Impact Factor-4.013 *e-ISSN: 2581-6667*
International Journal of Engineering and Creative Science, Vol. 8, No. 1, 2025
www.ijecs.net

Dihydropyrimidinone Derivatives: Green Approach Physicochemical Properties and Effect of Electronic Factor on their Antimicrobial Properties

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Abstract – *Study of antimicrobial properties is a priority in current research in this pandemic situation of Covid-19. Dihydropyrimidinones (DHPM's) and their derivatives shows significant antimicrobial properties depend upon the electronic factor of the phenyl ring. Present study focuses the synthesis of a series of DHPM's and their derivatives by Biginelli reaction in an eco-friendly and green condition. Various spectroscopic tools were used for characterization of synthesized compounds. It was observed that electron rich as well as electron deficient substituent of aromatic ring plays important role on their biological activities. Physicochemical properties of all the synthesized DHPMs compounds were studied to evaluate nature and magnitude of ion-solvent and ion-ion interactions by viscometric, surface tension and conductivity measurements.*

Keywords- ***Green synthesis, DHPM derivatives; Antimicrobial activities, Physicochemical study***

I- INTRODUCTION

In recent decades synthesis of Dihydropyrimidinones (DHPM's) and their derivatives becomes important in the field of medicinal chemistry because of its pharmacological properties [1]. The (DHPMs) have attracted great attention recently in synthetic organic chemistry due to application in the field of drug research and possess diverse biological activity such as antibacterial , anti-inflammatory, antiviral, antitumor, antioxidant, antiulcer, anticancer. Also dihydropyrimidinoness are important constituents of many bioactive heterocyclic compounds [2-4]. The Biginelli reaction is one of the way to synthesis the dihydropyrimidinone and its derivatives. Synthesis of functionalized of 3,4- dihydropyrimidinone derivatives and their thio analogue was achieved in good to excellent yields using phenylboronic acid as a catalyst [5-6].

Most of the researchers carried out synthesis dihydropyrimidinones using various methods. It was observed that under solvent free conditions using a catalyst give high yield [7-8]. Owning to increasing use of Green technology approach, due to its various merits over classical methodology and as a need for sustainable chemistry, this reaction has received renewed interest for preparing DHPMs in an environmentally thoughtful manner to improve yields [9-11].

Green synthesis method it is simple, cost-effective, efficient and eco-friendly and gives excellent yield in short time. Also, its operational simplicity and the avoidance of the use of organic solvents and friendly preparation is important for the present work. This method has been developed for the performing the Biginelli reaction at room temperature using some common fruit juice as reaction medium which acts as a catalyst rather than the solvent [12-15].

Density, viscosity and surface tension of liquids are important physiochemical properties which affect mass and heat transfer in solution [16-17]. Surface tension plays an important role in molecular interactions that exist on the surface and in the bulk of liquids [18]. Some new dihydropyrimidinone compounds shows different antibacterial activities against some Gram positive and Gram negative bacteria were depends upon substitution attached to different moieties its effect on bacterial strains changes in different solvents [19-23]. Conductivity of a solution is inversely proportional to its viscosity. Its measurement in aqueous and non-aqueous media received considerable importance in recent years due to its varied application in electrochemical study [24].

Present study deals with the synthesize of various Dihydropyrimidinone (DHPMs) derivatives using urea, ethyl acetoacetate with electron rich as well as electron deficient aromatic aldehydes using green approach. Lemon juice without processing is used as a catalyst. This study mainly focuses to evaluate antibacterial activity against some Gram-positive and Gram-negative pathogens. Physicochemical measurements have been carried out in different solvent systems.

II-METHODOLOGY

All chemicals 4-hydroxybezaldehyde, ethyl acetoacetate, thiourea, ethanol and Dioxane were of analytical grade, from SD Fine. The binary mixture of solvent system of 70% dioxane-water and 70% ethanol-water were prepared. Stock solution (0.01M) of derivatives of Dihydropyrimidinone was prepared and diluted to required strength in both the binary mixtures.

