SYNTHESIS AND STUDY OF SUBSTITUTED 1,3-THIAZINE AND ITS NANOPARTICLES ON PHYTOTIC GROWTH OF SOME VEGETABLE CROPS

C.D. Badnakhe[1] and P.R. Rajput[2]

[1]Department of Chemistry, Dr.Manorama and Prof.H.S.Pundkar, Arts, Commerce and Science College, Balapur, Dist. Akola, India

[2]Department of Chemistry,S.S.S.K.R.InnaniMahavidyalaya,Karanja (Lad), India

chhayadeotalu@rediffmail.com, prsrajput@rediffmail.com

ABSTRACT

The synthesis, spectral analysis and biological activities of 4-phenyl-2-hydroxy-chlorosubstituted-2-imino-1,3 thiazines have been carried out. In this case 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2- iminophenyl-3,6-dihydro-1,3-thiazine (B), and has been screened. The compound B was synthesized from 2'-hydroxy-3,5-dichlorophenyl-4-(4"-nitrophenyl) chalcone (a) by the action of phenylthiourea. The compound (a) was synthesized from 2'-hydroxy-3',5'-dichloroacetophenone by the action of p-nitrobenzaldehyde in ethanol and 40% NaOH. The nanoparticles of the compound B has been prepared by using ultrasonic technique. The titled compound and its nanoparticles were screened for their growth promoting activity on some vegetable crop plants viz.. Momordica charantia-L-Bitter guard (Karela), Lagneriasiceraria-snake guard (Lavki), Luffa cylindrica L-sponge guard (Gilke) and Benincasahispida-Pumpkin (Kohle).

Keywords :*Chalcone, thiazine, , phenylthiourea, growth promoting activities.*

Introduction

Thiazine is a six membered ring system, which contains two hetero atoms [N and S] placed in a heterocyclic ring at 1, 3 positions. Many workers have synthesized different 1,3-thiazines. The researchers have reported the synthesis of several thiazines[1-6]and also their potent biological activities such as blood platelet aggregation inhibitors[7], antibacterial[8-9] antiallergic[10], anticholesterenic[11] and antifungal[12]**.**Moreover thiazine nucleus is a pharmacophore of cephalosporin that occupy a very important place in the field, of antibiotics and drug chemistry. Chalcones and their analogues having α, β-unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds. The reaction of thiourea with α, β-unsaturated ketones also results in the formation of 1,3-thiazines.The chlorosubstitutedthiazines with amino group at position 2 in the ring exhibit promising biological activities[13-16].

In the present study, the chlorosubstituted 1,3-thiazine (B) has been prepared along with its nanoparticles and screened them for their growth promoting activity on some vegetable crop plants viz. *Momordica charantia-L-Bitter guard (Karela), Lagneriasiceraria-snake guard (Lavki), Luffa cylindrica L-sponge guard (Gilke) and Benincasahispida-Pumpkin (Kohle).*

Experimental

All the glassware's used in the present work were of pyrex quality. Melting points were determined in hot paraffin bath and are uncorrected. The purity of compounds was monitored on silica gel coated TLC plate. IR spectra were recorded on Perkin-Elmer spectrophotometer in KBr pelletes, H^1 NMR spectra on spectrophotometer in $CDCl_3$ with TMS as internal standard. UV spectra were recorded in nujol medium. The analytical data of the titled compounds was highly satisfactory. All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. Physical characterisation data of all the compounds is given in Table 1.

Table 1 :Characterisation data of newly synthesized compounds :

Compounds	Molecular formula	M.P. in ^{0}C	% of yield	% of element			
				C	H	N	S
	$C_8H_6O_2Cl_2$	54	80	47.90/48	2.95/3		
a	$C_{15}H_9O_4NCl_2$	250	70	53.10/53.25	2.40/2.66	3.98/4.18	
B	$C_{22}H_{15}O_3N_3Cl_2S$	100	75	55.93/56.01	3.177/3.285	8.89/8.92	6.77/6.82

2'-Hydroxy 3',5'-dichloroacetophenone :

2'-Hydroxy-5-chloroacetophenone (3g) was dissolved in acetic acid (5 ml), and mixed with sodium acetate (3g). To this reaction mixture chlorine in acetic acid reagent (40 ml; 7.5 w/v) was added dropwise with stirring. The temperature of the reaction mixture was maintained below 20^{o}C. The mixture was allowed to stand for 30 minutes and then poured into water. A pale yellow solid thus obtained was filtered, dried and crystallized from ethanol to yield the compound.

Preparation of 2'-hydroxy-3,5-dichlorophenyl-4-(4"-nitrophenyl)-chalcone (a) :

2'-Hydroxy-3',5'-dichloroacetophenone (0.1 mol) was dissolved in ethanol (50 ml) and p-nitrobenzaldehyde (0.1 mol) was added gradually to the solution and the mixture was heated to boiling. Then aquous sodium hydroxide solution [40%; 40 ml] was added dropwise with constant stirring. The mixture was stirred mechanically at room temperature for about half an hour and kept for overnight. It was then acidified by hydrochloric acid (10%) solution . The solid product thus separated, was filtered, and washed with sodium bicarbonate (10%) followed by water. Finally it was crystallized from ethanol acetic acid mixture to get the compound (a).

Preparation of 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2-iminophenyl-3,6-dihydro-1,3-thiazine (B) :

2'-Hydroxy-3,5-dichlorophenyl-4-(4"-nitrophenyl)-chalcone (a) (0.01 mol) and phenyl thiourea (0.02 mol) were dissolved in ethanol (30 ml). To this aquous solution of KOH (0.02 mol) was added. The reaction mixture was refluxed for three hours cooled, diluted with water and acidified with 1:1 HCl. The product thus separated was filtered and crystallized from ethanol to get the compound (B).

The newly synthesized compounds were characterised on the basis of elemental analysis, molecular determination, UV, IR, NMR. spectral data.

The UV, IR, and NMR spectral data :-

Compound (B) :

UV : Spectrum No. 1

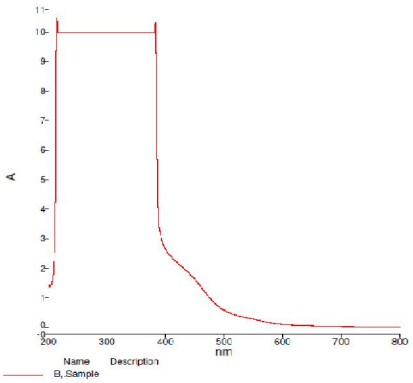
The UV-Vis spectrum of the compound B reported in dioxane showed λ_{max}value395 nm corresponding to n→π* transition.

IR KBr : Spectrum No. 2

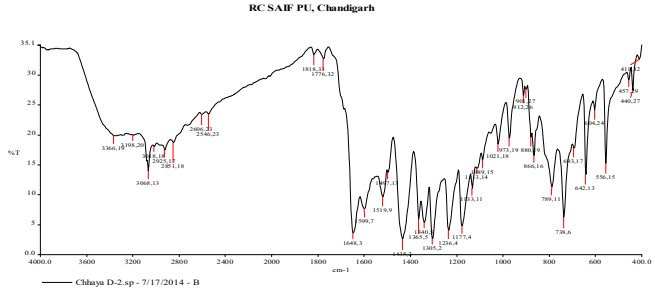
3366.19 cm^{-1} (O-H phenolic) , 2925.17 cm^{-1} (aliphatic -C-H stretching) , 3018.18 cm^{-1} (aromatic C-H stretching) , 3198.28 cm^{-1} (-NH stretching) , 1648.3 cm^{-1} (-C=N-stretching) , 1340.5 cm^{-1} [(C-N=) (C-NO$_2$) stretching] , 738.6 cm^{-1} [C-Cl stretching in aliphatic) , 1177.4 cm^{-1} [C-Cl stretching in aromatic].

PMR : Spectrum No. 3

∂ 2.6 (d, 1H, -C=C-C-**H**) ; ∂ 3.5 (hump 1H, -N**H**) ; ∂ 3.7 (d, 1H, -C=C- **H**) ; ∂ 7.1 to 8.4 (m, 11H, Ar-**H**) ; ∂ 12.6 (s, 1H, O-**H**).



Spectrum No.01



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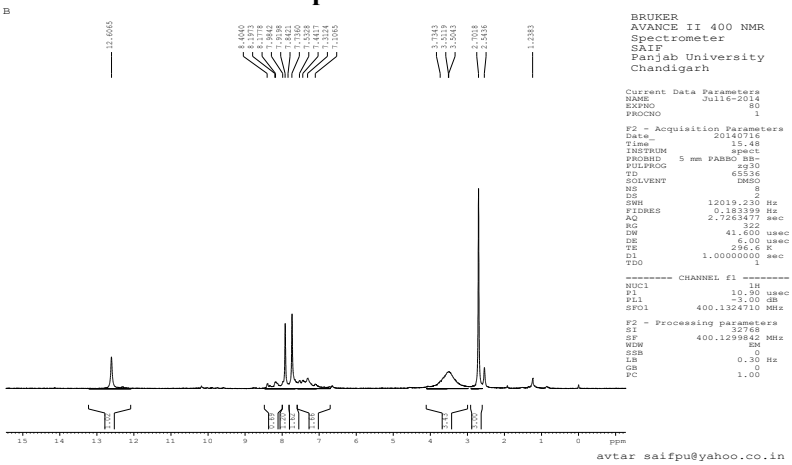
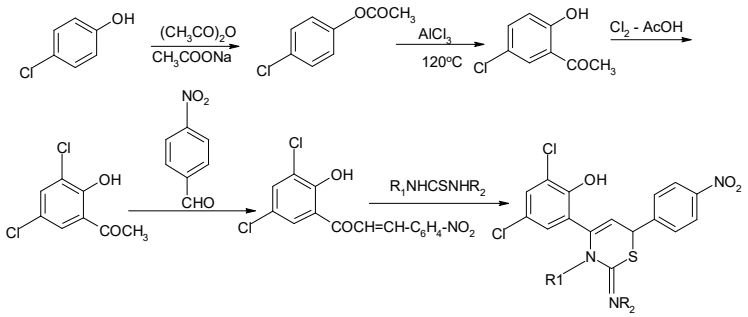


Spectrum No. 03

Scheme :



Where :

1) R_1 = -H
2) R_2 = $-C_6H_5$

Growth Promoting Effect on some Vegetable crop Plants :-

The experimental set up of the study was devided into two parts:

(i) Seed treatment (ii) Field experiment.

(i) Seed treatment :-

With a view to safeguard dormant seed's potential from harmful external agencies, the seeds of the test plants were treated by test compounds before sowing.

(ii) Field experiment :-

Pregerminated quality seeds of *Momordica charantia L-Bitter guard (Karela), Lagneriasiceraria -snake guard (Lavki), Luffa cylindrica L-Sponge guard-(Gilke) and Benincasahispida -Pumpkin (Kohle*) were procured from Department of Horticulture, Dr. PDKV, Akola.

The beds of cotton soil, 2.5 x 2.5 m size were prepared in an open field. The sowing of seeds of all four test vegetable crop plants were done in separate beds and irrigated periodically.

The plants from each bed were devided into two groups i.e. A and B and designated as "Control" and "Treated" group plants respectively.

The plants from group B were sprayed with the solution of test compounds at weekly intervals. The field experiments were conducted to compare the treated plants of group B with untreated plants of controlled group A. In this context, the observations were recorded on 7, 14, 21, 28, 35, 42, 45, 56, 63, 70, 77, 84, 91 days after sowing corresponding to early vegetative, late vegetative, flowering, pod filing and pod maturation, with special reference to number of leaves and height of shoots.

The results of field's experiments are tabulated in the tables 2, 3 and 4.

Table (2) : Activity of the test compounds B :

Table No. (02)

4-(2'-Hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2- iminophenyl-3-6-dihydro-1,3-thiazine (B)

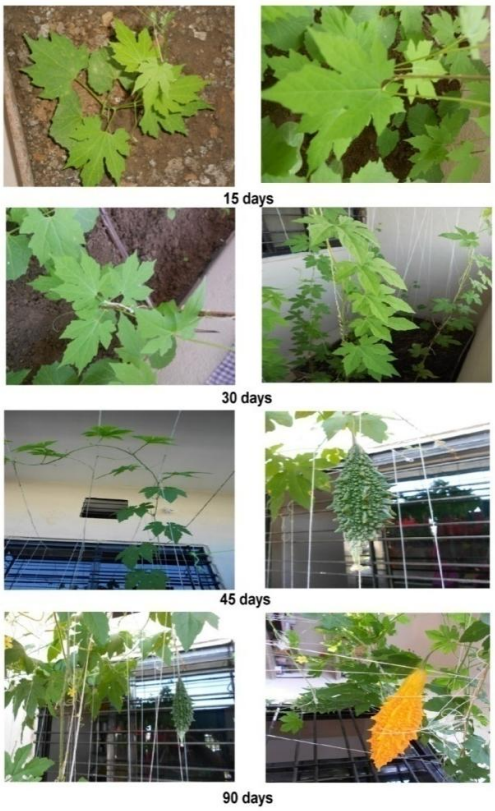
Periodicity of Observations [in days]	*Momordica charantia* (Bitter guard) (Karela)				*Lageneriasiceraria* (Snake guard) (Lavki)				*Luffa cylindrica* (Sponge guard) (Gilke)				*Benincasahispida* (Pumpkin) (Kohle)			
	Shoot height		No. of leaves		Shoot height		No. of leaves		Shoot height		No. of leaves		Shoot height		No. of leaves	
	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
7	2.5	1.5	2	2	2.5	1.5	2	2	4.5	4	2	2	20	20	2	3
14	7	1.7	2	2	7.5	5	2	2	10	5	2	2	20	22	2	3
21	25	15	7	6	8	8	2	3	15	12	3	7	23	23	3	4
28	35	33	9	10	9	9.5	3	4	16	23	4	7	25	27	4	6
35	47	40	10	12	11	12	4	5	20	30	5	8	27	32	5	8
42	51	60	12	15	17	14	5	6	25	40	7	11	30	37	6	9
49	55	72	14	17	25	17	6	6	30	44	8	13	35	39	8	10
56	60	90	16	21	28	30	7	8	35	52	10	15	38	52	10	14
63	67	96	18	25	31	35	8	9	40	57	12	17	42	60	12	16
70	72	102	20	32	34	38	9	11	45	62	14	19	46	64	14	18
77	75	108	22	34	36	39	10	14	50	66	16	28	49	70	16	19
84	80	123	24	35	38	47	11	17	55	69	18	30	53	76	18	20
91	82	127	26	38	40	49	12	19	57	72	20	32	56	78	20	24

Result and Discussion

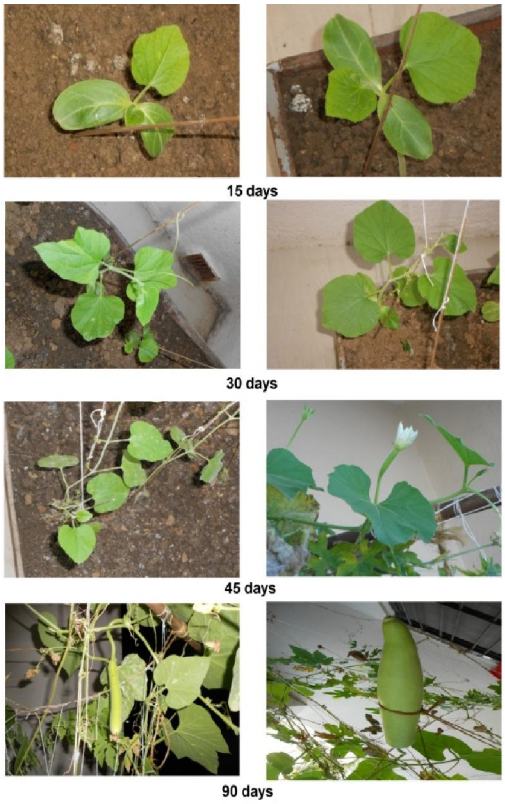
The titled compounds and their nanoparticles were screened for their growth promoting activity on test vegetable crop plants viz, *Momordica charantia-L-Bitter guard (Karela), Lagneriasiceraria-snake guard (Lavki), Luffa cylindrica L-sponge guard (Gilke) and Benincasahispida-Pumpkin (Kohle).*

When a comparison of morphological characters was made between those of treated and control group plants, it was interesting to note that all the treated plants exhibited significant shoot growth and considerable increase in the number of leaves as compared to those of untreated ones.

