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Green Synthesis of Dihydropyrimidinone Derivatives and Study of Physicochemical Properties and Antimicrobial Activity

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Abstract: *Versatile biological activity of dihydropyrimidinone (DHPM) derivatives makes it more interesting in medicinal chemistry.In present work green synthesis method was used to prepare a series of DHPM derivative by Biginelli reaction at room temperature in common fruit juice. Spectroscopic methods were used to characterize structures of all synthesized compounds.The viscometric and surface tension measurements have been carried out in different percentage solvent system. Viscosity increases with increases in concentration for all the tested derivatives may be attributed to the increases in solute – solvent interactions.Study was extended to find conductivity of synthesized derivative in different solvents. The data obtained was used to evaluate nature and magnitude of ion-solvent and ion-ion interactions. The primary purpose of this study to evaluate antibacterial activity against some Gram-positive and Gram-negative pathogens. It was observed that the compounds show poor or good activity which depend upon electronic factor of the phenyl ring of DHPM*

Keywords: DHPM Derivatives; Physicochemical Properties, Antimicrobial Study

I. INTRODUCTION

Dihydropyrimidinone (DHPM) are heterocycles with a pyrimidine moiety in the ring nucleus, it aroused interest in medicinal chemistry due to versatile biological activity such as antibacterial, anti-inflammatory, antiviral, antitumor, antimalarial agent, antioxidant, antiulcer, anticancer and as a important constituents of many bioactive heterocyclic compounds[1-4].There are many ways to synthesis the DHPM and its derivatives. Out of that Biginelli reaction is very important. In past decades, such Biginelli-type DHPMhas received a considerable amount of attention due to the interesting pharmacological properties associated with this heterocyclic scaffold [5-7].

The synthesis of 3,4-Dihydropyrimidinones and their derivatives via Biginelli routes involving an aldehyde, 1,3-dicarbonyl compound and urea and thiourea by using the catalysts such as bismuth nitrate in acetonitrile or PPh_3 without solvent lead to higher yields compared to method using HCL in ethanol[8]. There are many catalyst used in Biginelli reaction such as CaF_2, PPh_3 tetrabutylammonium bromide, copper(II) Sulfamate, Fe_2O_3/CuO and so on. Also microwave irradiation, ultrasound irradiation is used. Drawback of this method such as expensive and poisonous solvent is overcome by the Green chemistry technology, multi component reaction under solvent free conditions. [9-10].

The synthesis of dihydropyrimidinone (DHPMs) derivatives most commonly used the green synthesis method it is simple method to use and give excellent yield in short time, operational simplicity and the avoidance of the use of organic solvents and friendly preparation and it is important for the present work. A large of DHPMs were synthesized using urea, ethyl acetoacetate with electron rich as well as electron deficient aromatic aldehydesin presence of lemon juice in one pot-condensation. The lemon juice without processing was used as a catalyst. A green synthesis method is cost-effective, ecofriendly, simple and efficient method has been developed for the performing the Biginelli reaction at room temperature[11-14].

Viscosity describes fluids internal resistance to flow may be thought of as a measure of fluid friction. Physiochemical properties like density, surface tension and viscosity of liquids are important which affect mass and heat transfer in solution[15-17].Surface tension plays an important role in molecular interactions that exist on the surface and in the

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bulk of liquids[18].Many researchers have been studied antibacterial activity of dihydropyrimidiones derivatives and they have observed good antibacterial activity against both gram-positive and gram-negative bacteria[19-22].A study of conductivity is one of the important and simplest tools to understand the transport behavior in general and solvation behavior in specific for the ionic species involved in electrolytic system[23].

In present investigation an endeavor is made to synthesized different derivatives of Dihydropyrimidinone and study of their physicochemical properties and antimicrobial activities. The viscometric and surface tension measurements have been carried out in 70% ethanol-water and dioxane-water system. Study was extended to find conductivity of synthesized derivative in different solvents.

II. EXPERIMENTAL

The binary mixture of solvent system of 70% dioxane-water and 70% ethanol-water was prepared. Stock solution of 0.01M of synthesized derivatives of Dihydropyrimidinone was prepared. The required strength of solution was prepared by diluting the appropriate amount of the solution in both the binary mixtures.

