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Research Article

SYNTHESIS, STRUCTURAL ANALYSIS AND PHOTOPHYSICAL PARAMETERS OF ISOXAZOLINE DERIVATIVES

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ABSTRACT

In the present work, series of 5 substituted isoxazolines have been synthesized by reacting appropriate chalcone with hydroxylamine hydrochloride. The structures of synthesized compounds were confirmed by IR, NMR and Mass spectral analysis. The aim of this work is to synthesize and characterize new isoxazoline derivative. Also study was extended to antimicrobial activity, photophysical property, viscometric measurement and its thermodynamic parameter like Entropy, Enthalpy and Gibbs free energy at different concentrations. The maximum absorption of synthesized derivative -3(4' methyl phenyl)-5-(furan) isoxazoline was found at 311nm. The study shows positive value of ΔS, negative value of ΔG and positive value of ΔH which confirms that the reaction is endothermic and spontaneous. It was also observed that viscosity of solution increases with increase in the concentration of solution and positive value of B-coefficient may attribute to strong solute-solvent interaction. On the other hand value of A-coefficient is almost negative which indicates weak solute-solute interaction.

Keywords: Antimicrobial, Photophysical, Viscometric, Thermodynamics, Isoxazoline Derivative

1. INTRODUCTION

The heterocycles are important due to their chemical, biological, and technical significance. Heterocyclic compounds occur widely in naturally and non-naturally occurring compounds [1]. Heterocyclic compounds particularly five or six member ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities. The heterocyclic chemistry is composed of 5-membered, 6-membered and fused heterocycles. These compounds possess one or the other chemotherapeutic or pharmacological activities [2]. Different 5 substituted isoxazoline derivatives were synthesized by cyclization of chalcone intermediates in presence of hydroxylamine hydrochloride. Isoxazolines are the dihydro derivatives of isoxazoles and exhibits tautomerism in the formation of isoxazoline. It was assumed that unsaturated ketoxime may be intermediate. It may be considered that isoxazolines are not formed by direct ring closure of syn-oxime, but by the way of either oximio-oxime or disubstituted hydoxylamines. They have been synthesized by the interaction of chalcone and hydroxylamine and aqueous hydrochloride and aqueous KOH in ethanol medium.

Some isoxazolines possess anti-inflamatory, anti-tuberculosis, antinociceptive activity [3].The five member heterocyclic compounds containing nitrogen and oxygen atoms have been synthesized for their potentials in exhibiting some kind of activities and also for correlating it with its structure. The structural moieties such as isoxazolines have been found to be responsible for their various physiological, biological and agricultural activities. In recent years, attention has increasingly been given to the synthesis of isoxazoline derivatives as a source of new antibacterial agents. The synthesis of novel isoxazoline derivatives remain a main focus of medicinal research [4].

Isoxazoline are biologically active, synthetically useful and important heterocycles having a wide role in medicinal chemistry. Isoxazolines are also reported to possess good antimicrobial, analgesics and anti-inflammatory activity [5]. Isoxazolines have played a crucial role in the history of heterocyclic chemistry and has been used extensively important pharmacophores and synthons in the field of organic chemistry. In view of the biological activities some isoxazoline derivatives in this study have been synthesized and screened for their

antimicrobial activity [6-8]. Isoxazole derivatives have been widely employed in the commercial world and several applications in the pharmaceutical and agricultural fields can be found. Furthermore, isoxazoles derivatives have important application in material science, such as fluoresecence sensors, plastics and organogels. There are modest numbers of reports presenting U-V visible spectral properties of isoxazole derivatives [9-11]. In this study we are dealing with U-V visible spectral properties of synthesized isoxazoline derivatives in terms of their photophysical parameter.