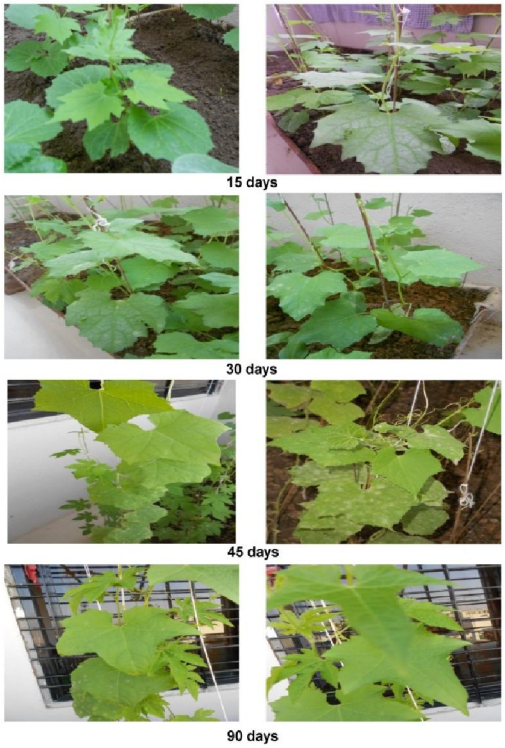
Impact of compound 4-(2'-Hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2- iminophenyl-3-6-dihydro-1,3-thiazine (B) on phytotic growth of *Momordica charantia*



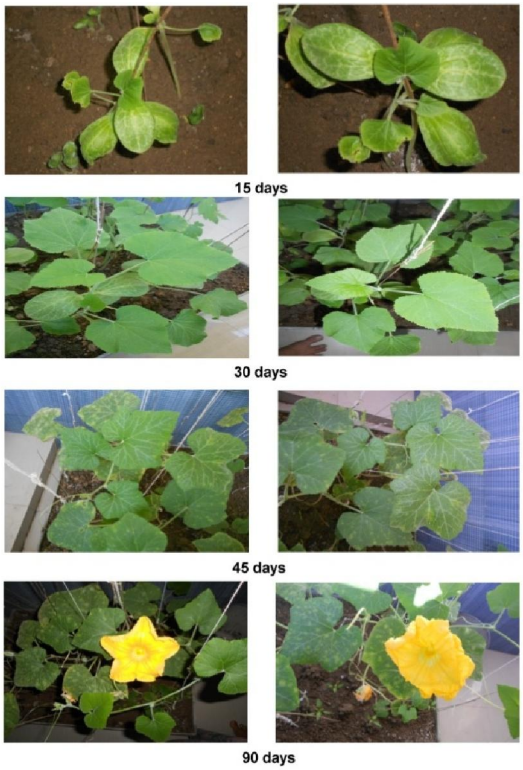
Impact of compound 4-(2'-Hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2- iminophenyl-3-6-dihydro-1,3-thiazine (B) on phytotic growth of *Lageneriasiceraria*



Impact of Compound 4-(2′-Hydroxy-3′-5'-dichlorophenyl)-6-(4"-nitrophenyl)-2-imino-3-6-dihydro-1,3-thiazine (A) on phytotic growth of *Luffa cylindrica*



Impact of compound 4-(2'-Hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2- iminophenyl-3-6-dihydro-1,3-thiazine (B) on phytotic growth of *Benincasahispida*



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EFFECT OF DIELECTRIC CONSTANT OF MEDIUM ON STABILITY CONSTANTS OF CO (II) COMPLEXES WITH SUBSTITUTED THIAZINE PH- METRICALLY

S.R. Singh[*1], S.D. Thakur[2], G.H .Kurhade[3] and J.Panjwani[4]

[1,2,4]Department of chemistry, Bar. R.D.I.K & NY K.D. college, Badnera Rly, Amravati (MS) india

[3]Department Of Chemistry VidnyanMahavidyalaya, Malkapur, DistBuldana (M.S) India

shalinisingh2808@gmail.com

ABSTRACT

Thiazine is six mamberedhetrocyclic ring containing Nitrogen and Sulpur placed at 1, 3 position. In present investigation the author enlighten the effect of dielectric constant of dioxane-water, DMF-water and DMSO-water mixtures on stability constant of thiazine by evaluating the log k and pk value of ligand L_1= 4-(2-hydroxy phenyl)-5-benzoyl-6-phenyl-2-imino-6-H-2,3-dihydro-1,3-thiazine. [BT-1] by keeping ionic strength 0.1 M constant at temperature 30°C. Here we study the dielectric constants. log K values increased with the increase in percentage of organic solvents.

Keywords: Thiazine , DMF, DMSO,Dioxane,Dielectric Constant**.**

Introduction

The dielectric constant is one of the characteristics of liquid. Dielectric constant is of great importance in determining the solvent potentialities of a solvent. If the forces leading the ions of a molecule are electrical in origin, they are diminished when a substance of high inductive capacity surrounds the molecule. To separate the ions, it is necessary to interpose between them or to surround one or both of the ions by a solvent layer so as to reduce their attraction for each other The proton-ligand and metal-ligand stability constants are strongly affected by the dielectric constant of the medium because of the fact that at least one of the constituents is charged and the other is either charged or has a dipole moment. Specific variations in relative strength of acids and bases with changing solvents should be the function of the charge, the radices of ion and the separate contribution of an individual constituent in mixed solvents particularly, at higher percentages of the organic solvents, where it is not known to what extent metal ions and H^+ ions are solvated. An understanding of the influence of medium on reactivity is, therefore difficult even at a qualitative level. It has been reported that an acid in solvents of dielectric constants exhibits different strengths e.g. dissociation of substituted benzoic acids in aliphatic alcohols and aqueous dioxane with identical dielectric constants is different[1]. The dissociation constants of carboxylic acids and phenols decrease almost invariably on addition of miscible organic solvent and solvent effect is quantitatively interpreted in terms of the decrease of dielectric constants of the solvent and decrease of water which solvates the proton released in dissociation[2]. GostaAkerl of have studied the dielectric constant of some organic solvent-water mixture at various temperature he found that in very dilute solutions of dielectric constant of pure solvent is used for limitation law.[3]Rahul Kaur et al.[4] have studied the effect of dielectric constant on reactivity like hardness chemical potential by taking into consideration of protic and aprotic solvent. The dielectric constants and excess dielectric constants of the binary systems of acetonitrile + butyl amine + ethylamine and methylamine have been studied at 303, 313, and 323K temperatures. The dielectric constants for these mixtures were measured using a microcontroller based system by Ramana [5]. Prof.J. R.Partington et al[6] have studied the dielectric constants of solutions of *m*-dinitro-benzene, phenol, and benzoic acid in benzene the dielectric constant increased steadily in *m*-dinitrobenzene and phenol as concentration appeared to approach the value for the pure solute in the fused state. In the case of benzoic acid, the dielectric constant increased with concentration to a maximum and then decreased.Very few compounds are soluble in ethyl acetate [7] which has dielectric constant comparable with acetic

acid. Solubilities of various solvates have been determined in monochloroacetic acid [10] and in dichloroacetic acid [8] which are solvents with moderate dielectric constants. Alcohols have moderate dielectric constant and dissolve a number of ionic compounds [9]. K.T. Kirnapure[10], et al have studied the effect of dielectric constants of methanol- water and acetone-water mixtures on proton-ligand and metal-ligand stability constants of Cu (II) - salicylic acid complex formation p^H metrically in different percentage of methanol-water and acetone-water mixture. K.P.Kakade et.al [11] have studied the effect of dielectric constant of medium on stability constants of Co (II) Complexes With halo substituted chaloneimine pH metrically.

Material and Method

1) **Synthesis of Ligands (1, 3-Thiazines)-** The 1,3 substituted thiazine are synthesized by amination of chalcone with substituted amines ,this chalcone are synthesized by using general claisen Schmidt method . For evaluating the stability constant the very pure and analytical grade solvent and extra pure double distilled water is used. The solutions of ligands were prepared in purified 70 %dioxane-water,DMF-Water,DMSO-water mixture and standardized by p^H metrictechnique. systronicmicro processor based instrument withaccuracy ± 0.01 units with glass and saturated calomelelectrode as used for the titrations. It was calibrated by buffersolution of pH7.00 and 9.20 at 30 ± 0.1^0C, before processingthe titrations. Titrations were carried out in an inert atmosphereby bubbling a constant flow of nitrogen gas
2) **(a) Ligands used for study of dielectic constant**
3) L_1= 4-(2-hydroxy phenyl)-5-benzoyl-6-phenyl-2-imino-6-H-2,3-dihydro-1,3-thiazine. [BT-1]

Observations

The present study deals with the study of the influence of dielectric constants of dioxane-water, DMF-water and DMSO-water mixtures. Following systems have been investigated in the present work for studying the influence of dielectric constant of different percentage of dioxane-water, DMF-water and DMSO-water mixtures.

a) pK- Values of
   i) BT (L_1) (Dioxane-water)
   ii) BT (L_1) (DMF-water)
   iii) BT (L_1) (DMSO-water)

b) Log K – values of
   i) Co (II) - BT (L_1) (Dioxane-water)
   ii) Co (II) - BT (L_1) (DMF-water)
   iii) Co (II) - BT (L_1) (DMSO-water)

Table 1
Proton-ligand stability constant (p K) of BT-1 (L_1) in different percentage of Dioxane-water at 0.1 M ionic strength

% of Dioxane	Dielectric Constant (D)	1/D	Mole Fraction	pK
80	10.90	0.09174	0.09174	8.6270
75	14.40	0.06944	0.06944	6.0597
70	17.69	0.03868	0.05652	4.3658

Table 2
Proton-ligand stability constant (pK) of BT-1 (L1) in different percentage of DMF-water at 0.1 M ionic strength

% of DMF	**Dielectric Constant (D)**	**1/D**	**Mole Fraction**	**pK**
80	29.61	0.0337	0.4843	4.9785
75	27.76	0.0360	0.4134	5.6849
70	25.69	0.0389	0.3539	6.4391

Table 3
Proton-ligand stability constant (pK) of BT-1 (L1) in different percentage of DMSO-water at 0.1 M ionic strength

% of DMSO	**Dielectric Constant (D)**	**1/D**	**Mole Fraction**	**pK**
80	69.80	0.0143	0.5039	5.7596
75	70.40	0.0142	0.4323	5.3251
70	71.08	0.0140	0.3720	4.2587

Table 4

Metal-ligand stability constants (log K) of Co (II)- BT-1 (L1) in different percentage of Dioxane-water at 0.1 M ionic strength

% of Dioxane	Dielectric Constant (D)	1/D	Mole Fraction	log K_1	log K_2	log K_1 - log K_2
80	10.90	0.09174	0.09174	8.7890	7.5457	1.2433
75	14.40	0.06944	0.06944	5.6009	4.3295	1.2714
70	17.69	0.03868	0.05652	4.7458	3.2	1.5201

Table 5

Metal-ligand stability constants (log K) of Co(II)-BT-1(L1) in different percentage of DMF-water at 0.1 M ionic strength

% of DMF	Dielectric Constant (D)	1/D	Mole Fraction	log K_1	log K_2	log K_1 - log K_2
80	29.61	0.0337	0.4843	4.6565	3.4492	1.2073
75	27.76	0.0360	0.4134	3.6897	2.4851	1.2046
70	25.69	0.0389	0.3539	2.9745	1.0258	1.9487

Table 6

Metal-ligand stability constants (log K) of Co (II)- BT-1 (L1) at different percentage of DMSO-water at 0.1 M ionic strength

% of DMSO	Dielectric Constant (D)	1/D	Mole Fraction	log K_1	log K_2	log K_1 - log K_2
80	69.80	0.0143	0.5039	5.7894	4.1489	1.6405
75	70.40	0.0142	0.4323	5.3756	4.0026	1.403
70	71.08	0.0140	0.3720	4.4732	3.0702	1.373

Table7

System : BT-1 (L1)

% Dioxane-water	Co(II)- BT (L1)	% DMF-water	Co(II)- BT (L1)	% DMSO-water	Co(II)- BT (L1)
	log K_1 - log K_2		log K_1 - log K_2		log K_1 - log K_2
80	1.2433	80	1.2073	80	1.6405
75	1.2714	75	1.2046	75	1.403
70	1.5201	70	1.9487	70	1.373

Results & Discussion

It could be seen from observation that pK values increased with the increase in the percentage of Dioxane, DMF and DMSO in mixture. The increase in pK value of ligand is due to the presence of group attached to phenyl ring is a electron withdrawing group. The difference between logK_1& log K_2,is greater than 1 (>1) which shows the formation of simultaneous complex.

It could be seen from Table 7 that the difference between log K_1 and log K_2continuously decreases with the increase in the percentage of dioxane, dioxane and in DMF This means that either log K_1 is relatively decreasing or log K_2 relatively increasing as the dielectric constant is increased. The increased dielectric constant would decrease the electrostatic forces of attraction between metal ion and negatively charged ligand to form 1:1 complex. The formation of 1:2 complexes on the other hand is due to the reaction between similarly charged ions. This would probably explain the observed behaviour.

Conclusion

From the observation it is concluded that the difference between LogK1 & log K2 greater than 1 this indicate that there is stepwise complex formation between CFB and Co (II) ligand .

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MICROWAVE ASSISTED SYNTHESIS OF PYRIMIDINE LINKED DITHIADIAZINES BY SULPHUR-SULPHUR BOND FORMATION THROUGH CYCLOCONDENSATION AND STUDY OF ANTIMICROBIAL PROPERTIES

K.A.Palaspagarand P.P.Deohate*
Department of Chemistry, Shri Radhakisan Laxminarayan Toshniwal College of Science, Akola, India
kpalaspagar31@rediffmail.com, pradip222091@yahoo.co.in

ABSTRACT

The microwave assisted synthesis and characterization of series of 1-(6-aryl/alkylimino-3-phenylimino-[1,2,4,5]-dithiadiazin-4-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones was initiated by treating 2-amino-4,6-dimethyl-pyrimidine with ethyl chloroacetate to give ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate. It on further reaction with hydrazine hydrate afforded (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide. The hydrazide was reacted with N-aryl/alkyl isothiocyanates and further with N-phenyl-S-chloroisothiocarbamoyl chloride and basified to afford the title compounds exhibiting differently substituted constrained pharmacophores. The purity of compounds was checked by TLC and constituents of compounds delineated by chemical transformations, IR, ^{1}H-NMR and mass spectral studies. Title compounds were assayed for their antimicrobial properties.

Keywords: *Microwave, pyrimidine linked dithiadiazines, antimicrobial properties*

Introduction

The sulphur and nitrogen containing heterocyclic compounds were found to possess a wide variety of biological activities[1,2] and proved to be excellent versatile drugs in the field of medicinal chemistry[3]. Pyrimidine as a heterocyclic compound is an excellent core structure with diversified therapeutic applications[4]. Its fascinating use as a medicinally important compound is evidential from its varied biological properties[5]. Synthesis, structural details and biological study of substituted [1,2,4,5]-dithiadiazines was reported earlier in some scientific communications[6-10]. It was found that, *N*-aryl/alkyl-*S*-chloroisothiocarbamoyl chlorideshave enough potentiality in the synthesis of nitrogen and sulphur containing 5, 6 membered heterocyclic compounds[11,12]. It has been observed that there is scanty work on the synthesis of pyrimidine linked [1,2,4,5]-dithiadiazines.

In the present work efforts are made for microwave assisted synthesis[13-14] and characterization of series of 1-(6-aryl/alkylimino-3-phenylimino-[1,2,4,5]-dithiadiazin-4-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones.

Experimental

Melting points of all the synthesized compounds were determined on a digital melting point apparatus (Veego, VMP-D) and are uncorrected. All chemicals used were of A.R. grade. The C, H and S analysis was carried out on Carlo-Erbaanalyser, N estimation was carried out on Colman-N-analyser-29. Purity of the title compounds were checked by TLC. All the reactions carried out in GMG20E-08-SLGX microwave oven at 800 W. IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr disc. ^{1}H-NMR spectra were obtained on a Bruker-DRX-600 spectrophotometer in $CDCl_3$ with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. Mass spectral measurements were carried out by EI method on a Jeol-JMC-300 spectrometer at 70 eV. The reagents used in the synthesis of 1-(6-aryl/alkylimino-3-phenylimino-[1,2,4,5]-dithiadiazin-4-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones (7a-h) have been prepared as follows.

Synthesis of ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2)

The parent compound ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (**2**) was prepared by irradiating the mixture of 2-amino-4,6-dimethyl-pyrimidine (**1**) (0.01 mol) and ethyl chloroacetate (0.01 mol) in 1,4-dioxane under microwave for 4 min 10 sec using anhydrous potassium carbonate as a catalyst[4]. When 1,4-dioxane was evaporated, crude solid mass was obtained, it was crystallisedfrom

absolute ethanol.

Synthesis of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3)

The compound (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (**3**) was prepared by irradiating the mixture of ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (**2**) (0.01 mol) and hydrazine hydrate (0.01 mol) in 1,4-dioxane under microwave for 1 min 30 sec, progress of the reaction was monitored by TLC. The crude solid mass obtained was crystallized from absolute ethanol in cold condition.

Synthesis of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a)

The mixture of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (**3**) (0.01 mol) and N-phenyl isothiocyanate (**4a**) (0.01 mol) in chloroform was irradiated in a microwave oven for 1 min 30 sec, progress of the reaction was monitored by TLC. The crude solid mass obtained was crystallized from ethanol in cold condition and identified as (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (**5a**). This reaction was extended to synthesize other compounds (**5b-h**)using different N-aryl/alkyl isothiocyanates (**4a-h**). The reactions were monitored on silica gel-G plates by TLC.

Synthesis of 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(3,6-diphenylimino-[1,2,4,5]-dithiadiazin-4-yl)-ethanone (7a)

The mixture of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (**5a**) (0.01 mol) and N-phenyl-S-chloroisothiocarbamoyl chloride (0.01 mol) in chloroform was irradiated under microwave for 2 min 30 sec, which leads to the formation of sticky mass. It was repeatedly washed with petroleum ether (60-80^{0}C). The separated solid was acidic to litmus and identified as 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(3,6-diphenylimino-[1,2,4,5]-dithiadiazin-4-yl)-ethanone hydrochloride (**6a**). It on basification with dilute ammonium hydroxide solution and on crystallization from ethanol afforded a free base (**7a**). This reaction was extended to synthesize other compounds (**7b-h**). The reactions were monitored on silica gel-G plates by TLC.