Pycnometer was used to measure the densities of pure liquids, their binary mixtures and ligand solutions. The accuracy of density measurements was within 0.1% kg m^{-3}. Ostwald's viscometer is used to measure viscosity of pure liquids and their binary mixtures. Viscosity data were analyzed in the light of Jones-Dole equation.

$$\eta_{sp} = A + \beta\sqrt{C}$$

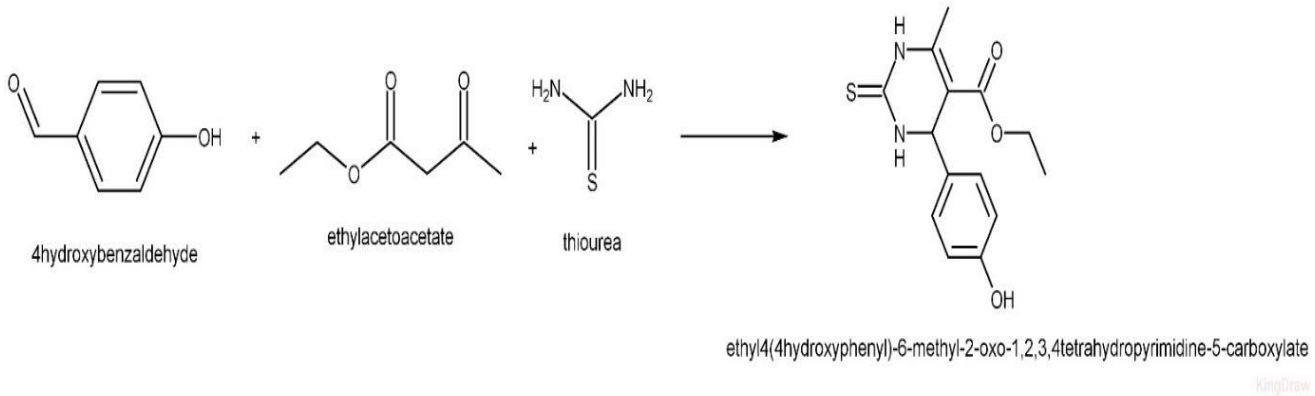
Where A and β are the Falkenhagen and the Jones-Dole coefficients.

Solute–solute and solute–solvent interactions were evaluated from value of 'A' and 'β' by plotting graph between η_{sp}verses$\sqrt{C}$. The study was extended to find out surface tension and conductivity for all prepared derivatives in binary mixtures and their antimicrobial against some pathogenic agents.

Synthesis and spectral characterization of Dihydropyrimidinone Derivatives

Synthesis of Ethyl 4-(4 hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate (HTTPC)

The mixture of 4-hydroxybezaldehyde (1.36g), ethyl acetoacetate and add thiourea (0.7g) was taken. In this mixture add 2-3 ml of lemon juice was added and reflux for 2 hour. After cooling the mixture at room temperature and it was pour into ice cube with constant stirring. The resulting precipitate was filtered and was allowed to dry. It was recrystallize from ethanol to obtained pure product. M.P.-184^{0}C ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.20 (s, 1H), 7.71 (s, 1H), 7.12 (s, 4H), 5.12 (s, 1H), 3.98 (q, 2H), 2.25 (s, 3H), 1.12 (t, 3H) ppm; IR (KBr): ν_{max} 3203, 2970, 1776, 1460, 1165, 1388 cm^{-1}

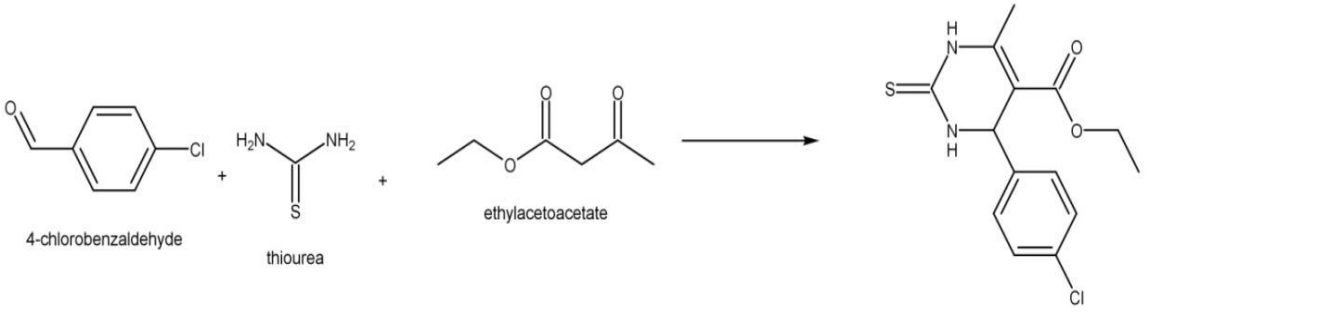


ethyl4(4hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4tetrahydropyrimidine-5-carboxylate