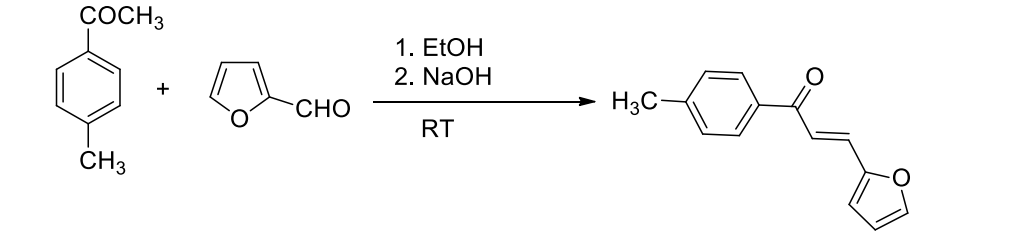
The viscosity is one of the hydrodynamic properties of a liquid and the viscous nature of liquid is due to its shearing effect which arises by the movement of liquid layers over each other. The viscosity and its derived parameters help study the structural change and intermolecular forces of the electrolyte solution at different concentration and temperatures. Viscometric studies of electrolyte solution provide important information regarding solute-solute, solute-solvent interactions and help in characterizing the structural properties of the solution. Various types of interactions help for better understanding about the nature of solute (electrolyte) and solvent, whether the solute modifies or distorts the structure of the solvent. Also it can be used for the development of molecular models for describing the thermodynamic properties of the electrolyte solutions [12].

The structure of making and breaking property of liquids has been considered as a measure of solute-solvent interactions. Viscosity measurement provides useful information about solute-solute and solute solvent interactions. These interactions have been studied in aqueous and non-aqueous solutions by many workers [13].

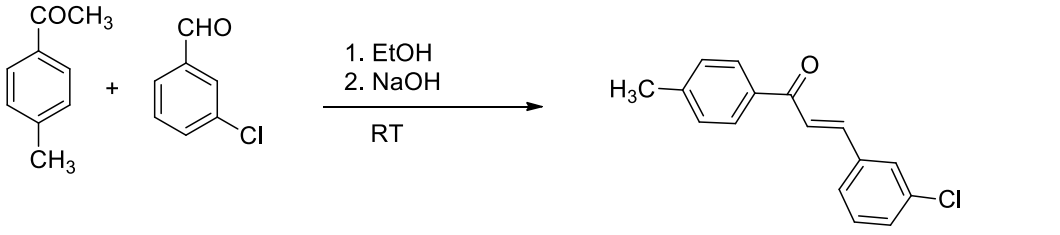
In the present study, viscometric and thermodynamic study of isoxazoline derivative was carried out. The value of B-coefficient was calculated. The result observed solute-solute interactions solute-solvent interactions was reported. From the effect of temperature, the viscosity of isoxazoline, the value of change in energy (ΔG), enthalpy (ΔH) and entropy (ΔS) can be calculated. It gives efficient information about change in viscosity with temperature.

2. MATERIAL & METHODS

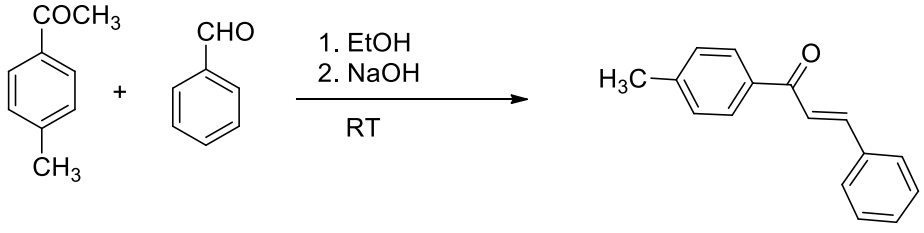
All the chemicals used were pure and of analytical grade. They include p-methyl acetophenone, furfuraldehyde, chlorobenzaldehyde, benzaldehyde, hydroxylamine hydrochloride.