Results and Discussion

The parent compound 2-amino-4,6-dimethyl pyrimidine (**1**) was treated with ethyl chloroacetate in 1,4-dioxane medium using anhydrous potassium carbonate as a catalyst to yield ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (**2**), 88%, m.p. 142^{0}C (Found: C, 55.11; H, 6.98; N, 20.10. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.41; H, 7.17; N, 20.09%). The compound (**2**) was reacted with hydrazine hydrate in 1,4-dioxane to give (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (**3**), 88%, m.p. 138^{0}C (Found: C, 48.17; H, 6.38; N, 35.01. Calcd. for $C_8H_{13}N_5O$: C, 49.22; H, 6.71; N, 35.87%); IR: ν_{max} 3401, 3310 (NH), 1705 (C=O), 1628 (C=N), 1336 (C-N), 1156 cm^{-1} (N-N); ^{1}H-NMR: δ ($CDCl_3$+DMSO-d_6): 7.38 (1H, s, CO-NH), 6.46 (1H, s, Pyrm-NH), 6.32 (1H, s, Pyrm-H), 3.57 (2H, s, CO-CH_2), 2.52 (2H, s, NH_2), 2.17 (6H, s, Pyrm-CH_3).

The IR spectrum of compound (**3**) showed intense absorption at 1705 cm^{-1} which suggested the presence of C=O group. The aromatic and aliphatic C-H stretching frequencies were observed in the regions 3410-3145 and 2990-2940 cm^{-1} respectively. The appearance of sharp peaks at 3401 and 3310 cm^{-1} indicated the presence of NH and NH_2 groups respectively in the molecular structure. In ^{1}H-NMR spectrum of compound (**3**) peaks at δ 7.38 and 2.52 confirmed the presence of CO-NH-NH_2 linkage which indicates the conversion of substituted ethyl acetate into acetic acid hydrazide.

The compound **(3)** on reaction with N-phenyl isothiocyanate (**4a**) afforded (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (**5a**), 79%, m.p. 134^{0}C (Found: C, 53.77; H, 5.05; N, 25.40; S, 9.08. Calcd. for $C_{15}H_{18}N_6OS$: C, 54.54; H, 5.45; N, 25.45; S, 9.69%); IR: ν_{max} 3402, 3311 (NH), 1764 (C=O), 1649 (C=N), 1311 (C-N), 1246 (C=S), 1170 cm^{-1} (N-N); ^{1}H-NMR: δ ($CDCl_3$+DMSO-d_6): 7.99 (1H, s, CO-NH), 7.75 (1H, s, Ar-NH), 7.73 (1H, s, CS-NH), 7.09-7.58 (5H, m, Ar-H), 6.41 (1H, s, Pyrm-NH), 6.29 (1H, s, Pyrm-H), 3.64 (2H, s, CO-CH_2), 2.21 (6H, s, Pyrm-CH_3).

In IR spectrum of compound (**5a**) intense absorptions at 1764 and 1246 cm^{-1} showed the presence of C=O and C=S groups respectively. The aromatic and aliphatic C-H stretching frequencies were observed in the regions 3410-3000 and 2990-2875 cm^{-1} respectively. The appearance of peaks in the region 3402-3311 cm^{-1} indicates the presence of NH groups. The ^{1}H-NMR spectrum of compound (**5a**) showed peaks at δ 7.99, 7.75, 7.73 and 6.41 which confirmed the presence of four NH groups in the molecular structure.

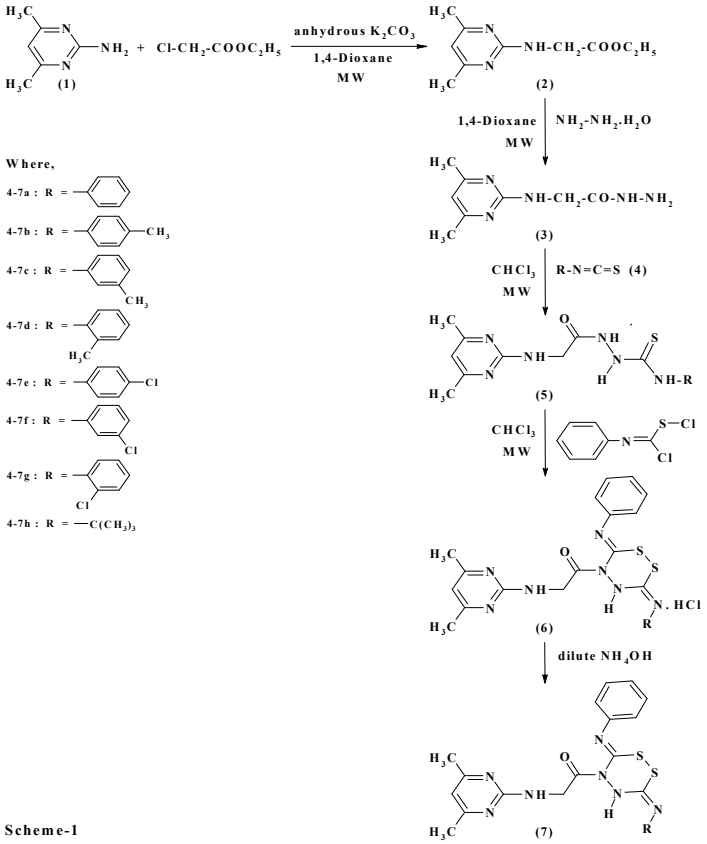
The above reaction was extended to synthesize the compounds (**5b-h**) using different N-aryl/alkyl isothiocyanates (**4a-h**): (**5b**), 84%, m.p. 118^{0}C (Found: C, 55.79; H, 5.66; N, 24.14; S, 9.18. Calcd. for $C_{16}H_{20}N_6OS$: C, 55.81; H, 5.81; N, 24.41; S, 9.30%); (**5c**), 87%, m.p. 112^{0}C (Found: C, 55.65; H, 5.77; N, 23.92; S, 9.29. Calcd. for $C_{16}H_{20}N_6OS$: C, 55.81; H, 5.81; N, 24.41; S, 9.30%); (**5d**), 88%, m.p. 111^{0}C (Found: C, 55.08; H, 5.80; N, 24.37; S, 9.21. Calcd. for $C_{16}H_{20}N_6OS$: C, 55.81; H, 5.81; N, 24.41; S, 9.30%); (**5e**), 79%, m.p. 64^{0}C (Found: C, 49.11; H, 4.61; N, 22.88; S, 8.56. Calcd. for $C_{15}H_{17}N_6OSCl$: C, 49.38; H, 4.66; N, 23.04; S, 8.77%); (**5f**), 91%, m.p. 149^{0}C (Found: C, 48.87; H, 4.44; N, 22.93; S, 8.70. Calcd. for $C_{15}H_{17}N_6OSCl$: C, 49.38; H, 4.66; N, 23.04; S, 8.77%); (**5g**), 88%, m.p. 210^{0}C (Found: C, 49.34; H, 4.69; N, 23.07; S, 8.72. Calcd. for $C_{15}H_{17}N_6OSCl$: C, 49.38; H, 4.66; N, 23.04; S, 8.77%); (**5h**), 90%, m.p. 94^{0}C (Found: C, 50.05; H, 7.12; N, 26.95; S, 10.23. Calcd. for $C_{13}H_{22}N_6OS$: C, 50.32; H, 7.09; N, 27.09; S, 10.32%).

The compound (**5a**) was then reacted with N-phenyl-S-chloroisothiocarbamoyl chloride in chloroform medium to yield 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(3,6-diphenylimino-[1,2,4,5]-dithiadiazin-4-yl)-ethanone hydrochloride (**6a**). It on basification with dilute ammonium hydroxide solution afforded a free base 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(3,6-diphenylimino-[1,2,4,5]-dithiadiazin-4-yl)-ethanone (**7a**), 91%, m.p. 112^{0}C (Found: C, 55.96; H, 4.49; N, 20.91; S, 13.51. Calcd. for $C_{22}H_{21}N_7OS_2$: C, 57.01; H, 4.53; N, 21.16; S, 13.82%); IR: ν_{max}3412, 3309 (NH), 1718 (C=O), 1653 (C=N), 1311 (C-N), 1170 (N-N), 773 (C-S), 447 cm^{-1} (S-S); ^{1}H-NMR: δ (CDCl3+DMSO-*d*6): 6.89-7.76 (10H, m, Ar-H), 6.40 (1H, s, Pyrm-NH), 6.32 (1H, s, Pyrm-H), 3.64 (2H, s, CO-CH_2), 2.43 (1H, s, Dthdz-H), 2.19 (6H, s, Pyrm-CH_3); MS: m/z 448 (M^+-CH_3), 386 (M^+-C_6H_5), 341 (M^+-$(CH_3)_2.C_4HN_2.NH$), 327 (M^+-$(CH_3)_2.C_4HN_2.NH.CH_2$), 299 (M^+-$(CH_3)_2.C_4HN_2.NH.CH_2.CO$), 164 $(CH_3)_2.C_4HN_2.NH.CH_2.CO^+$), 136 $(CH_3)_2.C_4HN_2.NH.CH_2^+$), 122 $(CH_3)_2.C_4HN_2.NH^+$), 107 $(CH_3)_2.C_4HN_2^+$).

The intense peak at 1718 cm^{-1} in IR spectrum of compound (**7a**) confirmed the presence of C=O group. Absorptions in the regions 3420-3010 and 3010-2860 indicate the aromatic and aliphatic C-H stretching frequencies respectively. The appearance of sharp peaks at 3412 and 3309 cm^{-1} indicates the presence of two NH groups in molecular structure. The ^{1}H-NMR spectrum of compound (**7a**) showed signals at δ 6.40 and 2.43 which confirmed the presence of pyrimidine-NH and dithiadiazine-NH respectively. The mass spectrum of compound (**7a**) confirmed the formation of various fragment ions. The fragment ion with m/z 299 has 100% intensity.

The above reaction was extended to synthesize 1-(6-aryl/alkylimino-3-phenylimino-[1,2,4,5]-dithiadiazin-4-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones (**7b-h**): (**7b**), 89%, m.p. 110^{0}C (Found: C, 57.22; H, 4.79; N, 20.18; S, 12.95. Calcd. for $C_{23}H_{23}N_7OS_2$: C, 57.86; H, 4.82; N, 20.54; S, 13.41%); IR: ν_{max} 3404, 3309 (NH), 1751 (C=O), 1647 (C=N), 1311 (C-N), 1170 (N-N), 775 (C-S), 447 cm^{-1} (S-S); ^{1}H-NMR: δ (CDCl3+DMSO-*d*6): 6.88-7.76 (9H, m, Ar-H), 6.33 (1H, s, Pyrm-NH), 6.30 (1H, s, Pyrm-H), 3.74 (2H, s, CO-CH_2), 2.43 (1H, s, Dthdz-H), 2.25 (3H, s, Ar-CH_3), 2.19 (6H, s, Pyrm-CH_3);(**7c**)), 92%, m.p. 122^{0}C (Found: C, 57.02; H, 4.84; N, 19.97; S, 13.36. Calcd. for $C_{23}H_{23}N_7OS_2$: C, 57.86; H, 4.82; N, 20.54; S, 13.41%); (**7d**), 90%, m.p. 103^{0}C (Found: C, 57.80; H, 4.61; N, 20.51; S, 13.12. Calcd. for $C_{23}H_{23}N_7OS_2$: C, 57.86; H, 4.82; N, 20.54; S, 13.41%); (**7e**), 89%, m.p. 94^{0}C (Found: C, 52.67; H, 3.89; N, 19.61; S, 12.85. Calcd. for $C_{22}H_{20}N_7OS_2Cl$: C, 53.06; H, 4.02; N, 19.69; S, 12.86%); (**7f**), 94%, m.p. 101^{0}C (Found: C, 53.10; H, 4.06; N, 19.71; S, 12.80. Calcd. for $C_{22}H_{20}N_7OS_2Cl$: C, 53.06; H, 4.02;

N, 19.69; S, 12.86%); (**7g**), 85%, m.p. 126^{0}C (Found: C, 52.99; H, 3.97; N, 19.59; S, 12.68. Calcd. for $C_{22}H_{20}N_7OS_2Cl$: C, 53.06; H, 4.02; N, 19.69; S, 12.86%); (**7h**), 85%, m.p. 114^{0}C (Found: C, 54.11; H, 5.50; N, 22.08; S, 14.21. Calcd. for $C_{20}H_{25}N_7OS_2$: C, 54.17; H, 5.64; N, 22.12; S, 14.44%) (**Scheme-1**).



Scheme-1

All these reactions were carried out by microwave irradiation. The products obtained were characterized by spectral method[15-17]. The elemental analysis[18] satisfied the structural properties of the synthesized compounds. To conclude, the chemistry of the reactions employed together with their chemical behaviour was discussed exhibiting the importance of novel molecular templates.

Antimicrobial activity

Various methods have been proposed and adopted for the measurement of antimicrobial activity[19]. In present antimicrobial study the newly synthesized compounds were screened for their antibacterial activity using Kirby-Baeur method[20-22]. Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 ml^{-1} and each well diameter 10 mm was loaded with 0.1 ml of test compound solution (1000 µg ml^{-1}). The zones of inhibition were recorded after incubation for 24 hr at 37ºC, using Vernier caliper. The bacterial organisms used included both gram-positive as well as gram-negative strains. The medium used for the study of antibacterial activity of newly synthesized compounds was Hi-media Laboratories Pvt. Ltd., India make nutrient agar. It was of bacteristatic grade and found to be suitable for the growth of all bacterial strains used in the present study.

The antibacterial activity and inhibition effect of the compounds (**7a-h**) on the growth of various bacterial organisms is summarised in table given below along with the inhibition effect of standard drug streptomycin for comparison purpose. The compound (**7e**) was found to be highly sensitive (bactericidal) against the microorganisms *E. coli* and *P. vulgaris* whereas moderately sensitive against *S. typhi* and *B. subtilis*. Majority of the compounds were found to be moderately sensitive against *S. aureus* and slightly sensitive against *S. typhi*. Compound (**7h**) was

resistant against almost all the microorganisms. To determine the minimum inhibitory concentration (MIC), the serial dilution technique was followed using nutrient broth medium. The MIC[23] values of compounds (**7e**) against *E. coli* and *P. vulgaris* were found to be 80 and 75 µg ml^{-1} respectively .

Antibacterial activity of 1-(6-aryl/alkylimino-3-phenylimino-[1,2,4,5]- dithiadiazin-4-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones (7a-h)

Compounds	Microorganisms				
	E. coli	*S. aureus*	*S. typhi*	*B. subtilis*	*P. vulgaris*
7a	S 12	S 17	S 12	S 15	R
7b	S 15	S 16	R	R	S 13
7c	S 11	S 14	S 14	S 17	R
7d	S 16	S 18	S 14	S 12	S 12
7e	S 23	S 18	S 19	S 18	S 23
7f	R	S 15	S 15	S 19	S 14
7g	S 18	S 19	S 13	S 19	S 17
7h	R	R	R	S 12	R
Streptomycin	S 23	S 20	S 22	S 18	S 13

(Concentration 100 µg/ml) (Diameter of inhibition zone in mm)

R (Resistant) : (11 mm and below)
S (Sensitive) (Bactericidal) : (11 mm above)
Slightly Sensitive : (11 mm above to 15 mm)
Moderately Sensitive : (15 mm above to 20 mm)
Highly Sensitive : (20 mm above)

Conclusion

In present work microwave irradiative synthesis of 1-(6-aryl/alkylimino-3-phenylimino-[1,2,4,5]-dithiadiazin-4-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones has been reported. The compounds obtained were of good quality and purity with high % yield. Microwave assisted method applied for the synthesis is quite simple, efficient, fast, clean, economic and eco-friendly.

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STUDIES ON INFLUENCE OF IONIC STRENGTH OF PR (III) METAL ION COMPLEX WITH 4-(BENZOYL)-3-(2-CHLORO PHENYL)-5-(O-HYDROXYL PHENYL) PYRAZOLE BY PH-METRIC TECHNIQUE

***S.B. Bansod and J.R.Bansod**
Department of Chemistry,smt. Narsamma arts, commerce and science college, Amravati (M.S.)India
Department of Chemistry, VidhaBharti Mahavidhalay Amravati (M.S)India
sbbansod@rediffmail.com

ABSTRACT

The interaction of Pr(III) metal ion complex with L1 4-(Benzoyl)-3-(2-chloro phenyl)-5-(o-hydroxy phenyl) pyrazole has been studied at various ionic strength pH _ metrically . The values of PK [Proton- Ligand stability constant] and log K [Metal – Ligand stability constant] are utilized to estimate the thermodynamic stability constant at zero ionic strength and to know exact nature of complexation equilibria Pk//log k values are found to be increasing with decreasing the values of ionic strengths

Keywords: *Pr(III), 4-(Benzoyl)-3-(2-chloro phenyl)-5-(o-hydroxy phenyl) pyrazole, ethanol*

Introduction

Sumer et al.,[1]studies of influence of ionic strength of medium on the complexation equilbria of substituted hydroxy 1-3 propanodiones with Cr(III)&La(III) metal ion PH- metrically . Jaising et al.,[2] have studied the stability constant of some bivalent metal chelates with 2-4-dihydroxy Valero – phenonoxime at various ionic strength Gudadhe et al.,[3] have investigate the stability constant of Cu(II) Complex with some substituted propanedious at various ionic strength potentiometrically Mandakmare et al.,[4] have studies stability constant of UO2 [II] Complex with some substituted Coumanins at 0.1M ionic strength potentiometrically and spetrophotometrically.Palaskar et al., [5] have studies the effect of ionic strength and dielectric constant of Cu(II)-3-nitrophalic acid potentiometrically at various ionicstrength.Mesharam et al.,[6] have studies stability constant of Pr(III) complex with substituted pynazoline May and Jones et al.,[7] have applied Hammet's equation to the complex of substituted benzoic acid Willims et al., [8] the entropy term is usually favourable when ligand in atomic and genrally in case of neutral ligands.Inving and rossotiet et al.,[9] have given a method for determining the metal-ligand stability constant of the complex by PH- metrically.Sawalakhe et al., [10] have investigated the metal-ligand stability constant Fe(III),Cr(III)and Al(III) metal ion complex with some substituted diketones and pyrazoles at 0.1M ionic strerngth

Narwade M. L. and jagirdar et al.,[11] have determined metal ligand stability constant of divalevt and trivalent metals ion with some substituted sulphonic acid . P.Agrawal and Narwade M. L.et al.,[12] have determined metal ligand stability constant at 0.1M ionic strength Ali asager et al., [13] have studies some metal ligands stability constant of some tranisition metals ion with some substituted pyrazolines and isoxazoline PH-metrically obtained very low values of stability constant due to weak chelating agent.