The densities of pure liquids, their binary mixtures and ligand solutions were measured using single capillary pycnometer. The accuracy of density measurements was within 0.1% kg m^{-3}. Viscosity of pure liquids and their binary mixtures was measured using Ostwald's viscometer calibrated with double distilled water. Viscosity data were analyzed in the light of Jones-Dole equation.

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

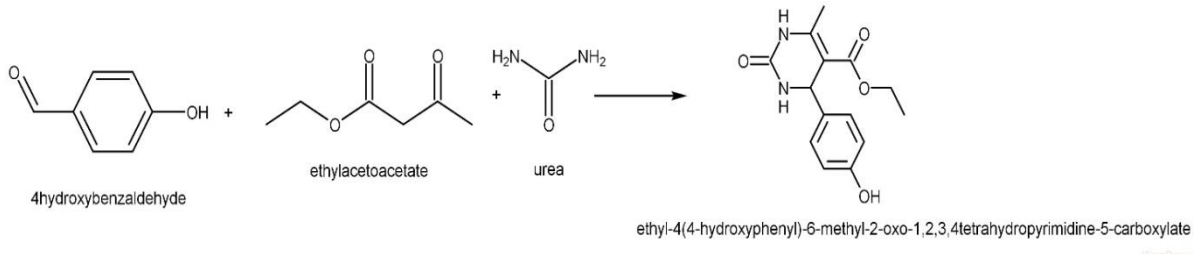
Where A and β are the Falkenhagen and the Jones-Dole coefficients.

Solute–solute and solute–solvent interactions was evaluated from value of 'A' and 'β' by plotting plotted 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.

III. SYNTHESIS OF DIHYDROPYRIMIDINONE DERIVATIVES

Synthesis of Ethyl 4-(4 hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4 tetrahydropyrimidine-5-carboxylate (HTPC):

Mixture of 4-hydroxybezaldehyde (1.36g), ethyl acetoacetate, urea (0.6g) was taken. To this mixture 2-3 ml of lemon juice was added. It was mixed well and reflux for 2 hour. Then the mixture was cool at room temperature and was poured into ice cube with constant stirring. After filtration resulting crude product was allowed to dry. It was crystallized from ethanol to obtained crystalline product. M. P. 60°C. ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.17 (s, 1H), 7.70 (s, 1H), 7.12 (s, 4H), 5.12 (s, 1H), 3.98 (q, 2H), 2.25 (s, 3H), 1.10 (t, 3H) ppm. IR (KBr): ν $_{max}$ 3512, 3331, 3278, 1680, 1460, 2978 cm^{-1}



Synthesis of Ethyl 4-(4chlorophenyl)-6-methyl-2-oxo-1,2,3,4tetrahydropyrimidine-5-carboxylate (CTPC)

Mixture of 4-chlorobezaldehyde (1.36g), ethyl acetoacetate and add urea (0.6g) was taken. To this mixture 2-3 ml of lemon juice was added. It was mixed well and reflux for 2 hour. Then the mixture was cool at room temperature and was poured into ice cube with constant stirring. After filtration resulting crude product was allowed to dry. It was crystallized from ethanol to obtained crystalline product. M. P. 220°C. ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.77 (s, 1H), 7.20 (s, 4H), 5.13 (s, 1H), 3.94 (q, 2H), 2.27 (s, 3H), 1.10 (t, 3H) ppm. IR (KBr): ν $_{max}$ 2964, 1685, 1492, 1793, 1174, 1315 cm^{-1}.

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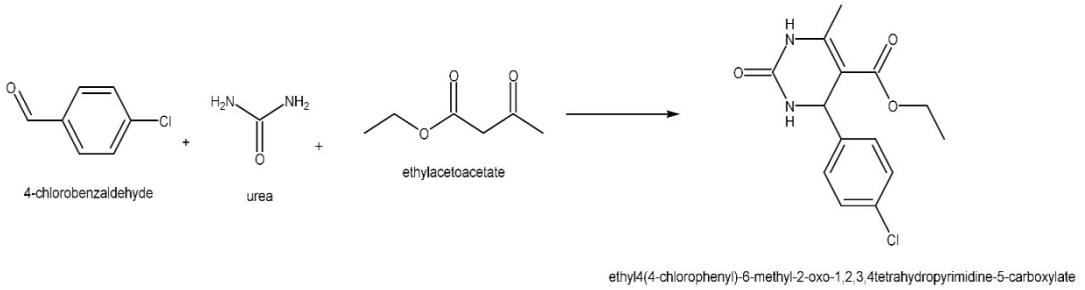

