial activity researchers synthesized series of esters with 10 to 18 carbon atoms in the alkyl chain they are B10-B18.

- Then tested them against S. Typhimurium 395MS. In 10 mM sodium phosphate buffer at pH 7.0 and 30°C, from the result, they observed that the B-18 showed the highest activity whereas derivatives B-10 and B-12 did not show any inhibitory activity at 20 µM concentrations.

- After comparing the bactericidal Activity of derivatives against CTAB, we found that the octadecyl (B-18) and the hexadecyl (B-16) derivative show the highest bactericidal activity against all the tested bacterial strains. B-14, B-16, and B-**18** were all highly effective at even concentrations below 10 mM, while the decyl (B-10) and the dodecyl (B-12) derivatives lacked activity at concentrations up to 20 mM**.**

- **Generally, CTAB was slightly more effective than B-14.**

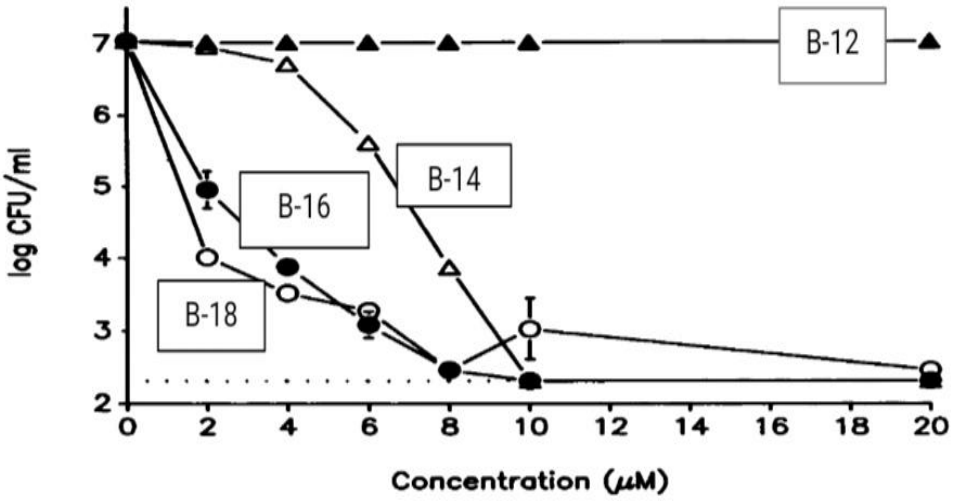

Figure No. 4: Relationship between the length of the alkyl chain and bactericidal activity of betaine esters against S. typhimurium 395MS.

- The above graph shows the relationship between the length of the alkyl chain and bactericidal activity of betaine esters against S. typhimurium 395MS in 10 mM sodium phosphate buffer (pH 7.0) at 30°C. Decyl betaine (B-10) showed the same result as B-12.

- This graph shows that the B-18, B-16 shows more bactericidal Activity even when at very low concentrations while B-10 and B-12 show very less or no bactericidal Activity at very high concentration.

CONCLUSION:

From this, we understood that the bactericidal effect of the Betaine ester increased with the increasing length of the hydrocarbon chain of the fatty acid alcohols moiety up to 18 carbon atoms.

5. Antimicrobial Activity of L- Phenylalanine and L-Tyrosine esters:[6,14,15]

Introduction:

In this case, L- phenylalanine, and L- tyrosine esters were synthesized and newly form esters were screened for their antimicrobial activity against gram-positive and gram-negative bacteria. From the detailed study, we got to know that the activity increased with increasing chain length, exhibiting a cut-off effect at different carbon atoms for gram-positive and gram-negative bacteria.

Antimicrobial activity study:

- L-phenylalanine and L-tyrosine esters Synthesized by reacting them with corresponding alcohol.

- Antimicrobial activity is determined by growth inhibition assay and this is performed with five gram-positive and four-gram negative bacteria that are *S. aureus* ATCC 25923, *S. aureus* ATCC 29213, *S. epidermis, B. cereus* ATCC 10876, B. cereus ATCC 11778, *S. Typhimurium, E. coli, P. aeruginosa, K. pneumonia.*

- The antibacterial activity of the series of L-Phenylalanine and L-Tyrosine was determined based on minimum inhibitory concentration (MIC).

- After getting the result it is observed that all the esters were more active against gram-positive than gram-negative bacteria. Esters with short-chain length have higher M.I.C. values and esters with long-chain have lower M.I.C values.

- So, we understood that the Increase in activity against gram-positive bacteria was observed with increasing chain length.

- The C12 derivatives of both L-Phenylalanine and L-Tyrosine esters showed the highest activity against S. aureus with MIC of 13.5 M and 2 M respectively. For gram-negative bacteria, C8 and C10 esters of L-Phenylalanine and C8 ester of L-Tyrosine show the highest activity.

- And also, we found that the L-Tyrosine esters were found to be more active than the L-Phenylalanine esters of the same alkyl chain lengths.

CONCLUSION:

So finally, we conclude that the antibacterial activities of the L- phenylalanine and L-tyrosine esters were found to be more in case gram-positive than gram-negative strains and their antimicrobial activity for gram-positive bacteria increased with chain length and then decreased with further increase in chain length exhibiting a cut-off effect at C12. In the case of gram-negative bacteria, this cut-off effect was observed at a lower chain length C8 and C10 due to the difference in the bacterial cell wall.

CONCLUSION:

From the Literature survey and above discussion, we conclude that the antimicrobial activity of the esters is increased due to slight structural modification such as increasing carbon chain length, condensation of two esters (i.e. formation of keto esters) in the structure of esters. Newly formed derivatives of esters effectively inhibit the growth of various gram-negative and gram-positive bacteria, fungi, and yeast strains.

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