Synthesis of Ethyl4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (CTTPC)

The mixture of 4-chlorobezaldehyde (1.36g) , ethyl acetoacetate and add thiourea (0.7g) was taken and lemon juice was added and reflux for 2 hour. After cooling at room temperature it was pour into ice cube with constant stirring. Resulting precipitate was filtered, dry at room temperature and recryastallize using ethanol. M.P.-168^{0}C ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.78 (s,

1H), 7.19 (s, 4H), 5.13 (s, 1H), 3.94 (q, 2H), 2.27 (s, 3H), 1.14 (t, 3H) ppm; IR (KBr): ν_{max} 2924, 1317, 1427, 1242, 1797, 761 cm^{-1}



III – RESULT AND DISCUSSION

Viscometric measurements of Dihydropyrimidinone derivatives in 70% dioxane-water and Ethanol-water system Solution study of synthesized Dihydropyrimidinone derivatives HTTPC and CTTPC using binary solvent system of 70% dioxane-water and 70% ethanol-water at different concentration was carried out using viscometric measurements. The result obtained were compute to calculate relative viscosity and density. Ionic interaction was studied by plotting graph between η_{sp} and $\sqrt{C}$ which shows the validity of Jones-Dole equation for all synthesised derivatives. The value of β and A coefficient which gives solute-solvent and solute-solute interaction was interpreted from the slope and intercept of the graph (Table-1).

Table 1 Viscometric study of HTTPC and CTTPC in 70% dioxane-water and Ethanol-water system at different concentration

System	Temp (K)	Conc. (M)	*Medium- Dioxane water*				*Medium-Ethanol-water*			
			Density	Relative Viscosity η_r	A	β	Density	Relative Viscosity η_r	A	β
HTTPC	301	0.01 0.005 0.0025	1.082 1.078 1.077	1.239 1.153 1.014	-1.37	39.90	0.877 0.876 0.873	0.967 0.878 0.837	-6.20	57.82
CTTPC	301	0.01 0.005 0.0025	1.081 1.076 1.075	0.919 0.900 0.859	-4.53	38.87	0.889 0.880 0.878	0.715 0.656 0.626	-11.76	91.06

It was observed that values of the relative viscosity and densities were decreases with decrease in concentration. Again the values of A were negative in all solvent system which shows the weak solute-solute interaction. On the other hand the values of β were positive shows strong solute-solvent interaction. More positive values in polar solvent as compare to non-polar solvent for all the tested ligands due to hydrogen bonding. This information useful to find out effect of nature of solvent on the solute molecules which is useful to study pharmacodynamics and pharmacokinetics activity.

Antimicrobial activity of Dihydropyrimidinone derivatives: Antimicrobial activity were tested by measuring the inhabitation area on agar plates with Staphylococcus aureus, Bacillus cereus gram positive bacteria and Salmonella typhy and Pseudomonas fluorescens gram negative bacteria as test germs. The Muller Hinton Agar medium is used for antimicrobial sensitivity test .For Bacteria (After 24 hours at 37˚). The result of antibacterial screening indicated that good activity was shown Ethyl-4- (4hydroxyphenyl) -6-methyl-2-thioxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate denoted by '2' against staphylococcus aureus, as gram positive and against salmonella typhy and Pseudomonas fluorescens as gram negative and other compounds i.e. Ethyl-4-(4 chlorophenyl)-6-methyl-2-thioxo-1,2,3,4 tetrahydropyrimidine -5-carboxylate and it denoted by '4' against staphylococcus aureus gram positive and pseudomonas

fluorescens gram negative . Other two show poor bacterial strains.

Methodology-In vitro antibacterial activity was carried out against 24-h old cultures of four bacteria by the cup plate method against bacterial strains using DMSO as solvent in a Mueller Hinton agar medium. The compounds were screened against Staphylococcus aureus, Bacillus cereus, Salmonella typhy and Pseudomonas fluoresces. For antibacterial studies, incubation was carried out at 37°C for 24 h. The compounds were tested at concentration of 50µg/ml in methanol against all organisms. After the period of incubation, the zone of inhibition was calculated in milli meters and compared with the standard. The results were reported in table 2.