IV. Result and Discussion

Viscometric Study of Dihydropyrimidinone Derivatives at Different Concentration

Viscometric study of synthesized Dihydropyrimidinone derivatives HTPC and CTPCat different concentration using 70% dioxane-water system and 70% ethanol-water system as a solvent was summarized in table 1. The data obtained were used to calculate relative viscosity and density of Dihydropyrimidinone (DHPMs)derivatives. The plot of graph between η_{sp} and $\sqrt{C}$ shows a linear relationship which shows the validity of Jones-Dole equation for all DHPMs. The slope of this graph shows the value of β-coefficient and intercept gives the value of coefficient A.

Table 1: Viscometric study of HTPC and CTPC 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
HTPC	303	0.01 0.005 0.0025	1.066 1.062 1.060	0.963 0.911 0.877	-4.38	41.08	0.864 0.839 0.719	0.959 0.876 0.635	-12.82	131.5
CTPC	303	0.01 0.005 0.0025	1.093 1.086 1.084	1.035 0.964 0.921	-3.34	37.76	0.864 0.863 0.861	1.012 0.097 0.070	-10.76	114.5

It was observed from above table that the values of A are almost negative in all the systems which shows weak solute-solute interaction and is also supported by decrease in relative viscosity. Again the values A are more negative in ethanol-water as compare to dioxane-water medium. Besides that the value of β-coefficient is positive shows strong solute–solvent interaction. The value of β-coefficient is more positive in ethanol-water may be due to strong hydrogen bonding. These different results for all the tested ligands may be due to different polarity index of solvent dioxane and ethanol.

Antimicrobial Activity of Dihydropyrimidinone Derivatives

The synthesized compounds were tested for their antimicrobial activity 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-(4chlorophenyl)-6-methyl-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate denoted by '3' against staphylococcus aureus, Bacillus Cereus as gram positive and against salmonella typhye and Pseudomonas fluorescence as gram negative and other compounds i.e. Ethyl-4-(4hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate and it denoted by '1' doesn't shows activity against these four bacterial strains

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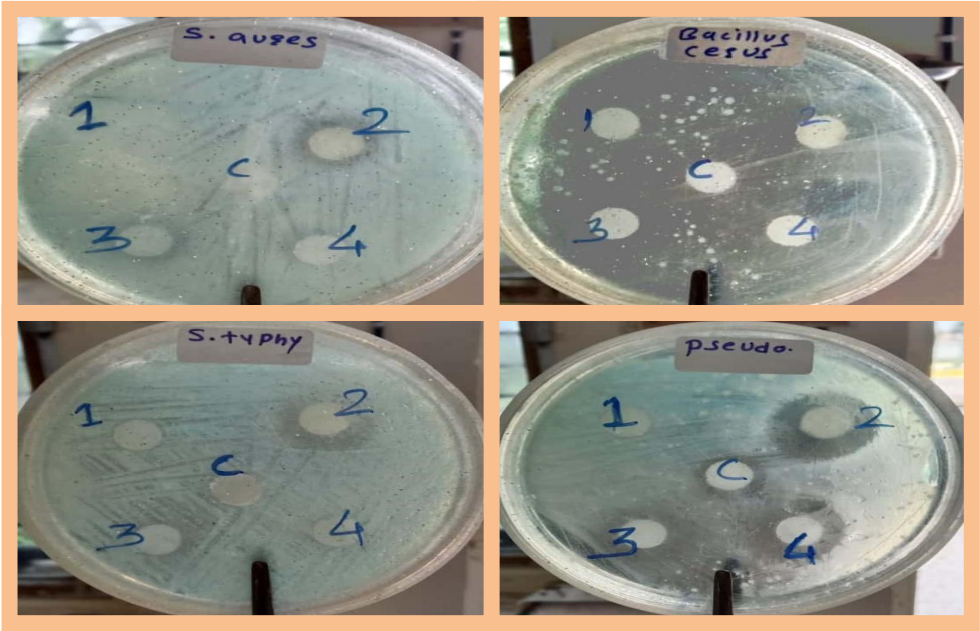
V. METHODOLOGY