Present work is determination of protan-ligand stability constant and metal- ligand stability constant of Pr(III) and L1 4-(Benzoyl)-3-(2-chloro phenyl)-5-(o-hydroxy phenyl) pyrazole at different ionic strength at29±0.1 o C temp.

II. Experimental

Equip-tronics digital PH- meter modeEQ-610 was used(accuracy±Type equation here.0.05 units) for measuring PH of the solution. Metal solution was prepared in double distilled water.Ligand solution is prepared in 70% ethanol-water(v/v) solution nitric acid, sodium hydroxide and nitrate used were of A. R. Grade.The titration were conducted in an inert atmosphere of nitrogen . The ionic strength of solution was maintained constant adding appropriate amount of 1M KNO3 solution

.The value were recorded by PH- meter and converted of [H+] value by applying the correction proposed by Van Uitert and Hass[14]

III. Result and discussion

Pr(III)metals ion complex wit4-(Benzoyl)-3-(2-chloro phenyl)-5-(o-hydroxyl phenyl) pyrazole may be monobasic acid replace H+ ion from ligand .The titration data were used to construct the curve between volume NaOH Vs PH they are called acid ligand and metal titration curve.

Table – 1 : proton ligand stability constant at various ionic strength

Ionic strength	Pk value
0.10	3.30
0.08	3.50
0.06	3.80
0.03	3.90
0.01	4.10

Table – 2 : Metal ligand stability constant at various ionic strength

Ionic strength	Log K1	Log K2
0.10	6..24	4.25
0.08	7.14	6.05
0.06	8..54	7.85
0.04	9.05	8..50
0.02	9..55	8.90

Table-3 ΔZ^2 Values for dissociation and association equilibria

Reaction equilibria	constant	ΔZ^2	
		Expected	Found
HL ↔H+ +L-	Pk	2.00	2.45
HL+Pr3+ ↔ H+ + PrL+	Log k_1	-2.00	2.±20
HL+ PrL^+ ↔+ H+ + PrL_2	Log k_2	0.00	3.20

The Pk value of ligand & logk value of Pr(III) complexes at various ionic strength was calculated by Irving & Rossotti's method and are presented in Table-1 and Table-2 respectively. From the table-2 seen that the stability constant values of Pr(III) are greater. This is may be due to greater tendancy of elements to form complexes. It means Pr(III) is a good complexing agent.Also it is clear that pk/logk values are found to be decreased with increasing ionic strength. The pk/logk values were used to calculated the thermodynamic constant with the help of Bronsted equation [15]

Logk= logk0+AΔZ2-√μ And Pk=Pko-AΔZ2-√μ Where, A is the Debye-Huckel constant ΔZ2 is the difference in the square of change of product and reactant ions and ko is the formation constant at the ionic strength. The value of pk, logk1 & logk2 were plollted against √μ. The plot at log k/Pk v/s√μ gave strength lines. The magnituted of ΔZ^2 & slopes were calculated from graphs. The data obtained of pk & logk could be utilized to known the mechanism of complexation equilibria is in given Table-3.

Table-4:Thermodyanamic dissociation constant at zero ionic strength[pk/logk]

plots	Ligand[L1]	Pr(III)-Metal L1 Complex
Pk v/s √μ	Pko 6.73	
Pk v/s √μ. (1+√μ.).	6.50	
Pk v/s [√μ. (1+√μ.)]-0.3 √μ.	6.65	
Logk1 v/s √μ		Logko 11.40
logk 1 v/s √μ. (1+√μ.).		11.33
Logk1 v/s [√μ. (1+√μ.)]-0.3 √μ.		11.36
Logk2 v/s √μ		9.87
Logk2 v/s √μ. (1+√μ.).		9.64
Logk2 v/s [√μ. (1+√μ.)]-0.3 √μ.		9.14

It is from Table-3 that the slope of Pk and logk do not give a conclusive evidence regarding the magnitude of the change of reacting species.The discrepancy may be due to the limited applicability of Bronsted equation.

The plots of Pk/logk v/s√μ. (1+√μ.) and [√μ. (1+√μ.)]-0.3 √μ are also plotted and slope values were determined. It showed that modified Debye-Huckel equation also did not show much improvement in the slope values. The discrepancy between expected and observed slope values was thought of to be due to the concentration and not the reactivity term used in the equation of stability constant.

Thermodynamic stability constants[Pk/log k]

The thermodyanamic constant observed from various plots at zero ionic strength are presented in Table-4,which show a good agreement among thermodynamic constant obtained from various plots.

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ULTRASONIC STUDY OF MOLECULAR INTERACTION OF 2- SUBSTITUTED 4,5-DIPHENYL IMIDAZOLE WITH ETHANOL AT DIFFERENT TEMPERATURE

T.M. Bhagat, K.K. Kumbhare, A.N. Gaikwad and P.B. Rathod
P.G.Department of Chemistry, G.S. Gawande College, Umarkhed, Dist. Yavatmal (M.S.), India
bhagat.t@gsgcollege.edu.in

ABSTRACT

The measurement of density and ultrasonic velocity of 2- substituted 4,5-diphenyl imidazole with ethanol have be measured in aqueous solution at different concentration and different temperature.The simple physical properties like density and ultrasonic velocity and viscosity are used to explain the molecular interaction in aqueous solution of ethanol. The apparent molar volume, adiabatic compressibility, apparent molar compressibility, acoustical impedance, intermolecular free length,and viscosity relaxation time have been calculated . The result are discussed in the light of solute-solvent interaction and structural effects on the solvent in solution.

Keywords : *Ultrasonic velocity, density, viscosity, adiabatic compressibility,apparent molar volume, viscosity relaxation time.*

1. Introduction

The measurement of ultrasonic speed in liquid mixture enables accurate determination of some useful acoustical and thermo dynamical parameters are highly sensitive to molecular interaction in their mixture. Acoustic and thermodynamic parameter have been used to understand different kinds of association the molecular packing , molecular motion and various type of intermolecular interaction and their strength influenced by the size in pure components and in the mixture [1-5].These parameter play vital role in assessing the compactness due to molecular arrangement and the extent of molecular interaction in the liquid mixture through charge transfer, dipole-dipole and dipole induced dipole interaction [6].Their dependence on concentration, temperature and frequency are of applied research and also find application in many important chemical,industrial and biological processes [7]. Study of molecular intreaction between solute molecule and solvent media has got great important in many field of science including medicinal chemistry,industrialprocess, biochemistryetc. The solute-solvent and solvent-solvent intraction can be studied by the measurement of relative viscosity and ultrasonic velocity of an electrolyte in solution.This type of study helps us to understand the structure making and breaking properties of solutes [8]. Ultrasonic wave in recent year ,have acquired the status of an important probe for the study of structure and properties of matter in a basic science .The ultrasonic velocity and absorption studies in case of electrolyte solution have led to new insight into the process of in ion association and complex formation[8-9]. Ultrasonic parameter are being extensively used to study mecular interaction in pure liquids, liquid mixture and electrolytic solution[10-16].

2. Material and Method

2.1. Prepration of 2- substituted 4,5-diphenyl imidazole by using 2-nitrobenzaldehyde.

In a round bottom flask take Benzil (2.1gm), 2-Nitrobenzaldehyde (1.51 gm) and ammonium acetate (4.62gm) in glacial acetic acid (20 ml) then reflux the content for 3-5 hrs. After refluxing the reaction mixture solid seperstesout.The obtained solid product was filtered and wash with water then recrystallised by using ethanol. Yield of compound is 3.08 gm and M.P.-230^{0}C

Physical Measurement:

Solutions of varying concentration were prepared on molarity basis from 0.04 stock solution of each complex sample with double distilled water. All the measurements were carried out at 303.15K, 308.15K, 313.15K, and . Density measurements were carried out for different solutions at 303.15K,

308.15K, 313.15K, and using a open capillary density bottle. The ultrasonic velocity in the solutions was measured using an ultrasonic interferometer at a frequency of 2 MHz with an accuracy of ±0.05 %. The relative viscosity was measured using a pre-calibrated Ostwald viscometer.

Methods of calculation:

The data of density (ρ), ultrasonic velocity (u) and viscosity (η) has been used to evaluate many acoustical parameters by using the following standard expressions for understanding solute-solvent, solvent-solvent interaction and structural changes.

(i) Adiabatic compressibility:- $\beta_s = \frac{1}{\rho_s u_s^2} \text{-------(1)}$

Where ρ_s = density of solution, u_s = sound velocity solution.

(ii) Intermolecular free length (L_f) **:-** $L_f = K\sqrt{\beta_s} \text{------(2)}$

Where 'K' is a temperature dependent constant known as Jacobson constant [(m)].

(iii) Specific acoustic impedance (Z):- $Z = u_s \rho_s \text{-------(3)}$

(iv) Molar sound velocity or Rao'sconstant (R) :- $R = \left(\frac{M}{\rho_s}\right) \cdot u_s \, 1/3 \text{-------(4)}$

Where 'M' molar mass of the solution.

(v) Relative association (R_A):- $R_A = \left(\frac{d_s}{d_o}\right)\left(\frac{u_o}{u_s}\right)^{1/3} \text{------(5)}$

Where ρ_o = density of solvent, u_o = velocity of solvent

(vi) Apparent molar volume (Φ_V):- $\Phi_V = \left(\frac{1000}{m\rho\rho_o}\right)(\rho_o - \rho) + \left(\frac{M}{\rho_0}\right) \text{----(6)}$

Where 'm' molarity of solution.

(vii) Apparent molar compressibility (Φ_β): $\Phi_\beta = \left(\frac{1000}{m\rho\rho_o}\right) - (\rho_o\beta - \rho\beta_0) + \left(\frac{\beta_0 M}{\rho_0}\right) \text{---(7)}$

(viii) Viscosity relaxation time :- $\Gamma = \frac{4\eta}{3\rho.u^2} \text{----------(8)}$

(ix) Ultrasonic attenuation : $(a/f2) = \frac{8\pi^2\eta}{\rho \times u^2} \text{------(9)}$

(x) Relative viscosity(η):- $\eta_r = \left[\frac{d_s.t_s}{d_w t_w}\right]\eta_w \text{----------(10)}$

- **The units of -**Density(ρ):k **g cm^{-3}** ,Viscosity(η): **cp ,** Ultrasonic velocity (U) : **ms^{-1}**

Adiabatic compressibility (β_s): **cm^{2}dyne^{-1}**, Apparent molar volume (Qv): **cm^{-3}mol^{-1}**,Apparent molar compressibility (Qk): **cm^{-3}mol^{-1}bar^{-1}**, Acoustical Impedance (z): **kg. m^{-2}s^{-1}**Intermolecular free length (L_f): **m**,Viscosity relaxation time (τ): s

3. Result & Discussion

Compound In Ethanol

Table 1: Density (ρ), ultrasonic velocity (u),Viscosity (η), adiabatic compressibility (β_s),apparent molar compressibility (ϕ_β), apparent molar volume (ϕ_V) for Compound IN ethanol at different temperatures.

Conc	ρ g/ml	u m s^{-1}	η Ns/m^{-2}	β_s m^2N^{-1}	Φ_V m^3 mol^{-1}	Φ_β m^2n^{-1}
T=303.15K						
0.04	0.4905	1162.4	1.0559×10^{-3}	2.7546	4.9057×10^{2}	4.1059×10^{3}
0.02	0.4901	1161.6	1.0469×10^{-3}	2.7531	4.9013×10^{2}	4.1024×10^{3}
0.01	0.4899	1158.8	9.073×10^{-4}	2.7410	4.8991×10^{2}	4.0691×10^{3}
0.005	0.4892	1155.6	8.958×10^{-4}	2.7297	4.8920×10^{2}	4.0550×10^{3}
T=308.15K						
0.04	0.4888	1152.2	8.953×10^{-4}	2.7159	4.8887×10^{2}	4.0436×10^{3}
0.02	0.4878	1146.8	8.950×10^{-4}	2.6960	4.8783×10^{2}	4.0111×10^{3}
0.01	0.4873	1144.3	8.897×10^{-4}	2.6870	4.8731×10^{2}	3.9964×10^{3}
0.005	0.4861	1139.2	8.803×10^{-4}	2.6697	4.8610×10^{2}	3.9674×10^{3}
T=313.15K						
0.04	0.4853	1132.8	7.860×10^{-4}	2.6442	4.8537×10^{2}	3.9297×10^{3}
0.02	0.4845	1126.4	7.546×10^{-4}	2.6187	4.8453×10^{2}	3.8906×10^{3}
0.01	0.4835	1123.2	7.363×10^{-4}	2.6092	4.8351×10^{2}	3.8754×10^{3}
0.005	0.4827	1121.8	7.189×10^{-4}	2.6070	4.8270×10^{2}	3.8710×10^{3}

Table 2:. Acoustical Impedance (z), Intermolecular free length (L_f),viscosity relaxation time (τ),Ultrasonic attenuation (α/f^2)Rao's constant (R), relative association (R_A),

Conc.	z Ns/m^3	L_f m	τ s	α/f^2	R	R_A
T=303.15K						
0.04	5.701×10^{1}	5.0285×10^{2}	9.3306×10^{-1}	2.6668×10^{2}	808.11	1.1710
0.02	5.693×10^{1}	5.0273×10^{2}	9.2308×10^{-1}	2.6408×10^{2}	808.21	1.1703
0.01	5.676×10^{1}	5.0161×10^{2}	7.9581×10^{-1}	2.2730×10^{2}	806.59	1.1709
0.005	5.653×10^{1}	5.0058×10^{2}	7.8028×10^{-1}	2.2289×10^{2}	805.51	1.1718
T=308.15K						
0.04	5.631×10^{1}	5.0755×10^{2}	7.7463×10^{-1}	2.2098×10^{2}	803.80	1.2999
0.02	5.594×10^{1}	5.0570×10^{2}	7.6555×10^{-1}	2.1826×10^{2}	801.67	1.1893
0.01	5.576×10^{1}	5.0487×10^{2}	7.5693×10^{-1}	2.1578×10^{2}	800.75	1.1901
0.005	5.537×10^{1}	5.0324×10^{2}	7.4044×10^{-1}	2.1118×10^{2}	799.15	1.1913
T=313.15K						
0.04	5.497×10^{1}	5.0893×10^{2}	6.5264×10^{-1}	1.8570×10^{2}	795.97	1.2131
0.02	5.457×10^{1}	5.0649×10^{2}	6.1849×10^{-1}	1.7557×10^{2}	792.78	1.2127
0.01	5.430×10^{1}	5.0555×10^{2}	5.9883×10^{-1}	1.7020×10^{2}	792.16	1.2128
0.005	5.414×10^{1}	5.0536×10^{2}	5.8225×10^{-1}	1.6583×10^{2}	792.48	1.2068

Result and Discussion

Density decrease and ultrasonic velocity and viscosity are also decrease with decrease in concentration of solute. The linear behavior with decrease in velocity with concentration indicates the interaction between unlike molecule, which suggests weak solute-solvent (dipole-dipole) interaction between the component molecules. As density decreases the number of solute particles in the given region decreases [11]. It shows reverse trends in ultrasonic velocity and density with increase in temperature show molecular forces are weakening at high temperature. The increase in ultrasonic velocity is structure making type.

Decrease in concentration of 2- substituted 4,5-diphenyl imidazole results the linearly decreases in adiabatic compressibility and free length. This trend supports weak solute-solvent interaction and suggests aggregation of solvent molecules around solute molecules [12,13]. The magnitude of adiabatic compressibility and free length decreases with increase in temperature, it clearly reveal that interaction become stronger at higher temperature [14] .The specific acoustic impedanceis the parameter related to the elastic properties of the medium. The specificacoustic impedance is the impedance offered to the sound wave by the components of the mixture. In present investigation, specific acoustic impedance decrease with decrease in concentration. This trend further supports that there was no possibility of molecular interaction due to H-bonding between solute-solvents and solvent-solvent molecules which restrict the free flow of sound waves [15]. The specific acoustic impedance is directly proportional to density, ultrasonic velocity and inversely proportional adiabatic compressibility [16].

Molar sound velocity (Rao′s constant) non linearly increase or decrease with decrease in concentration which indicates that the magnitude of molecular interaction is enhanced in the system, which indicate interaction between solute-solvent molecule decrease. This leads to tight packing of the medium by decrease the molecular interactions [17]. Relative association is the measure of extent of association of components in the medium. The relative association is depends on either breaking up of the solvent molecules on addition of solute to it or the solvation of present ions. The relative association non-linearly decreases with decrease in concentration. The apparent molar compressibility and apparent molar volume decreases with decrease in concentration which indicates interaction between solute-solvent molecules enhanced. V Values are positive due to the compressibility of solvent due to the weak electrostatic force in the vicinity of ions. This trendssupports that the availability of more number of components in a given regions of space. This leads to tight packing of the medium and there by increases the interactions [18]. The viscosity relaxation time is the time required for the excitation energy to appear as translational energy. In present work viscosity relaxation time non-linearly decreases with decrease in molar concentration and decreases with increases in temperature. Where, with increase in temperature, it shows the instantaneous conversion of excitation energy to translational energy. This indicates strong molecular interaction between the solute and solvent molecules, where it show the instantaneous conversion of excitation energy to translational energy [19]. Absorption coefficientdecreases with decrease in concentration and this trend suggest that the extent of complexity decreases with decrease in concentration [20].