(*E*)-3-(furan-2-yl)-1-(*p*-tolyl)prop-2-en-1-one



(*E*)-3-(3-chlorophenyl)-1-(*p*-tolyl)prop-2-en-1-one



(*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one

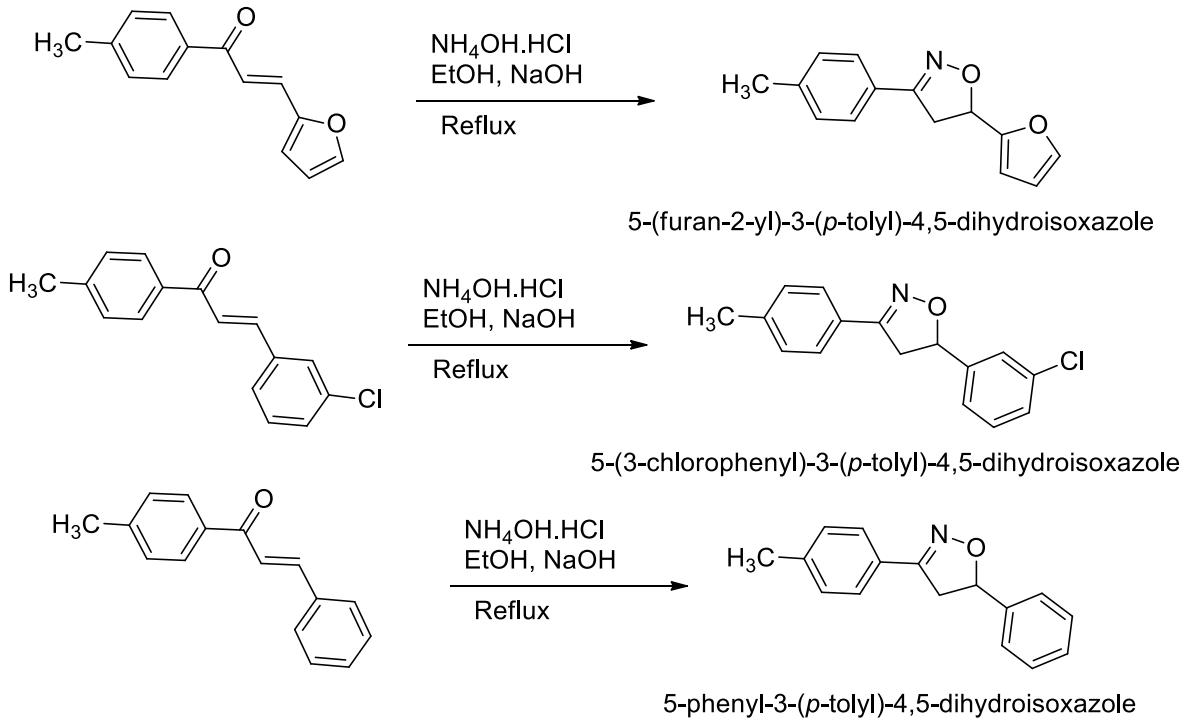
2.1. General procedure for the preparation chalcones

The chalcone was prepared by dissolving (0.04 M) 4 methyl acetophenone, (0.04 M) appropriate aldehyde (furfuraldehyde, 3 chlorobenzaldehyde, benzaldehyde) and 5ml ethyl alcohol in 200ml beaker. The mixture was allowed for continuous stirring for proper mixing of the reaction mixture. 40% NaOH was added drop by drop upto 10 ml to obtain the crude solid. The solid obtained was then kept overnight at room temperature and then transferred to crushed ice followed by neutralization with ice cold HCl. The solid product was filtered, dried and recrystallized with ethanol.

2.2. Synthesis of isoxazoline derivatives

In a 250 ml round bottom flask mixture of respective chalcone (2 g), hydroxylamine hydrochloride (1 g in 10 ml water) and ethanol (10 ml) was added. The reaction mixture was refluxed for 4 hours. It was cooled at room temperature and kept overnight in freezer. The reaction mixture was acidified with aqueous HCl (10%). The resulting precipitate was washed with distilled water, dried and recrystallized from ethanol to afford crystals.

The compounds were characterized by ^{1}HNMR, Mass and IR spectroscopy.