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 Mullurhinton agar medium. The compounds were screened against Staphylococcus aureus, Bacillus cereus, Salmonella typhye and Pseudomonas fluorescence. For antibacterial studies, incubation was carried out at 37°C for 24 h. The compounds were tested at a concentration of 50µg/ml in methanol against all organisms. After the period of incubation the zone of inhibition was calculated in millimetres and compared with the standard (Table 2).

Table 2: Study of Antimicrobial activity of Dihydropyrimidinone derivatives against Gm+ve and Gm-ve bacteria

Zone of inhibition in mm				
Test compound	Gm +ve bacteria		Gm -ve bacteria	
	Staphylococcus aureus	**Bacillus cereus**	**Salmonella typhy**	**Pseudomonas fluorescence**
Ethyl-4-(4 hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate	-----	-----	- ----	-----
Ethyl 4-(4 Chlorophenyl)-6-methyl-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate	17mm	25mm	13mm	21mm



The result of antibacterial screening indicated that good activity by Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylateagainststaphyloclococus aureus (17mm) and Bacillus cereus (25mm) gram positive and salmonella typhy (13mm), Pseudmonasfluorescence (21mm) gram negative. Other compound doesn't showed activity against four bacterial strains.

Surface Tension Measurement of Dihydropyrimidinone Derivatives

Surface tension study of Dihydropyrimidinone derivatives were carried out in ethanol water and dioxane water system using Stalagmometer. The results are listed in the Table-3.

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Table 3: Surface tension study of HTPC and CTPC 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
HTPC	303	0.01	1.066	36.68	0.864	24.09
		0.005	1.062	40.71	0.839	24.17
		0.0025	1.060	42.22	0.719	24.28
CTPC	303	0.01	1.093	38.81	0.864	22.65
		0.005	1.086	39.67	0.863	23.22
		0.0025	1.084	42.22	0.861	25.98

From the above it is found that the value of surface tension decreases with increasing of concentration of ligands in both the solvent system. The surface tension in ethanol-water is less than dioxane-water confirms the fact that dielectric constant is directly proportional to surface tension. Again this decrease in value is due to breaking of hydrogen bonds when DHPMs are added in ethanol-water system.

Conductometric Measurements of Dihydropyrimidinone Derivatives

Conductivity measurements are more useful and having wide applicability in electrochemical investigations theories related with liquid mixtures. It is used to examine the nature and magnitudeofion-solvent and ion-ion interactions. Here the conductivity of all the DHPMs derivatives was studied in 70% ethanol and 70% DMSO. The data obtained was evaluated in terms of specific conductance and equivalent conductance (Table4).

Table 4: Specific conductivity of HTPC and CTPC 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
HTPC	303	0.01	0.050	0.030
		0.005	0.049	0.028
		0.0025	0.047	0.024
CTPC	303	0.01	0.033	0.029
		0.005	0.032	0.028
		0.0025	0.030	0.025

From above table it was observed that specific conductivity values are decreases with decrease in concentration. Again HTPC and CTPC show different values in both the solvent system. This change in values may attribute to dielectric constant dipole moment and polarity of solvent system. The high value of specific conductivity in dioxane-water medium because of high dielectric constant and dipole moment of dioxane as compared to ethanol. Also specific conductivity values are more in HTPC than CTPC in dioxane-water medium because its high polarity allows them to dissolve charged species used as nucleophile like OH^- than Cl^- leads to increase in the ions per unit volume.

VI. Conclusion

Green synthesis method used for synthesis of DHPMs derivatives found to be cost-effective, ecofriendly, simple and efficient. Viscometric, surface tension and conductivity study found to be effective physicochemical parameters to explain molecular interactions.Dihydropyrimidinone derivative shows weak solute-solute and strong solute–solvent interaction. CTPC showed good activity against four bacterial strains than HTPC. Hence it is conclude that there is ample scope for further study in developing these compounds for treatment of bacterial strains which may show poor to good antibacterial activity.

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