Conclusions

From the present investigation experimental values of density, ultrasonic velocity, viscosity and related acoustic parameter values indicate that thermodynamic parameters are sensitive to molecular interactions for ternary liquid mixtures at different concentrations and at varying temperatures. Thus it is conclude that in mixture of studied compound, solute-solvent interaction is existed. Some parameters specially, free length and adiabatic compressibility indicate strong interaction between solute-solvent molecules in the studied systems.

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MEASUREMENT OF DENSITY, REFRACTIVE INDEX AND CONDUCTANCE OF SOME HETEROCYCLIC COMPOUNDS

P.M. Kadam[a] and D. R. Munde[b]
[a]Department of Chemistry, Shri Vyankatesh Arts and Commerce College, Deulgaon Raja
[b]Department of Chemistry Science College, Nanded
pavankadam001@gmail.com

ABSTRACT

2-(1H-benzo[d] imidazol-2-yl) quinoline derivatives were synthesized and characterized by M.P, Infrared spectroscopy, thin layer chromatography, 1H NMR and mass data. Refractive index, molar refractivity and molar polarizability constant of synthesised compound have been studied in Ethanol, DMF, DMSO, and THF media at 303 K ± 0.10 C temperature and different concentration (0.625x 10-3 to 10.0x 10-3 M). The values of molar refraction (Rm) and molar polarizability (α) constant are found to be decreased with decreasing concentration of solute in solvent. These parameters throw the light on the solute – solvent interaction and solute – solute interaction.

***Keywords**: Molar polarizability constant, Molar refractivities and density.*

Introduction

Heterocyclic compound plays an important role in medicinal chemistry [1], Benzo-fused azoles containing heterocyclic compounds are biologically active and medicinally significant compounds [2]. Among them, benzimidazole and benzothiazole structural motifs are found in a wide range of natural products [3,4] as well as in materials [5] They also exhibit important biological activities such as anticancer [6], anti-HIV [7] and antibacterial,[8]. In spite of their biological importance, not many practical synthetic approaches have been reported in the literature [9]. Refractive index is an important additive property of a molecule. The refractive index is the ratio of angle of incident to the angle of refraction and it depends on the temperature and wave length of light. When a beam of light passes from rarer to denser medium such as from air to a glass or liquid, it bends towards the normal at the interface. This phenomenon is known as refraction. According to Snell's law of refraction the ratio of the sine of the angle of incidence and that of refraction is constant and is called as the refractive index of the liquid. It is given by formula n = sin i / sin r, where I is the angle of incidence and r is the angle of refraction. The refractive index of a medium is also defined as the ratio of velocity of light in vacuum to its velocity in given medium. The properties of liquid such as refractive index , ultrasonic velocity and viscosity of binary mixture are studied by many workers [10,11]. A. N. Sonar et. al [12] has studied on viscosity, density and refractive index of substituted heterocyclic compounds in different media. S R Ingle and Y K meshram [13] has studied on additive properties of some simple heterocyclic drugs in different solvent by refractometrically. R. B. Dhake [14] studied on viscosity, density and refractive index of bicalutamide in mixed solvent at 303.15 K. S. K. Chavan and B. A. Gop [15] studied on refractive indices of 3-(4-fluorophenyl)-1-phenylprop-2-en-1-one in methanol and benzene mixtures 298 K. Sonune et. al. [16] has been studied additive properties such as molar refractivity and molar polarizability constant of allopurinal, acenocoumarol, warfarin and amoxicillin in different media. Syal et.al. has been studied the ultrasonic velocity and viscosity of PEG-8000, PEG-study of acoustical properties, viscosity coefficient of substituted heterocyclic compounds under suitable condition. The present work deals with the study of measurement of refractive index of 2-(1H-benzo[d] imidazol-2-yl) quinoline in different solvents was done by refractive index measurement different parameters such as molar refraction, polarisability and specific refraction have been calculated at 303 K and conductance was measured in DMF.

Experimental

The solution of 2-(1H-benzo[d] imidazol-2-yl) quinoline derivatives are prepared in different solvent like ethanol, DMF, DMSO and THF by dissolving an appropriate amount by weight. The compound is synthesized in the laboratory by standard method and checked for purity by M.P, TLC, IR, NMR and Mass. The weighing was done by using electronic balance with a Precision ± 0.001 mg. The double walled capillary pycnometer was used for the measurement of densities of mixtures with an accuracy 0.1 Kg/m3. The refractive indices of solvent mixture and solutions were measure by Abbe's refractometer at 30^0C. The accuracy of Abbe's refractometer was within (+0.01) unit at different concentrations (0.63 x 10-3 to 10.0 x 10-3M). The temperature of the prism box is maintained constant by circulating water from thermostat calibrated with glass piece (n=1.5220) provided with the instrument. The specific refraction of solution mixtures is determined from the equation.

$$r = \frac{n^2 - 1}{n^2 + 2} \times \frac{1}{\rho}$$

where r is the specific refraction, n is refractive index and ρ is the density of liquid.
Molar refraction of solvent and solute is determined from the equation.

$$Rm = \frac{n^2 - 1}{n^2 + 2} \times \frac{M}{\rho}$$

Where M is molecular of the substance.
Molar refraction of a homogeneous mixture solution is the sum of the molar refractions of its constituents.

$$[R]_{mix} = X_1 [R_1] + X_2 [R_2]$$

Where X_1 and X_2 are the mole fractions and $[R_1]$ and $[R_2]$ are molar refractions of the component. The molar refraction of the mixture can also be determined by the formula.

$$[R]_{mix} = \frac{n^2_{mix} - 1}{n^2_{mix} + 2} \times \frac{X_1 M_1 + X_2 M_2}{\rho}$$

Similarly Rm can be calculated by using the equation.

$$Rm = \frac{}{3} \pi N \alpha$$

$$\alpha = \frac{3}{4} \times \frac{Rm}{\pi N}$$

where α is polarizability constant, N is avagodras number.

The solutions of different concentrations were prepared for compound in DMF and the conductance of each solution was measured by using Equip-tronics Conductivity Meter (Model No. 664) having cell constant 0.98 cm^{-1} at 298.15 K. The measured conductance was corrected by subtracting the conductance of pure solvent. Observed conductance and equivalent conductance is shown in table no. 5.

Table no. 1 Refractometry data, Solvent – THF

Sr. No	Molarity	Density ρ	Refractive Index (n)	Specific Refraction (R)	Molar Refraction (Rm)	Polarizability constant A
1	0.01	0.858	1.346	0.2481	11.7668	0.4667×10^{-23}
2	0.005	0.850	1.334	0.2425	11.3433	0.4499×10^{-23}
3	0.0025	0.847	1.322	0.2354	10.9267	0.4333×10^{-23}
4	0.00125	0.834	1.316	0.2350	10.8669	0.4310×10^{-23}

Table no. 2 Refractometry data, Solvent – DMF

Sr. No	Molarity	Density ρ	Refractive Index (n)	Specific Refraction (R)	Molar Refraction (Rm)	Polarizability constant A
1	0.01	0.972	1.360	0.2388	18.4872	0.7266×10^{-23}
2	0.005	0.965	1.348	0.2276	16.8424	0.6864×10^{-23}
3	0.0025	0.958	1.340	0.2183	16.1564	0.6444×10^{-23}
4	0.00125	0.942	1.327	0.2064	15.3478	0.6142×10^{-23}

Table no. 3 Refractometry data, Solvent – DMSO

Sr. No	Molarity	Density ρ	Refractive Index (n)	Specific Refraction (R)	Molar Refraction (Rm)	Polarizability constant A
1	0.01	1.122	1.342	0.1867	14.7836	0.5863×10^{-23}
2	0.005	1.114	1.338	0.1860	14.6314	0.5803×10^{-23}
3	0.0025	1.104	1.325	0.1803	14.1380	0.5607×10^{-23}
4	0.00125	0.992	1.317	0.1782	13.8860	0.5436×10^{-23}

Table no. 4 Refractometry data, Solvent – Ethanol

Sr. No	Molarity	Density ρ	Refractive Index (n)	Specific Refraction (R)	Molar Refraction (Rm)	Polarizability constant A
1	0.01	0.924	1.388	0.2552	18.9070	0.74980×10^{-23}
2	0.005	0.916	1.376	0.2504	18.3221	0.7266×10^{-23}
3	0.0025	0.909	1.368	0.2475	17.9707	0.7127×10^{-23}
4	0.00125	0.901	1.352	0.2399	17.3590	0.6885×10^{-23}

Table no. 5- The Conductance (k) and equivalent conductance (λC) of compound in DMF at 308.15 K.

Conc.	**Observed conductance 10^5 (mho)**	**λ_C mho. Cm^2.equi.$^{-1}$**
0.00	2.84	-
0.001	2.96	1.176
0.002	3.02	0.882
0.004	3.08	0.588
0.006	3.12	0.457
0.008	3.18	0.416
0.01	3.26	0.411
0.02	3.40	0.274
0.04	3.58	0.181
0.06	3.68	0.137
0.08	3.80	0.117
0.10	3.88	0.101

Result & Discussion

From the table no. 1,2,3 & 4 it is observed that specific refraction, molar refraction and molar porazability constant decreases with decrease in concentration of solute. The refractive index was maximum in ethanol and it was lowest in THF. The measured conductance (k) of each solution after correction was used to determine the specific conductance (κ), which is then used for the calculation of equivalent conductance (λ_c). The equations used for calculating specific conductance (κ) and equivalent conductance (λ_c) are:

$$\kappa = k\,\theta$$

$$\lambda_c = 1000\,\frac{\kappa}{C}$$

where, θ is the cell constant (= 0.98 cm-1) and c is the concentration (g.equi./lit.) of solution.
It is observed that conductance increases with concentration.

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VISCOSITY BEHAVIOUR OF SUBSTITUTED 1,3,4-THIADIAZOLIDINES IN DIFFERENT PERCENTAGES OF SOLVENT

Jitesh R. Choudhari
Department of Chemistry, Yashwasntrao Chavan Arts and Science College, Mangrulpir Dist. Washim
jrchoudhari@gmail.com

ABSTRACT

The viscosities and densities of 2-Phenylimino-3-cinnamoyl-5-cinnamoylhydrazino-1,3,4-Thiadiazolidine(I), 2-Phenylimino-3-salisyloyl-5-salisyloylhydrazino-1,3,4-Thiadiazolidine(II),2-Phenylimino-3-benzoyl-5-benzoylhydrazino-1,3,4-Thiadiazolidine(III), 2-Phenylimino-3-acetyl-5-acetylhydrazino-1,3,4-Thiadiazolidine(IV), 2-Phenylimino-3-n-butanoyl-5-n-butanoylhydrazino-1,3,4-Thiadiazolidine(V), 2-Phenylimino-3-p-hydroxybenzoyl-5-p-hydroxybenzoyl -1,3,4-Thiadiazolidine(VI) in different percentages of acetone- water, ethanol-water, dioxane-water mixtures have been measured. From the data obtained the relative viscosities have been calculated which are used to measure the molecular interactions in the solutions and to study the viscosity behavior of substituted 1,3,4-Thiadiazolidines on the basis of the presence of different substituents.

Keywords: *Viscosity, Substituted 1,3,4-Thiadiazolidines*

Introduction

The present work deals with the study of molecular interactions of substituted 1,3,4-Thiadiazolidines (I-IV) in different percentages of acetone-water, ethanol-water and dioxane-water mixtures at (29±0.1°c) and their viscosity behavior on the basis of presence of different substituents. Viscosity is one of the important properties of liquids. It implies resistance to flow. Viscosity measurements, like other transport properties of electrolytes, provides useful information about solute-solute and solute-solvent interactions in non aqueous and aqueous solutions[1-3]. Molecular interactions of binary mixtures have also been studied by many workers[4-7]. Many attempts have been made to study viscosities of binary liquid mixtures, but no satisfactory results seems to have been reported[8].

Experimental

Synthesis of 2-Phenylimino-3-cinnamoyl-5-cinnamoylhydrazino-1,3,4-Thiadiazolidine(I), 2-Phenylimino-3-salisyloyl-5-salisyloylhydrazino-1,3,4-Thiadiazolidine(II), 2-Phenylimino-3-benzoyl-5-benzoylhydrazino-1,3,4-Thiadiazolidine(III), 2-Phenylimino-3-acetyl-5-acetylhydrazino-1,3,4-Thiadiazolidine(IV), 2-Phenylimino-3-n-butanoyl-5-n-butanoylhydrazino-1,3,4-Thiadiazolidine(V) and 2-Phenylimino-3-p-hydroxybenzoyl-5- p-hydroxybenzoyl -1,3,4-Thiadiazolidine(VI) have been carried out by the interaction of bis-1,5-aroyl/acyl-3-thiocarbohydrazides with N-phenylisocyanodichloride. The product obtained on basification with dilute ammonium hydroxide afforded free base. The structure of these compounds were established on the basis of elemental analysis, equivalent weight determination, IR and PMR spectral data. The solvents used were of AR grade and doubly distilled water was used. Weighing was made on Shimadzu Japan BL-2204 balance (±0.001g). The densities of ligand solutions and solvents were determined by a bicapillary pyknometer (±0.2%). The viscosities were measured by means Ostwald's viscometer (±0.11% $Kgm^{-1}s^{-1}$) which was kept in equilibrium Elite thermostatic water bath (±0.1°c). The solutions were prepared in different percentages (70,80,90 and 100%) of acetone-water, ethanol-water and dioxane-water mixtures. For each measurement sufficient time allowed to maintain constant temperature by attaining thermal equilibrium in a thermostat.

Results and Discussion

The relative viscosity of each of the ligand solutions is determined by using the impirical formula,

$$n_r = d_s \times t_s / d_b \times t_b$$

Where n_r indicates relative viscosity of ligand solution, d_s is density of ligand solution and d_b is density of respective solvent; t_s is time of flow for ligand solution and t_b is time of flow for respective solvent.

The relative viscosity and density data for ternary mixtures in different percentages of solvents are obtained in Table 1 to 3. It can be seen that relative viscosity increases with decrease in the percentage of acetone, ethanol and dioxane, which may be due to increase in molecular interactions. Also change in the structure of solvent or solution as a result of hydrogen bond formation or disruption leads to decrease or increase in interactions. Solutes can occupy interstitial spaces in the solvent. The increase in viscosity arises from the fact that solute particles lie across the fluid stream lines and are subjected to torsional force[9,10].

Acetone-Water > Ethanol-Water > Dioxane-Water

This may be due to the effect of greater polarity of acetone as compared to the less polar ethanol and non-polar dioxane solvent. The polar compounds are having more viscosity than non-polar compounds. In polar compounds cohesive forces attributed to the presence of different types of intermolecular forces which results increase in viscosity.

It can be seen from Tables 1 to 3 that the order of relative viscosities in compounds is I>VI>II > III>V>IV.

Also as molecular weight increases, viscosity increases and is related to density. Molecular weight is directly proportional to density as the density increases distance between ligand molecules decreases. That result cohesive forces between molecules increases and viscosity of liquid increases.

Table-1

Viscosity Data for Substituted 1,3,4-Thiadiazolidines(I-VI)

Acetone-Water Mixtures

Compounds/Relative viscosity (n_r) at (29 ± 0.1°c).						
Percentage of acetone	I	II	III	IV	V	VI
70	1.2832	1.2510	1.2450	1.2359	1.2401	1.2622
80	1.2411	1.2271	1.2162	1.2122	1.2143	1.2301
90	1.1923	1.1729	1.1688	1.1563	1.1621	1.1810
100	1.1124	1.1032	1.1029	1.0078	1.1011	1.1089

Table-2

Viscosity Data for Substituted 1,3,4-Thiadiazolidines(I-VI)

Ethanol-Water Mixtures

Compounds/Relative viscosity (n_r) at (29 ± 0.1°c).						
Percentage of ethanol	I	II	III	IV	V	VI
70	1.1992	1.1747	1.1620	1.1428	1.1552	1.1821
80	1.1625	1.1466	1.1331	1.1160	1.1288	1.1586
90	1.1411	1.1292	1.1142	1.1011	1.1056	1.1326
100	1.1185	1.1021	1.0120	1.0023	1.0092	1.1057

Table-3
Viscosity Data for Substituted 1,3,4-Thiadiazolidines(I-VI)
Dioxane-Water Mixtures

Compounds/Relative viscosity (n_r) at (29 ± 0.1°c).						
Percentage of dioxane	I	II	III	IV	V	VI
70	1.1420	1.1246	1.1121	1.0910	1.1082	1.1382
80	1.1289	1.1031	1.1005	1.0721	1.0926	1.1154
90	1.1025	1.0825	1.0611	1.0084	1.0211	1.1008
100	1.0084	1.0007	0.9652	0.7179	0.8910	1.0021

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ANTIMICROBIAL ACTIVITY OF SILVER NANOPARTICLES BY USING WILD VEGETABLE *LAUNAEA PROCUMBENS*

S.K. Mengane
Department of Botany, M.H.Shinde Mahavidyalaya, Tisangi, Kolhapur, India
Corresponding author: skmengane@gmail.com

ABSTRACT

The present investigation focuses the use of aqueous extract of Launeaprocumbensfor producing silver nanoparticles (AgNPs) from silver nitrate aqueous solution.The presence of phytochemicals such as alkaloid, flavonoides, terpenoids,carbohydrates and proteins in the leaf extract of L. procumbens serve as effective reducing and cappingagents for converting silver nitrate to silver nanoparticles. The nanoparticles werecharacterized by UV (Ultra violet)spectorphotometry, FT-IR spectroscopy (Fourier Transform Infrared spectroscopy), and TEM (Transmission Electron Microscope). The appearance of SPR peak at 446 nm by UV visible spectorphotometry. The size of prepared AgNPs is in the range of 30 to 40 nm. FTIR confirmed the presence of flavonoids, terpenoids, polyphenols as biomolecules in the plant extract of L. procumbens, act as reducing and capping agent in the synthesis of AgNPs. Moreover,the antifungal activity of synthesized AgNPs was studied by using food poisoning technique. The synthesized AgNPs are observed to have a good antifungal activityagainst plant pathogenic fungi Fusariumoxysporum andMacrophominaphaseolina.