3(4' methyl phenyl)-5- (furan) isoxazoline (2a):
IR [KBr, cm^{-1}]: 3491.31 (Ar-CH_3 stretch), 1361.80 (CO- N stretch), 1022.32 (C-O stretch); ***MS (m/z):*** 228 (M+1), 229 (M+2), ***^{1}H-NMR (400 MHz, DMSO-d6):*** δ 2.3 (s, 3H, -CH_3), δ 6.39-7.71 (m, 7H, -ArH), 5.6-5.7(dd,2 H isoxazoline ring).

3-(4'methylphenyl)-5-(3-chlorophenyl) isoxazoline (2b):
IR [KBr, cm^{-1}]: 3460.44 (Ar-CH_3 stretch), 1369.52(C-O-N stretch), 1655 (C=N stretch), 698 (C-Cl stretch), ***MS (m/z):*** 271 (M+1), 272 (M+2), ***^{1}H-NMR (400 MHz, DMSO-d6):*** δ 2.27 (s, 3H, -CH_3), δ 6.31-7.71 (m, 9H, -ArH).

3-(4'methyl phenyl)-5-phenyl isoxazoline (2c):
IR [KBr, cm^{-1}]: 3433.44(Ar-CH_3 stretch), 1361.80 (C-O-N stretch), 1666.57 (C=N stretch); ***MS (m/z):*** 238 (M+1), 239 (M+2), ***^{1}H-NMR (400 MHz, DMSO-d6):*** δ 2.31 (s, 3H, -CH_3), δ 6.42-7.83 (m, 8H, -ArH).

2.3. Antimicrobial Activity

In this study *in vitro* antibacterial activity was carried out by the cup plate method against 24-hold cultures of two bacteria using DMSO as solvent in a nutrient agar medium. The compounds were screened against *Staphylococcus aureus and Escherichia coli*. For antibacterial studies, incubation was carried out at 37°C for 24 h. Ofloxacin was used as a standard drug for antibacterial activity. The compounds were tested at a concentration

of 50μg/ml against both the organisms. After the period of incubation the zone of inhibition was observed & was calculated in millimeters and compared with the standard [5].

2.4. Photophysical Property

In present study we are dealing with U-V visible spectral properties of synthesized isoxazoline derivatives in terms of their photophysical parameter. Ultra-violet (UV) spectra were recorded using UV 1800 Shimadzu, UV spectrophotometer and 10mm path length quartz cell, with respect to pure solvent reference. The stock solution of compound was preparedin DMSO (1:1 v/v) to ensure solubility. The stock solution is then diluted to desired concentrations i.e. 0.1%, 0.05%, 0.025%.

2.5. Viscosity Measurements

Standard solutions of isoxazoline derivatives were prepared in particular diluents, according to their solubility. The viscosity measurements were carried out using thoroughly cleaned, dried Ostwald's viscometer.

The present study deals with the viscosity measurements of isoxazoline derivativesat different compositions at 310K, 320K and 330K respectively and values of A and B coefficient was calculated.

3. RESULTS &DISCUSSION

3.1. Antimicrobial Study

The preliminary antibacterial screening of the synthesized isoxazoline derivatives have been tested against the two bacteria *E. coli and S. aureus,* strains by the cup plate method. The results revealed that the compounds show poor to good activity. The compound 3(4' methyl phenyl)-5-(furan) isoxazoline found to exhibit potent in-vitro antimicrobial activity with the zone of inhibition 15 mm against *Staphylococcus aureus* bacterial strain. While other compounds show poor antibacterial activity against both the bacterial strain. The results were reported in Table 1.