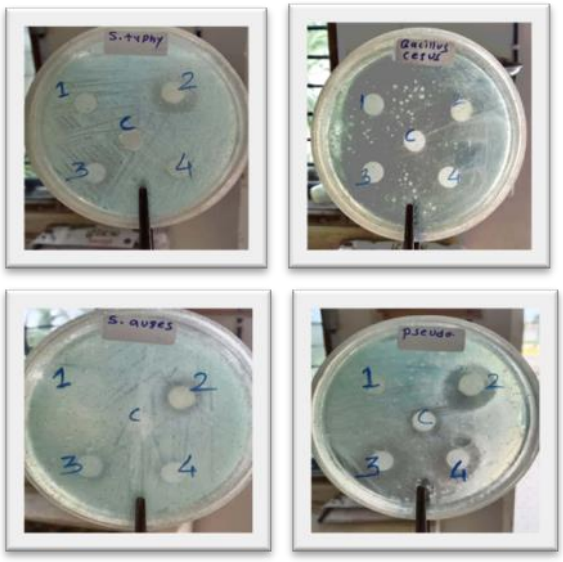


Table 2 Study of Antimicrobial activity of Dihydropyrimidinone derivatives against Gram-positive bacteria and Gram-negative bacteria

Zone of inhibition in mm				
Test compound	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	Bacillus cereus	Salmonella typhy	Pseudomonas fluorescens
HTTPC	20mm	-----	22mm	24mm
CTTPC	14mm	----	----	23mm

It was observed that nature of substituent of aromatic ring plays important role on their antimicrobial activities. HTTPC shows good activity against staphylococcus aureus (20mm) gram positive and salmonella typhy (22mm), pseudomonas fluorescens (24mm) gram negative. On the other hand CTTPC have good activity against staphylococcus aureus (14mm) gram positive and Pseudomonas fluorescens (23mm) gram negative. Bacillus cereus does not show any activity against HTTPC and CTTPC. Also, Salmonella typhy was inactive towards CTTPC.

Study of surface of Dihydropyrimidinone derivatives: Surface tension study of dihydropyrimidinone derivatives were carried out in 70% ethanol water and 70% dioxane water system. The results are listed in the Table-3.

Table 3 Surface tension study of HTTPC and CTTPC in 70% dioxane-water and Ethanol-water system at different concentration

System	**Temp (K)**	**Conc. (M)**	***Medium- Dioxane water***		***Medium-Ethanol-water***	
			Density	**Surface Tension**	**Density**	**Surface Tension**
HTTPC	301	0.01 0.005 0.0025	1.082 1.078 1.077	43.38 47.79 51.02	0.887 0.876 0.873	25.99 27.23 27.36
CTTPC	301	0.01 0.005 0.0025	1.081 1.076 1.075	43.79 49.00 53.75	0.889 0.880 0.878	23.14 27.36 27.66

Above data shows the inverse relationship in between surface tension and concentration of ligand in binary solvent system. A lower value of surface tension in polar solvent as compare to non-polar confirms inverse relationship between surface tension and dielectric constant. Also it shows breaking hydrogen bonds due to addition of DHPMs in ethanol-water system.

Conductometric measurements of Dihydro pyrimidi none derivatives:

Measurements of conductivity provide useful information about mobility of ionic species in solution. This technique used to study extent of ionic association and solute-solvent interaction. Lower value of conductance shows more solute-solute interaction and Higher value shows more solute- solvent interaction. In present work conductivity of all the DHPMs derivatives was studied in polar and non-polar solvent. (Table 4).

Table 4 Specific conductivity of HTTPC and CTTPC in 70% dioxane-water and Ethanol-water system at different concentration

System	Temp (K)	Conc. (M)	*Medium- Dioxane water*	*Medium-Ethanol-water*
			Specific conductance	Specific conductance
HTTPC	301	0.01 0.005 0.0025	0.021 0.020 0.018	0.023 0.021 0.020
CTTPC	301	0.01 0.005 0.0025	0.039 0.038 0.037	0.044 0.043 0.041

It was observed that specific conductivity decreases with decrease in concentration. Viscosity and conductivity value plays most important role to study dynamic properties.

IV - CONCLUSION

Present work involves synthesis of novel dihydropyrimidinone derivatives to explore their antimicrobial activity followed by green route. Various physicochemical parameters were used to study molecular interaction. Negative values of A and positive values of β shows the weak solute-solute and strong solute-solvent interaction in both solvent system. Hydrogen bonding affect the value of interaction in polar and non-polar solvent. This information useful to find out effect of nature of solvent on the solute molecules which is useful to study pharmacodynamics and pharmacokinetics activity. Hydroxyl substituent of phenyl ring showed good activity against all bacterial strain than chloro substituent. Green synthesis approach which minimized chemical hazardous, easy applied and high yields.

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