Keywords: *Nanoparticles,Launeaprocumbens, UV- visible, FTIR, TEM, antifungal activity.*

Introduction

The current research endeavors are mainly centered on metal nanoparticles due to their scarce properties such as electronic, optical, and magnetic; which often differentiate it from their bulk counterparts. Enormous progress have been achieved, to date, in metal nanoparticles synthesis; wherein, nanoparticles of palladium (Pd)[1], silver (Ag)[2], magnesium (Mg)[3], gold (Au)[4], Zinc (Zn)[5] have been prepared with different morphologies. Among these, AgNPs could especially be promising due to their features such as excellent electrical performance, chemical inertness, thermal stability, antimicrobial activities, non-toxic and environmentally safe[6]. Patil et al. reviewed synthesis of metal nanoparticles using herbal extracts [7].

As a consequence, the synthesis protocol for AgNPs nanoparticles that rigorously control the nano-size and morphological features of colloidal AgNPs are significant. Among diverse synthetic techniques solution-based protocol succeed towardspreparation of monodisperse colloidal nanoparticles with controllable shapes and sizes. Various synthetic parameters have been found such as metal precursor, reducing agent, capping agent, reaction time, reaction temperature and pressure. In this regards, since last four decades researchers have been reported many techniques for synthesis of AgNPs, wherein all the above mentioned reaction parameters were screened.

Although the current strategies suffers with some drawbacks such as use of toxic chemicals, high temperature, high pressure and production of hazardous by-products and waste etc. Eventually, it is necessary to search an alternative technique that overcomes above mentioned limitations in the synthesis of silver nanoparticles.

In this concern, we describe a novel and green protocol that provide important new insights into the synthesis of colloidal AgNPs using plant extract. This suggested technique gives bypass to hazardous and expensive chemicals and offer size controlled AgNPs at mild reaction conditions, which is inexpensive, easy, simple, rapid, quick, simple scale up, easy to control and less energy extensive process. In typical synthesis protocol plant extract of *L. procumbens*leaves possessing rich concentration of biomolecules such as vitamins, polysaccharides, proteins, amino acids, enzymes, flavonoids, triterpenoids, polyphenols and organic acids will be used as a reducing as well as capping agent. *L.procumbens* is widely used as wild vegetable

by many rural peoples.The synthesized silver nanoparticles were also characterized by UV-Vis spectrophotometry, FTIR spectroscopy and TEM. The reaction progress has been analyzed using FTIR that revealed the role of *L. procumbens*leaves extract as a reducing agent in nanoparticles synthesis. The size of prepared AgNPs is in the range of 30 to 40 nm, which determined by transmission electron microscope (TEM). The AgNPs synthesized by *L. procumbens*leaves extract is a green solution with potent antifungal activities against plant pathogenic fungi *Fusariumoxysporum* and *Macrophominaphaseolina.*

2. Materials and methods

2.1. Preparation of leaf extract:

All the chemicals were obtained from Hi Media Laboratories Pvt. Limited, Mumbai, India. The fresh and healthy leaves of *L. procumbens*(Figure 1)were collected from Tisangi, Kolhapur, India, dried and powdered. 20 g of powder was taken and mixed with 200 ml of Milli Q water and kept in boiling water bath at 60^0C for 10 min. The extracts were filtered and stored in refrigerator at 4^0C for further studies.

2.2. Biosynthesis of silver nanoparticles by *L. procumbens*

For the biosynthesis AgNPs, 10 ml of plant extract is mixed with 90 ml of $AgNO_3$ solution (5 mM/ml) and incubated at 28^0C for 12 h. The reaction mixture was kept into dark room condition until the color change was arisen from light green to dark brown (Fig. 2 inset). The solution of AgNPs was later centrifuged at 15,000 rpm for 25 min to collect the AgNPs.

2.3. Characterization of AgNPs

The biosynthesized AgNPs were characterized by using UV–Vis Spectrophotometer (Elico, India) at 300–700 nm range. Fourier Transform Infrared Spectrometer spectra were recorded under identical conditions in the 4000-400 cm^{-1} region using Fourier Transform Infrared Spectrometer (spectrum RX-I, FT-IR system, Perkineliner model). The particle size wasmeasured by Transmission electron microscopy on a JEOL 1200EX instrument at a voltage of 200 kV.

2.4. Antifungal activity of AgNPs

The antifungal potential of the biosynthesizedAgNPs was investigated by food poisoning method[8]. Potato dextrose agar (PDA) medium was used in the study. Five mL of the AgNPs at various concentrations(50 and 100 mg/mL in sterile distilled water) was added into 5 mL of the autoclavedPotato dextrose agar (PDA) media before it solidified. The mixture was poured into the sterile 8 cm petridishes.The medium with inoculum disc of each fungus but without silver nanoparticles served as control. The petri dishes were then incubated in the dark at 25^0C for 48 hours, after which each separate the petri dishes were inoculated with agar plugs of the growing fungal mycelia of *Fusariumoxysporum* and*Macrophominaphaseolina* (5 mm in diameter). The plates were incubated in the dark at 25^0C for further five days and the radial growth of fungalmycelia was calculated. Theinhibition potency of AgNPs towards each fungal strain was calculated using the following equation: Inhibition rate (per cent) R - r / R x 100 where R is the radial growth of fungal mycelia in the negative control (mm) and r is the radial growth of fungal mycelia challengedwith the AgNPs.

3. Results and discussion

3.1. Characterization of the bio synthesized AgNPs

3.1.1. UV-vis spectroscopy

In the present study the formation of silver nanoparticles was initially confirmed using UV–vis spectroscopy by measuring surface plasmon resonance peaks. On adding the leaf extract of *Launaeaprocumbens*to the silver nitrate solution, the solution becomes dark brown in colour(Fig. 2 inset).It shows that the reduction of silver ions and formation of stable NPs. The appearance of SPR peak at 446 nm (Figure 2) provides a convenient spectroscopic signature for the formation of silver nanoparticles[9].The presence of abundant phytochemicals such as alkaloids, flavonoids, saponins, terpenoids, steroids and proteins in the leaf extract of *Launaeaprocumbens*appears to be responsible for accelerating the reduction process and capping of AgNPs synthesis.

3.1.2. Transmission electron microscopy analysis

Microscopic features of the AgNPs, including morphology and particle size, were assessed through TEM analysis. As depicted by the TEM image, the particles were mostly spherical in shape with a diameter ranging from 30 to 40 nm (Figure 3). The particle size of plant mediated AgNPs synthesized from *Launaeaprocumbens*is in the range of 20-50 nm[10].

3.1.3. FT-IR analysis

The FT-IR analysis was carried out to identify the possible biomolecules responsible for the reduction of AgNPsand capping of the bioreduced Ag nanoparticles synthesized by the leaves extract[21].The spectra showed absorption peaks at 3463 cm^{-1}, 1624 cm^{-1}, 1070 $cm^{-1}$and 1038 cm^{-1}in the 4000–500 cm^{-1} regionindicating the presence of capping and stabilizing agents respectively(fig. 4). The role of these main biomolecules in stability/capping of AgNPswas found in many papers[11]. The peak 3463 cm^{-1} indicated phenolic or amide N-H, O-H stretching peak was observed at 1624 $cm^{-1}$and last important peak at 1038 cm^{-1} characteristics to terpenoids (C-O-C) groups present in the plant extract are observed in Figure 6[12,13,14]. Major functional groups such as C-O, N-H and C-N groups in different chemical classes such as flavonoids, terpenoids, polyphenols, proteins, and pigments present in the plant extract might be responsible for bioreduction of Ag+ to AgNPs[15].

3.1.4. Antifungal activity of AgNPs

Silver nanoparticles have been using in many industries suchas the health, pharmaceuticals, water treatment, paint, food storagebecause of its antimicrobial properties[15]. In the present study, theantifungal activity of bio synthesized AgNPs was tested against twoplant pathogens *Fusariumoxysporum* and *Macrophominaphaseolina.*From the results of the antifungal activity tests, it can be inferred that the size of the nanoparticles clearly influenced their antifungal activity. According to different authors[16,17,18]silver nanoparticles have the ability to anchor the microbial cell wall and then penetrate it, thereby causing structural changes that affect the permeability of the cell membrane and cause cell death. The size and surface area of the nanoparticles are closely related because a decreasing size increases the relative surface area of AgNPs, leaving a greater number of atoms exposed on the surface, which will be available to redox reactions, photochemical reactions and physicochemical interactions with cells.The inhibition of the mycelia growth by the AgNPs at various concentrations were daily evaluatedand the radial growth was measured in comparison to the control. It was found that AgNPs synthesized by *L.procumbens* inhibit growth of both *Fusariumoxysporum* and*Macrophominaphaseolina*when compared with control (Table 1.)

Fig.1. *Launaea procumbens*

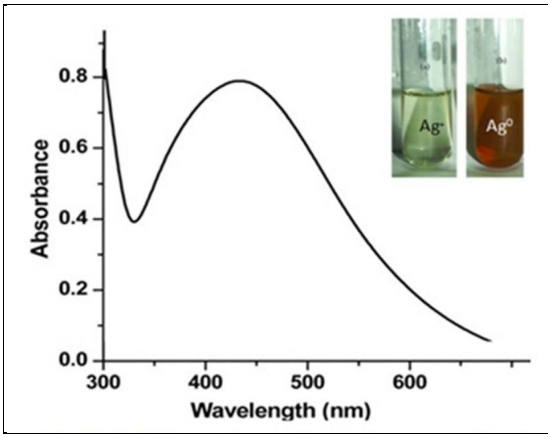

Fig. 2. UV visible spectrum with reaction progress (inset) observed by colour change

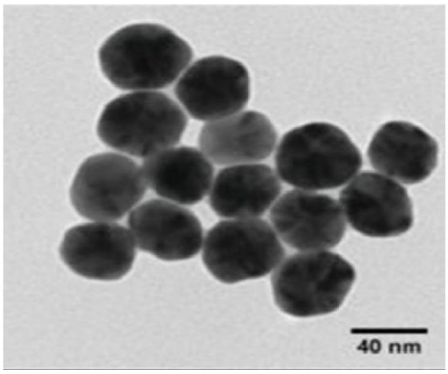

Fig. 3.Typical TEM image of silver nanoparticle synthesized by *L.procumbens*

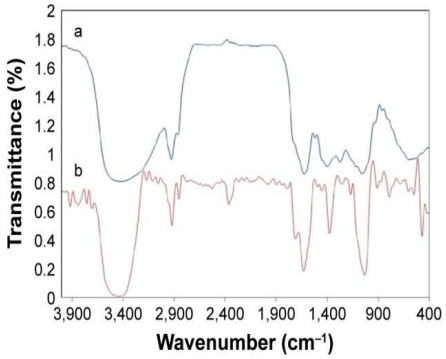

Fig.4. FTIR spectra of: (a)*Launaeaprocumbens*leaf extract (b) silver nanoparticles

Table No.1:Effect of silver nanoparticles on plant pathogens

Sr.No	Component	Zone of Inhibition (mm) Food poisoning method			
		Fusariumoxysporum		*Macrophominaphaseolina*	
		(50mg/ml Ag NPs)	(100 mg/ml Ag NPs)	(50mg/ml Ag NPs)	(100 mg/ml Ag NPs)
1.	Silver nanoparticles	38.00	15.00	20.00	10.00
2.	Control	90.00	90.00	90.00	90.00

Conclusion

One pot green synthesis of silver nanoparticle using *L.procumbens*leaves extract has been reported. Silver nanoparticle has beensuccessfully synthesized by this simple, fast, cost effective, environmentfriendly, efficient method supported by the physicochemicalcharacterization viz. TEM. FTIR and UV-Vis analysis confirmed the reduction of Ag(+) ions to Ag(0) which is supposedthrough the plant extract.The phytochemical like flavonoids, terpenoids, polyphenolsinvestigated in leaf extract acting as the reducing and capping agents. The synthesizedsilver nanoparticles showed efficient antifungal activities.

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AN EFFECTIVE ONE-POT SYNTHESIS OF INDENO[1,2-B]QUINOLINE-7-ONES CATALYZED BY AMMONIUM METAVANADATE AND ITS ANTICANCER EVALUATION

S.S. Idhole[a], M.S. More[a], P.S. Khursade[b], S.C. Jadhavar[a] and S.R. Bhusare[a]*

[a]Department of Chemistry, Dnyanopasak College, Parbhani, MS, India.

[b]Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

bhusare71@gmail.com

ABSTRACT

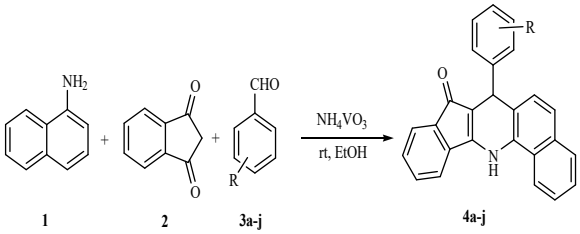
Ammonium metavanadate has been used as an efficient catalyst for the synthesis of indeno[1,2-b]quinoline-7-ones via a one-pot three component reaction of aromatic aldehydes, 1-naphthylamine and 1,3-indandione in solvent ethanol. The mild reaction conditions, environmentally benign, easy experimental workup and excellent yields of desired products are some of the delightful features of the method.

Keywords: *One-pot synthesis, Ammonium metavanadate, Indeno[1,2-b]quinline-7-ones, 1,3-Indandione, 1-Naphthylamine.*

Introduction

Multi-component reactions [1] involving domino processes, [2] combining at least three different substrates in a one-pot operation, have emerged as powerful tools and complementary substrate-directed synthetic alternatives to other well-known methods [3-6]. Quinoline derivatives are reported to possess interesting pharmacological activities such as antiplasmodial, intrinsic, cytotoxic, functional, antibacterial, antiproliferative, antimalarial, and anti-cancer activities [7-8]. Therefore, various methods such as the Skraup, Doebner-von Miller, Friedlander, and Combes procedures have been developed for the synthesis of quinoline derivatives [9-10].

Indeno-quinolines are one of the most important groups of quinoline derivatives that have a wide range of medicinal activities such as anticancer [11], anti-inflammatory, anti-tumour [12] and inhibitor of steroid reductase. Therefore, much effort has been focused on the synthesis of indeno-quinoline skeletons from new, simple and direct methods [13-20]. Most of the literature reports require refluxing systems, organic solvents, expensive catalysts, multiple steps and tedious work-up procedures [14]. Herein we report successful method for synthesis of indeno quinolines in excellent yields under ambient temperature condition using ammonium metavanadate as catalyst (**Scheme 1**).



Scheme 1

Experimental

All solvents were employed as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (100-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-300 MHz spectrometer in $CDCl_3$ solvent.

General procedure for synthesis of indeno[1,2-b]quinoline-7-ones:

A mixture of aromatic aldehyde (1 mmol), 1,3-indandione (1 mmol), 1-naphthylamine (1 mmol), NH_4VO_3 (0.2 mmol), and ethyl alcohol (10 mL) was added to a round-bottomed flask. The reaction mixture was stirred at room temperature for appropriate time (Table 2).

After the completion of reaction indicated by TLC, the resulting solid was collected by filtration and dissolved in 20 ml dichloromethane and combined organic layer was dried over anhydrous calcium chloride and filtered. Evaporation of the solvent afforded crude product which was purified by column chromatography with pet ether and ethyl acetate (4:1) to give pure product.

7-(4-Chlorophenyl)-8,13-dihydro-7-*H* -benzo[h]indeno[1,2-b]quinolin-8-one (4a):

IR (KBr): 1708, 1607, 1518, 1089. cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H, NH), 7.68-7.87 (m, 8H, Ar-H), 7.38-7.47 (m, 2H, Ar-H), 6.93-7.29 (m, 4H, Ar-H), 5.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.8, 112.7, 121.4, 121.5, 121.9, 123.3, 124.4, 124.9, 126.6, 127.8, 128.6, 129.5, 130.7, 131.0, 131.8, 134.0, 135.1, 135.9, 137.0, 142.4, 143.7, 148.9, 158.9, 190.8.

7-(4-Fluorophenyl)-8,13-dihydro-7-*H*-benzo[h]indeno[1,2- b]quinolin-8-one (4c):

IR (KBr): 1710, 1605, 1572, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H, NH), 7.69-7.88 (m, 10H, Ar-H), 7.20-7.30 (m, 2H, Ar-H), 6.71-6.88 (m, 2H, Ar-H), 5.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.1, 105.4, 115.3, 115.6, 121.6, 123.9, 125.2, 125.9, 127.4, 127.8, 128.0, 129.5, 131.4, 131.5, 131.7, 132.0, 134.6, 135.4, 137.1, 142.1, 146.5, 153.5, 162.3, 189.4.