Table 1: Data of Antimicrobial Activity of Synthesized Isoxazoline Derivatives

Test compound	Zone of inhibition in mm	
	Gram positive bacteria	Gram negative bacteria
	Staphylococcus aureus	*Escherichia coli*
3-(4' methyl phenyl)-5-(furan) isoxazoline	12mm	-
3-(4'methyl phenyl)-5-(3-chlorophenyl) isoxazoline	-	-
3-(4'methyl phenyl)-5-phenyl isoxazoline	-	-
Reference antibiotic (Ofloxacin)	25mm	30mm

3.2. Photophysical Property

The absorption spectra of 3(4' methyl phenyl)-5-(furan) isoxazoline for different concentration in dilute DMSO solution are shown in the Figure-1. The concentration varies from 0.1%, 0.05%, 0.025%. It was observed that the absorption peak centered at 311 nm, 277 nm & 272 nm for 0.1%, 0.05% & 0.025% respectively. Again for higher concentration i.e. 0.1% there are three optical absorption peak at 285nm, 305nm & 311nm. For lower concentration 0.05% & 0.025% the absorption peaks shows nearly same value. The UV- visible absorption spectra of the hydrolysis product, isoxazoline amine was observed at 289nm [10].

The molar extinction coefficient (ϵ) were evaluated from slope of the curves from inset, using Beer-lambert's law, where the absorbance is proportional to molar concentration (c), light path length (l), and molar extinction coefficient(ϵ). The ϵ value for compound at 311 nm is 44.91 L/mol.cm.

Thus the absorption in ultraviolet region makes it suitable material for UV light filter for organic solar cells.

3.3. Viscosity Measurement

Viscosity is one of the crucial physical property of liquid which throws light for better understanding of the molecular interaction as well as structural changes occur in the solutions. From the Table 2 it is observed that the values of relative viscosity (η) decreases with decrease in concentration. This increasing value of η shows the existence of molecular interaction in the solutions.

Viscosity data were analysed in the light of Jones-Dole equation.

$$(\eta r - 1) / \sqrt{C} = A + B\sqrt{C}$$

where A and B are the Falken-Hagen and the Jones-Dole coefficients respectively.

From the graph of (η_r -1) /√C verses √C, 'A' which is the measure of solute – solute interactions and 'B' which is the measure of solute-solvent interactions has been calculated.

Data in table shows that, the values of the 'A' coefficient are almost negative. This represents the contribution from weak inter-ionic electrostatic forces or indicates the presence of weak solute-solute interactions. The coefficient B is the measure of effective solvodynamic volume of solvated ions which accounts for the solute-solvent interaction which measures the order or disorder introduce by the solute in the solvent [12]. The slope of straight line gave value of B –coefficient. Table 2 shows that the values of the 'B' coefficient for isoxazoline derivatives in their specific solvent systems are positive, thereby suggesting the presence of strong solute-solvent interactions.

Table2: Viscometric study with variation in concentration

System	Medium	Conc. (M)	√C ×10⁻²	Time flow (sec.)	Relative Viscosity η_r	Specific Viscosity ηr -1/√C	A coefficient	B coefficient
3-(4'methyl phenyl)- 5-(furan) isoxazoline	70% DMSO-water system	0.1 0.05 0.025	0.316 0.223 0.158	45 43 41	0.878 0.842 0.806	-0.386 -0.706 -1.227	-1.97	5.19
3-(4'methyl phenyl)-5-(3-chlorophenyl) isoxazoline	70% 1,4 Dioxande -water system	0.1 0.05 0.025	0.316 0.223 0.158	46 44 42	0.929 0.862 0.810	-0.224 -0.618 -1.199	-1.58	6.037
3-(4'methyl phenyl)-5-phenyl isoxazoline	70% DMSO-water system	0.1 0.05 0.025	0.316 0.223 0.158	46 42 39	0.940 0.841 0.752	-0.189 -0.711 -0.224	-1.43	8.489