Results and Discussion

Herein an effective method was developed for the synthesis of indeno[1,2-b]quinoline-7-ones catalyzed by ammonium metavanadate at ambient temperature. Initially for optimization study, we employed different solvent for model reaction of 1,3-indanedione, 1-naphthyl amine and 4-chloro benzaldehyde in presence of 10 mol % ammonium metavanadate as catalyst at room temperature. In the solvent acetonitrile, 54 % product yield is obtained in 9 hours reaction time (Table 1, Entry 1). The reaction in water solvent required 15 hrs for completion with 39 % product yield (Table 1, Entry 2). Furthermore in solvent dichloromethane, reaction offered 32 % yield with extended reaction time (Table1, Entries 3). The suitable results were observed in solvent methanol and ethanol, the consequent product was gained in 68 and 89 % yield respectively (Table 1, Entries 4 and 5 respectively). So considering ethanol as best solvent for the reaction, subsequently we scrutinized the influence of catalyst concentration on the model reaction with ethanol as solvent. At catalyst concentration of 5 mol %, the reaction afforded 72 % yield of the product (Table 1, Entry 6). Further increase in catalyst concentration up to 15 mol % does not show any improvement in the product yield (Table 1, Entry 7).

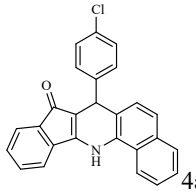
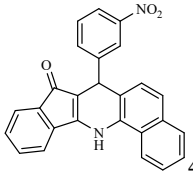
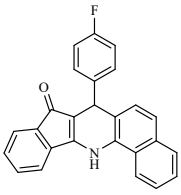
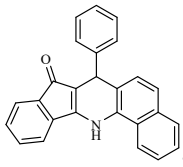
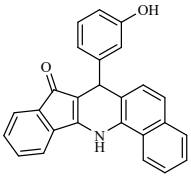
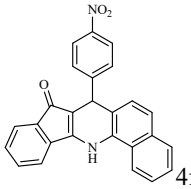
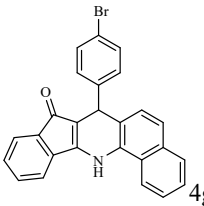
Table 1. The screening of solvent and catalytic loading on the synthesis of indeno[1,2-b] quinoline-7-ones

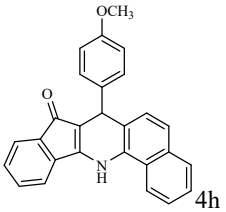
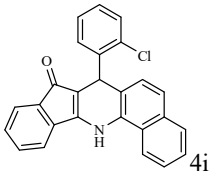
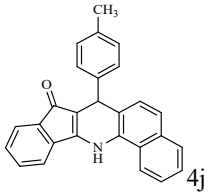
Entry	Solvent	NH_4VO_3 (mol %)	Time(h)	Yield[a] (%)
1	Acetonitrile	10	9	54
2	Water	10	15	39
3	DCM	10	17	32
4	Methanol	10	6	68
5	Ethanol	10	3	89
6	Ethanol	5	4	72
7	Ethanol	15	2.5	87

[a]Isolated yield

The ultimate result for the reaction was observed at the catalyst concentration of 10 mol% of ammonium metavanadate in ethyl alcohol. The reaction was accomplished in 3 hours and offered the product in excellent yield of 89% (Table 1, Entry 5).

Table 2: An one-pot synthesis of indeno[1,2-b]quinoline-7-ones

Entry	R	Products (4a-j)	Time (h)	Yield[a] (%)
1	4-Cl	 4a	3.00	89
2	3-NO_2	 4b	3.30	91
3	4-F	 4c	3.00	87
4	-H	 4d	5.00	84
5	3-OH	 4e	4.30	86
6	4-NO_2	 4f	3.30	89
7	4-Br	 4g	3.00	90

8	4-OCH_3	 4h	4.00	88
9	2-Cl	 4i	3.30	89
10	4-CH_3	 4j	4.30	88

[a]Isolated yield

So the using this optimized reaction condition, we used a different aromatic aldehyde for the synthesis of corresponding indeno[1,2-b]quinoline-7-one derivatives. We observed that all products were gained with good to excellent yields (Table 2, Entries 1-10). The reaction proceeded smoothly with aromatic aldehyde having electron-withdrawing or electron-releasing substituents.

Anticancer Activity
Material and methods
In vitro MTT assay for anticancer activity

Quinoline derivatives are known to having various biological activities particularly anticancer activity. To evaluate the biological activity of synthesized compounds we have performed *in vitro* anticancer activity against MCF7 (human breast cancer) which is determined by MTT MTT (3-(4, 5-dimethyl thiazol-2yl)-2, 5-diphenyl tetrazolium bromide) assay, as described by Florento L *et al.* [21] with slight modification. To the start with 1×10^5 cells/mL cells were seeded at in 96 well microtiter plates and supplemented with Minimum Essential Medium with fetal bovine serum and incubated overnight. All the compounds were dissolved in DMSO to get final concentration of 0.1M and were serially diluted with complete medium to get the test concentration of 0.001, 0.01, 0.1, 1.0 and 10uM. The 96 well plate seeded with MCF-7 breast cancer cells and treated with different concentrations of the test compounds incubated for 96 hours and temperature of 37°C with 5% CO_2 concentration to maintain pH of the system. Thereafter the cells were treated with MTT reagent and incubated further for 4 hours. Supernatant from each well containing medium and MTT were removed carefully and the dark blue formazan product formed by the cells were dissolved in 100ul of DMSO. Absorbance was read at 570nm by 96 well plate reader to determine the cell viability. Percentage inhibitions were calculated using following formula and plotted against the concentrations used to calculate the IC_{50} values.

$$\%\ \textbf{cell inhibition} = \frac{(\textbf{OD control} - \textbf{OD treated})}{\textbf{OD control}} \times \mathbf{100}$$

Results

Production of mitochondrial enzyme succinate dehydrogenases the characteristics of living cell which can be quantify by using MMT assay. This enzyme reduces the pale-yellow colored MTT in to dark blue formazan product and can be measured by colorimetric method. The number of viable cells present is proportional to amount of blue formazan production. Here we have determined antiproliferative activity of all synthesized compound against the MCF7 cells using MTT assay. Standard anticancer drug Adriamycin was used as positive control. The results indicate that all the compound possesses shows potent amount of anti-proliferative activity against MCF7 cells with IC50 value varies from high of 18 uM to as low as 1uM in case of compound 4j and 4a respectively Table No 3. From the results it was apparent that compounds 4a with IC_{50} values of 1.01uM and 4c with IC_{50} values of 1uM 3.07 are most potent compound against the MCF7 cell line when compared to other synthesized compound. The results also indicate that with IC_{50} values of 17.25uM the nascent Quinoline compound 4d without any functional group also shows anticancer activity.

Table 3: IC50 values for synthesized derivatives against cell line MCF7.

Drug Concentration(mg/ml) / Compounds	0.001	0.01	0.1	1	10	IC-50 (uM)
4a	4.59	7.39	12.28	48.21	98.59	1.01
4b	1.05	3.28	15.04	24.36	39.35	12.04
4c	4.59	7.39	12.28	16.12	98.17	3.07
4d	1.72	2.98	8.65	12.58	27.92	17.25
4e	1.85	3.56	10.56	23.24	34.25	13.76
4f	2.11	6.35	21.62	32.58	68.95	6.97
4g	2.02	6.56	13.58	21.02	33.15	14.26
4h	1.98	7.01	13.20	24.25	33.02	14.19
4i	1.15	6.95	14.35	23.64	34.06	13.80
4j	1.25	3.01	11.2	19.04	25.89	18.10
ADR	13.42	27.36	49.64	82.49	96.71	0.57

Conclusion

In conclusion, we have developed a convenient one-pot method for the synthesis of indeno[1,2-b]quinoline-7-one derivatives. The satisfying features of this protocol are easy to accomplish, use of environmentally benign reaction solvents and catalyst, mild reaction condition and excellent yields of corresponding derivatives. The initial assays indicated that newly synthesized compounds displayed significantly good inhibition activities against human breast cancer cell (MCF-7), cell lines compared with the control (Adriamysin), which might be developed as novel lead scaffold for potential anticancer agents.

Acknowledgements

We are thankful to Dr. S. S. Kadam, Principal, Dnyanopasak College, Parbhani for providing necessary facilities to the research work. We are also thankful to Vishnu Chemicals Laboratory, Hyderabad for providing spectral data and Deshpande Laboratories Pvt. Ltd., Bhopal, for providing anticancer activity.

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SYNTHESIS, CHARACTERIZATION OF BIODYNAMIC HETEROCYCLIC SYSTEM OF 3-ACETYLCOUMARINS BY KNOEVENAGEL CONDENSATION REACTION AND ACETYLATION OF COUMARINWITHSTUDY OF BIOLOGICAL SCREENING

Dongare G.M.
Department of Chemistry, Shri Shivaji Science College, Amravati, India
infogmdongare@gmail.com

ABSTRACT

Ecofriendly, solventfree,conveniently synthetic procedure adopted to synthesis of substituted 3-acetyl coumarin afforded via Knoevenagel condensation Reaction(KCR).The spontaneous cyclization of 3-methoxy salicyldehyde and 4-diethylaminosalicyldehyde with β–ketoester(ethylacetoester) possessing active methylene group using piperidine in pyridine as a catalystto yield heterocyclic 8-methoxy-3-acetyl--2H-chromen-2-one(HAC)and3-acetyl-7-(diethyl amino)-2H-chromen-2-one (DAC)respectively. Another synthesis bydirect acetylation of 7-hydroxy coumarin and 4-methyl 7-hydroxy coumarin using piperidine in pyridine catalyst to form 7-hydroxy-3-acetyl--2H-chromen-2-one (HAC)and 7-hydroxy-4-methyl-3-acetyl-2H-chromen-2-one (HMAC).These four-product formed with high acceleration reaction rate,high yield shows(solvatochromic)superb optical propertiesand dynamic in biological activities.

Keywords: *Acetyl Coumarin, Knoevenagel condensation reaction, acetylation, Biological Screening.*

Introduction

Coumarins is the vernacular name of the tonka bean (Dipteryxodorata Wild, Fabaceae family) from which coumarin, it was isolated in 1820 (Bruneton,1999). There are four major class of coumarin: the simple coumarins, furanocoumarins, pyranocoumarins and the pyrone-substituted coumarins.The sources of coumarins at high levels in some essential oils in cinnamon bark oil (7,000 ppm), cassia leaf oil (up to 87,300 ppm) and lavender oil. Coumarin isalso found in fruits (e.g. bilberry, cloudberry), green tea and other foods such as chicory (Lake, 1999) [1]The π- expanded coumarin have been used in various research areas due to their unique photophysical properties [2,3]. Thevarious π -expanded coumarins have been prepared and studied past 15 years coumarin derivatives [4]. π- expanded coumarins possessing additional benzene or heterocyclic rings fused in different ways with chromen-2-one, were synthesized for the first time by Pechmann in 1884 [5]and π -expanded chromophores attracted attention due to the natural occurrence of various derivatives especially possessing due to skeleton of benzo[c]coumarin and shifted in the last few years towards cutting-edge optoelectronic applications [6]. The constant demand for synthesis of novel tailor-made functional π-systems, new with reliableaccesses . Diversity-oriented syntheses are highly advantageous for exploring structural and functional characteristics leads to a heterogenic product library [7].The photo physical properties and electronic structure of 2-Substituted 3-ethynylquinoxalines synthesized from electron rich π nucleophiles, oxalyl chloride, terminal alkynes, and 1,2-diaminoarenes. The obtained compounds are highly fluorescent with remarkable emission solvatochromism[8]. A straightforward, regioselective, and step-economical ligand-free palladium-catalysed decarboxylative functionalization of coumarin-3-carboxylic acids is devised. This protocol is compatible with a wide variety of electron-donating and withdrawing substituents and allows for construction of various biologically important π-electron extended coumarins [9], biomedical imaging agents[10,11],potential use as light emitters in organic light-emittingdiodes,therapeutic agents[12]

Fig-1.3D Structure of MAC

Fig-2.3D Structure of DAC

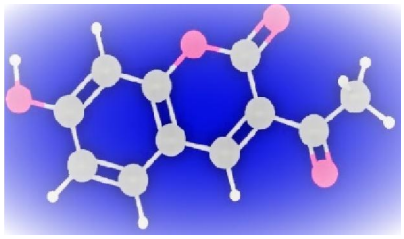


Fig-3.3D Structure of HACFig-3.3D Structure of HMAC

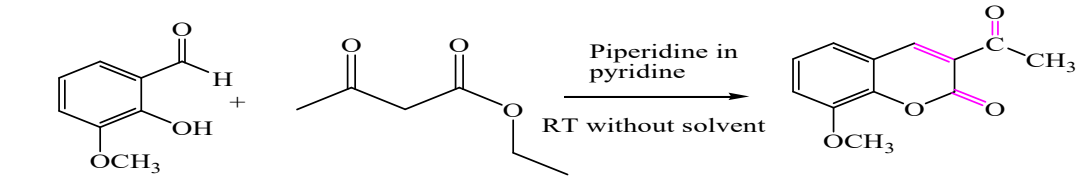
Material and Method:3-methoxy salicyldehyde (9 9%), 4-diethylaminosalicylaldehyde (99%), 7-hydroxycoumarin(98%),7-hydroxy-4-methyl coumarin (97%),ethyl acetoacetate(99+%),Piperidine (99%) chemicals were purchased from Alfa Aesar (Great Britain) and Pyridine (99%) and Acetyl chloride (97%),DMF (97%), DMSO (97%) from S.D fine chemicals AR grade and used without purification. Ethanol, Methanol, Acetone, n-hexane, Ethyl acetate purified on rotavapor.

Measurements: IR spectra recorded on Bruker FT-IR Spectrophotometer Alpha-II having Platinum ATR single reflection diamond ATR moduled (withoutKBr) at Research Lab, Chemistry Department Sant Gadge Baba Amravati University, Amravati(M.S.).Elemental analysis carried out at CHN analyzer at SAIF Chandigarh(Punjab).^{1}H and ^{13}C spectrarecorded on Bruker advance Neo and Mass spectra on mass spectrophotometer at SAIF -Panjab University, Chandigarh. UV-Visible absorbance spectrawererecorded in DMSO solvent on Shimadzu (double beam) at Central Instrumentation Centre (CIC) at Shri Shivaji Science College, Amravati.

Experimental

Synthesis of 3-acetyl coumarin by Knoevenagel Condensation Reaction (KCR):

1. Synthesis of 8-methoxy-3-acetyl--2H-chromen-2-one (MAC):-To the round bottom flask equimolar quantities of 0.0125 mole (1.90 gram)3-methoxy salicylaldehyde thoroughly mixed withethyl acetoacetate 0.0125 mole (1.75 gram) with addition of 0.5 ml piperidine in pyridine (1:1) as a base catalyst. The reaction mixture was stirred for 10 minutes without addition of any solvent. The reaction was monitored by TLC using 7:3 proportions of ethyl acetate and n-hexane as a solvent system. The faint yellow vigorous solutionwas formedand neutralized with 1M HCl. The product was recrystallizedfrom dry ethanol. The yield of pure product 1.52gm (94%).M.P. was determined with open capillary on classic electrical m. p. apparatus. The structure of Coumarins confirmed by CHN analyzer, spectral physical tools, IR, ^{1}H-NMR, ^{13}C-NMR and HR-Mass Spectroscopy.



2-hydroxy -3-methoxy benzadehyde ethylacetoacetate 8-methoxy-3-acetyl -2*H*-chromen-2-one

2. Synthesis of 7-(diethyl amino)3-acetyl - 2H-chromen-2-one (DAC) –

To the round bottom flask equimolar quantities of 0.0125 mole (2.415gram) of 4-diethyl amino salicylaldehyde thoroughly mixed with ethyl acetoacetate 0.0125 mole (1.932ml) with addition of 0.5 ml piperidine in pyridine (1:1) as a base catalyst. The reaction mixture was stirred for 10 minutes without addition of any solvent. The reaction was monitored by TLC using 7:3 proportions of ethyl acetate and n-hexane.The bright yellow vigorous solution was formed and neutralized with 1M HCl. The product was collected by suction filtration recrystallized from dry ethanol. The yield of pure product1.94gm (82.55%).Melting Point was determinedwith open capillary on classic electrical melting point apparatus. The structure of Coumarins confirmed by CHN analyzer, spectral physical tools, IR, ^{1}H-NMR, ^{13}C-NMR and HR-Mass Spectroscopy

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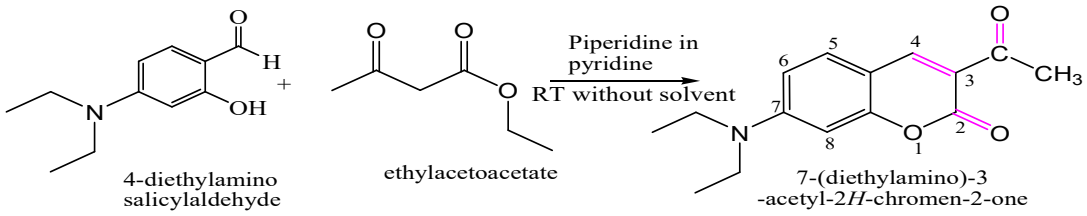
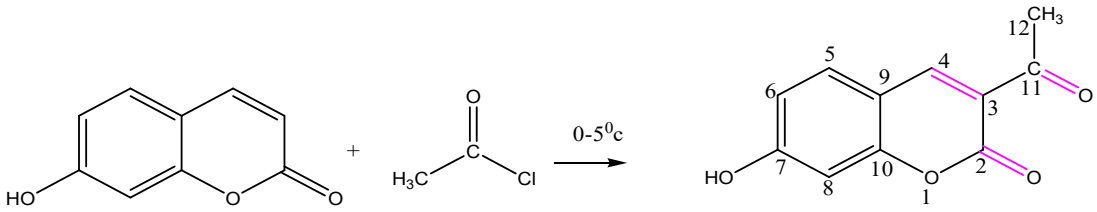


4-diethylamino salicylaldehyde ethylacetoacetate 7-(diethylamino)-3 -acetyl-2*H*-chromen-2-one

3. Synthesisof 7-hydroxy-3-acetyl--2H-chromen-2-one (HAC) by direct acetylation –

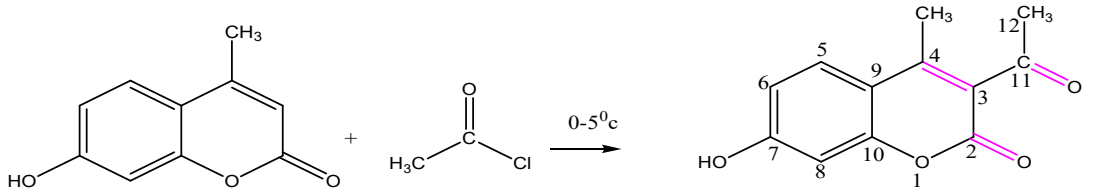
In two necked round bottom flask the equimolar quantities of 0.0125 mole (2.02 gram) of 7-hydroxy coumarin (umbelliferrone) was dissolved in minimum quantity of dry MeOH and added slowly 0.0125mole (0.981ml) acetyl chloride with constant stirring using 0.5 ml piperidine in pyridine (1:1) as a base catalyst. [24].The reaction was exothermic, temperature of reaction mixture maintained between 0-5^{0}c. The reaction mixture was refluxed for 30 minutes. The reaction was monitored by TLC using 70:30 proportion ratio of ethyl acetate and n-hexane. The brown colour product was obtained and neutralized with 1M HCl. The product was collected by suction filtration and recrystallized from dry ethanol to afford the compound.Melting Point was determinedwith open capillary on classic electrical melting point apparatus. The yield of pure product 1.90 gm (%).