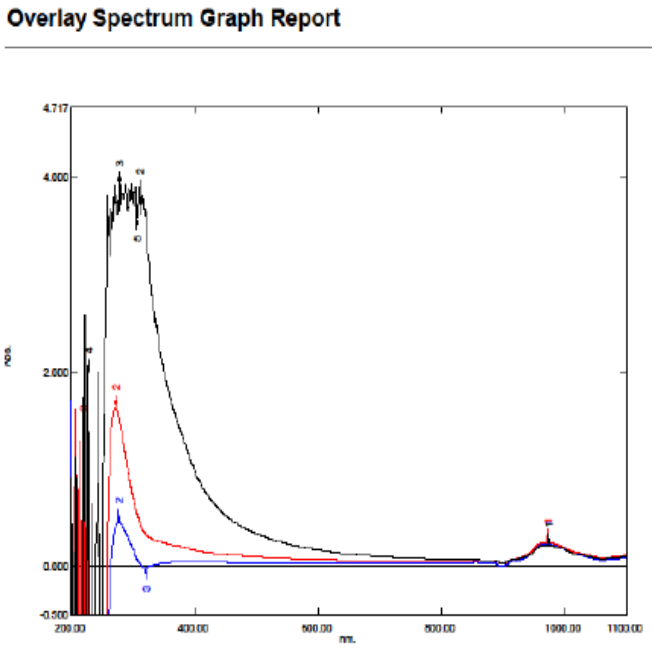


Fig. 1: Normalized Absorption Spectra of Compound (2a) in DMSO Solution with Increasing Molar Concentration

The viscosity of a liquid generally decreases with rise in temperature. This decreasing value of η with temperature may be due to more thermal agitation and reduction of attractive forces between the solute molecule or ions which might be attributed to the decrease in solvation of ions by water.

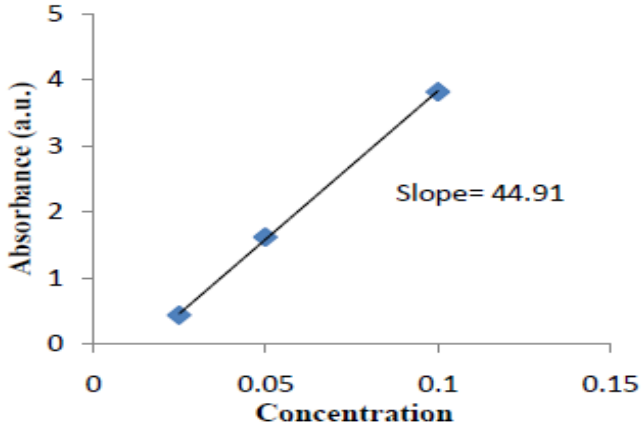


Fig. 2: Graph Plotted between Absorbance and Concentration

Table 3: Thermodynamic temperature with variation in temperature

System	Medium	Conc. (M)	Temp (K)	1 / T $(K^{-1})\times10^{-3}$	Time flow (sec.)	Density (ρ) $g.cm^{-3}$	Relative Viscosity η_r	Log (η_r)
3-(4'methyl phenyl)- 5-(furan) isoxazoline	70% DMSO-water system	0.1	310	$3.22x10^{3}$	45	0.893	0.878	-0.056
			320	$3.12x10^{3}$	35	0.889	0.680	-0.167
			330	$3.03\ x10^{-3}$	33	0.870	0.628	-0.202
		0.05	310	$3.22x10^{3}$	43	0.896	0.842	-0.074
			320	$3.12x10^{3}$	32	0.884	0.619	-0.208
			330	$3.03\ x10^{-3}$	29	0.870	0.552	-0.258
		0.025	310	$3.22x10^{3}$	41	0.899	0.806	-0.093
			320	$3.12x10^{3}$	30	0.876	0.575	-0.240
			330	$3.03\ x10^{-3}$	27	0.864	0.510	-0.292
3-(4'methyl phenyl)-5-(3-chlorophenyl) isoxazoline	70% 1,4 Dioxan-water system	0.1	310	$3.22x10^{3}$	44	0.893	0.859	-0.066
			320	$3.12x10^{3}$	42	0.88	0.796	-0.085
			330	$3.03\ x10^{-3}$	40	0.878	0.749	-0.120
		0.05	310	$3.22x10^{3}$	46	0.925	0.929	-0.031
			320	$3.12x10^{3}$	43	0.915	0.861	-0.064
			330	$3.03\ x10^{-3}$	41	0.896	0.804	-0.094
		0.025	310	$3.22x10^{3}$	42	0.882	0.929	-0.031
			320	$3.12x10^{3}$	40	0.876	0.766	-0.115
			330	$3.03\ x10^{-3}$	31	0.865	0.719	-0.143
3-(4'methyl phenyl)-5-phenyl isoxazoline	70% DMSO-water system	0.1	310	$3.22x10^{3}$	46	0.934	0.940	-0.026
			320	$3.12x10^{3}$	41	0.9117	0.818	-0.087
			330	$3.03\ x10^{-3}$	38	0.8858	0.737	-0.132
		0.05	310	$3.22x10^{3}$	42	0.915	0.843	-0.075
			320	$3.12x10^{3}$	37	0.897	0.726	-0.138
			330	$3.03\ x10^{-3}$	34	0.878	0.654	-0.184
		0.025	310	$3.22x10^{3}$	39	0.882	0.7528	-0.123
			320	$3.12x10^{3}$	34	0.857	0.638	-0.195
			330	$3.03\ x10^{-3}$	30	0.815	0.535	-0.271

Table 4: Values of Thermodynamic parameters in Different Systems

System	Concentration (%)	ΔG $(J\ mole^{-3}K^{-1})\ x\ 10^{-34}$	ΔH $(J\ mole^{-3}K^{-1})$	ΔS $(J\ mole^{-3}K^{-1})$
3-(4'methyl phenyl)- 5-(furan) isoxazoline.	0.1	-14.815	2556.33	8.24
	0.05	-18.668	3086.02	9.95
	0.025	-20.200	3385.41	10.92
3-(4'methyl phenyl)-5-(3-chlorophenyl) isoxazoline	0.1	-5.612	437.57	1.43
	0.05	-6.347	759.99	2.47
	0.025	-11.37	1934.52	6.27
3-(4'methyl phenyl)-5-phenyl isoxazoline	0.1	-10.68	1404.33	4.56
	0.05	-10.99	3086.02	9.99
	0.025	-14.87	3385.41	10.96

The decrease is appreciable being about two percent per degree rise of temperature in many cases. This has been explained in terms of 'Hole theory of liquids'. A liquid molecule therefore, needs some energy to move into hole. As the energy becomes increasingly available at increasing temperature, a liquid can flow more easily at higher temperature [14, 15]. The coefficient of viscosity thus, flows appreciably with rise in temperature as presented in Table 3.

The graphs are plotted between log η_r and 1/T. The graph for each system gives linear straight line showing the validity of equation. The viscosities determined at different temperatures were used to compute thermodynamic parameters and were calculated by using expressions

$\Delta G = -2.303\ R \times slope$,

$\log \eta_{r1} - \log \eta_{r2} = [\Delta H / 2.303] [1/T1 - 1/T2]$ and

$\Delta S = (\Delta H - \Delta G) / T$

4. CONCLUSION

A new series of 5 substituted isoxazolines was synthesized to explore their antimicrobial, photophysical property. The compound 3**(**4' methyl phenyl)-5-(furan) isoxazoline exhibits higher antimicrobial activity with the zone of inhibition 15 mm against *Staphylococcus aureus*bacterial strain. Other compounds show poor antibacterial activity against both the bacterial strain. The absorption spectra of 3**(**4' methyl phenyl)-5-(furan) isoxazoline exhibits optical absorption in the Ultra-Violet region (from 285 to 311nm). The results from viscosity measurement show that positive values of viscosity 'B' coefficient for isoxazoline derivative which indicates the presence of strong solute-solvent interactions. The viscosity determined at different temperatures were used to evaluate thermodynamic parameters enthalpy change (ΔH), entropy change (ΔS), & free energy change (ΔG). For all tested compounds the positive value of ΔH indicates the reaction is spontaneous & endothermic. Isoxazoline derivatives in their specific solvent shows that the change in free energy (ΔG) and the change in entropy (ΔS) decreases with decrease in concentration.

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