7-hydroxy-2*H*-chromen-2-one acetyl chloride 3-acetyl-7-hydroxy-2*H*-chromen-2-one

4. Synthesisof 7-hydroxy-4-methyl-3-acetyl-2H-chromen-2-one (HMAC) by direct acetylation

In two necked round bottom flask the equimolar quantities of 0.0125 mole (2.2 gram) of 7-hydroxy -4-methyl coumarin (hymercromone) was dissolved in minimum quantity of dry MeOH and added slowly 0.0125mole (1.08ml) acetyl chloride with constant stirring using 0.5 ml piperidine in pyridine (1:1) as a base catalyst. The reaction was exothermic, temperature of reaction mixture maintained between 0-5^{0}c. The reaction mixture was refluxed for 30 minutes. The reaction was monitored by TLC using 70:30 proportion ratio of ethyl acetate and n-hexane. The brown colour product was obtained and neutralized with 1M HCl. The product was collected by suction filtration and recrystallized from dry ethanol to afford the compound. The yield of pure product 1.1 gm (67.48%). Melting Point was determinedwith open capillary on classic electrical melting point apparatus. The structure of coumarins confirmed by spectral analytical techniques-Elemental analysis by CHN analyzer, IR, ^{1}H-NMR, ^{13}C-NMR and HR-Mass Spectroscopy.



7-hydroxy-4 methyl-2*H*-chromen-2-one acetyl chloride 7-hydroxy-4 methyl-3-acetyl-2*H*-chromen-2-one

Result and Discussion-Micro analytical data – The synthesised coumarins are coloured and insoluble in water, soluble in ethanol, in DCM, in warm DMF and DMSO. The % values of element are found with agreement with calculatedvalues.The mol.wt calculated using standard procedure as well as m.p.by determined repeatedly in open capillary on melting point apparatus,

Table No.1 Micro analytical data of substituted derivatives of 3-acetyl 2-*H*-chromene-2-one

Coumarin	Mol.Formula	Mol.wt. g.mol^{-1}	Colour	Elemental		Solubility	M.P.^{o}C	Yield %
				Found %	Calc%			
MAC	($C_{12}H_{10}O_4$)	218.20	Yellow	C, 66.0 H,4.61	C,65.98 H,4.51	EtOH,DMF DMSO	178-180	94
DAC	($C_{15}H_{17}O_3N$)	259.30	Bright yellow	C,69.47 H, 6.6 N,5.4	C,69 H,6.3 N,5.1	EtOH, DMF, DMSO	152-154	82.55
HAC	($C_{11}H_8O_4$)	204.17	brown	C, 64.70 H,3.94	C, 64 H,3.50	EtOH,DMF DMSO	170-172	90
HMAC	($C_{12}H_{10}O_4$)	218.20	Light yellow	C, 66.05 H,4.61	C,65 H,3.68	EtOH,DMF DMSO	100-102	67.48

FT-IR Spectra-The IR spectra (table 1) of all coumarins shows characteristics of (ν C=O lactone) at 1727, 1717,1716 cm^{-1}.A high intensity band at C=O of ketone at 1679,1659,1658,1588 cm^{-1} in four type of coumarins.1345(ν C-N amine), the band at 1345 cm^{-1} due to C-N in amine, The band appears of ethylenic C=C at 1449,1381,1564 cm^{-1}.The absorption of (νOH-Phenolic) observed in HAC and HMACat 2960,3120 cm^{-1} characteristics of -OH group in this compound.**FT-IR spectra**of all these given in fig-5,6,7,8

Table No.2-FT-IR spectra(cm^{-1}) data of substituted derivatives of 3-acetyl 2-*H*-chromene-2-one

Coumarins	Vibrational Frequencies data **(cm^{-1})**
MAC	1727 (ν C=O lactone), 1335(ν C=C Ar),1679 (ν C=O ketone), 1564(νC=C Ar), 1469(νC=C ethylenic), 1601(νC-HAr), 1356(νC-C acetyl), 1092(ν C-O methoxy).
DAC	1717(ν C=O lactone), 1659 (ν C=O ketone), 1612 (ν C=C Ar), 1565 (ν C=O Methoxy),1501(ν C=H Ar), 1345(ν C-N amine), 2960(νC-C, CH3-C, SP^3).
HAC	1716 (ν C=O lactone), 2960w(νOH-Phenolic),1658(νC=O ketone),1611(C=C Ar),1564 (νC=C ethylenic), 1501 (νC=H Ar).
HMAC	3120b(νOH-Phenolic),1672 (ν C=O lactone), 1588 (ν C=O ketone),1381 (ν C=C ethylenic).

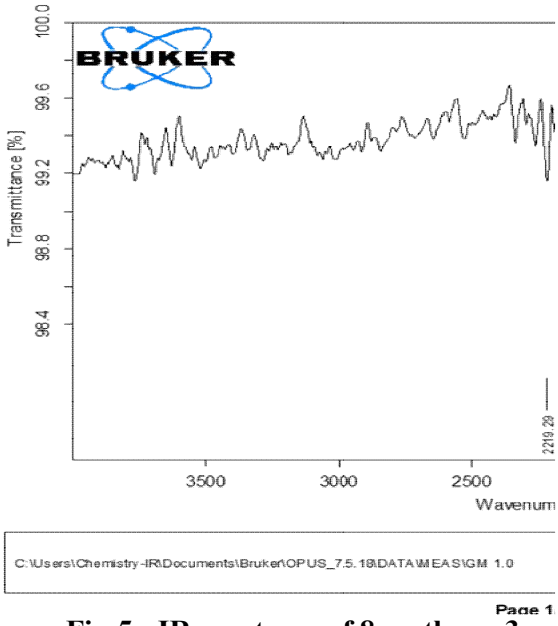


Fig-5 : IR spectrum of 8-methoxy-3-acetyl--2H-chromen-2-one (MAC)

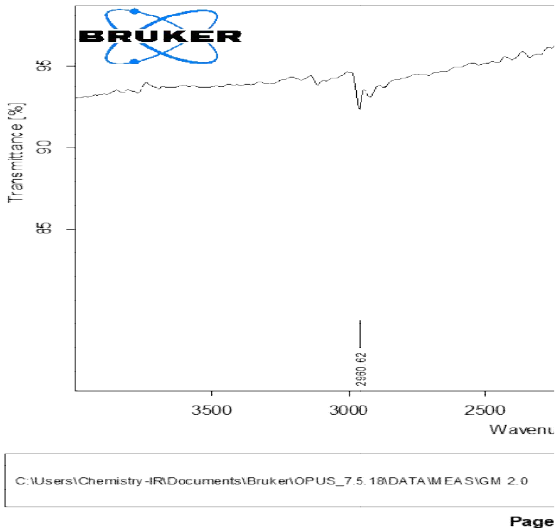


Fig-6 : IR spectrum of 7-(diethyl amino)-3-acetyl-2H-chromen-2-one (DAC)

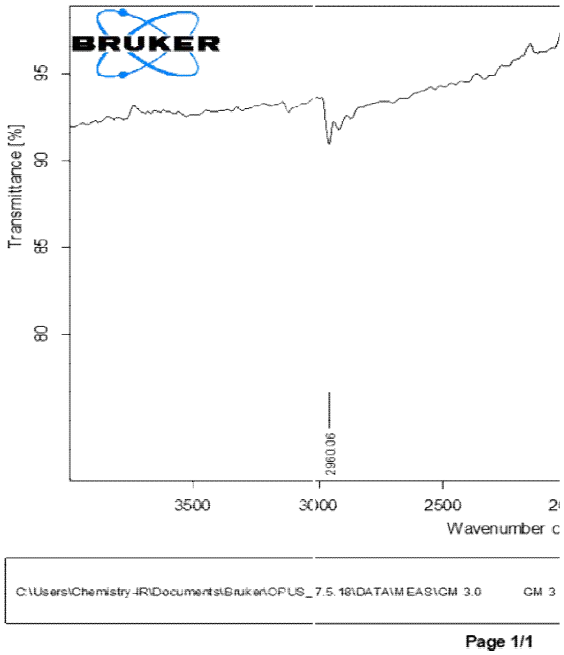


Fig-7: IR spectrum of 7-hydroxy-3-acetyl--2H-chromen-2-one (HAC)

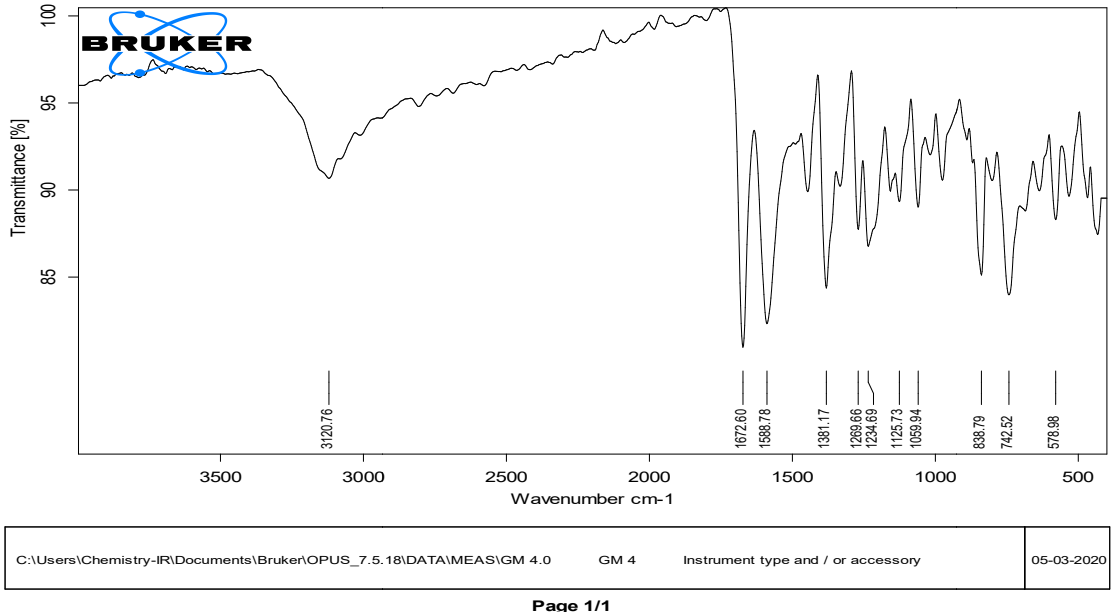


Fig-8: IR spectrum of 7-hydroxy-4methyl-3-acetyl--2H-chromen-2-one (HMAC)

^{1}H spectra-The spectrum of ^{1}H NMR in DMSO-d_6 was recorded at 500MHz in ambient temperature. The coumarins MAC, DAC, HAC, HMAC of sharp singlet at δ 3.31, 2.51, 2.5 suggests the methyl group respectively. The multiplate,d-d and singlet observed shows the aromatic ring current of proton lies at δ 7.30-6.5 in all cases.The phenolic hydrogen clearly represented at high splitting value at δ10.59,10.55 in third and fourth coumarin. The triplet and quartet at 1.15 and 3.51-CH_3 and -CH_2 group in 7-diethylamino-3-acetyl coumarin.The singletsuggested ethylenic proton at 4th position >CH=C<at spectral value of δ8.59, 8.48, 7.59 in all cases.^{1}H spectra of all these given in fig-9, 10, 11, 12.

Table No.3- ^{1}H spectraldata (ppm) of substituted derivatives of 3-acetyl 2-*H*-chromene-2-one

Types of Coumarins	(δ in ppm 500MHz DMSO-d_6)
MAC	3.31(3H, s,-OCH_3),2.57(3H,s,$COCH_3$-H), 8.59(1H,s, ethylenic),7.30(1H,t,Ar-H),7.41,7.47 (2H,dd,Ar-H).
DAC	1.15(6H,t,two of CH_3 in amine), 3.51(4H,q,two of CH_2 in amine),2.51(3H,s,OCH_3-H), 7.66 (1H,d,Ar-H),6.67 (1H,d,Ar-H),6.5 (1H,s,Ar-H),8.48(1H,s,-ethylenic).
HAC	2.52(3H, s, methyl), 7.95(1H,s,ethylinic), 10.59(1H,s,Ar-OH), 6.80 -7.50 (3H,s,d-d,Ar-H).
HMAC	2.37(3H, s,4-methyl), 6.83(1H,d,Ar-H), 6.73(1H,s,Ar-H), 7.5(1H,d,Ar-H),2.5(3H,s, OCH_3), 10.55(1H,s,Ar-OH).

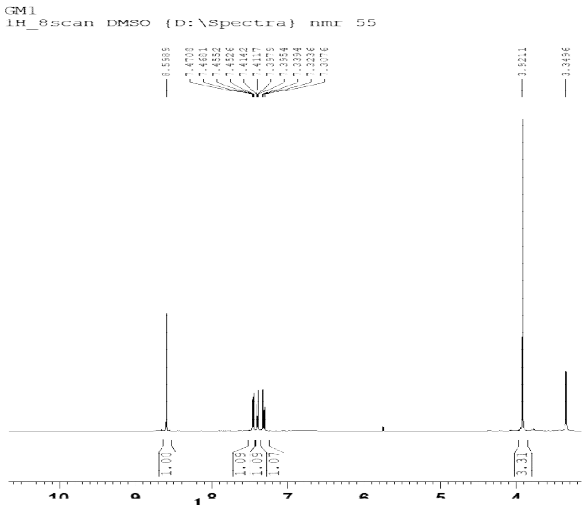


Fig-9.^{1}H spectrum of 8-methoxy-3-acetyl--2H-chromen-2-one (MAC)

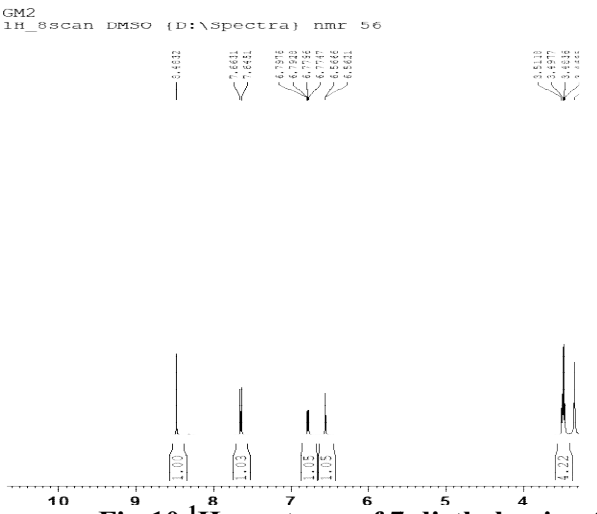


Fig-10.^{1}H spectrum of 7-diethylamino-3-acetyl--2H-chromen-2-one (DAC)

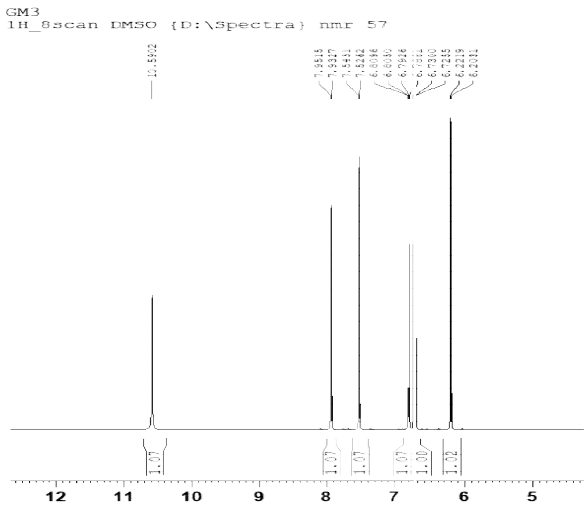


Fig-11: 1H-NMR spectrum of 7-hydroxy-3-acetyl--2H-chromen-2-one (HAC)

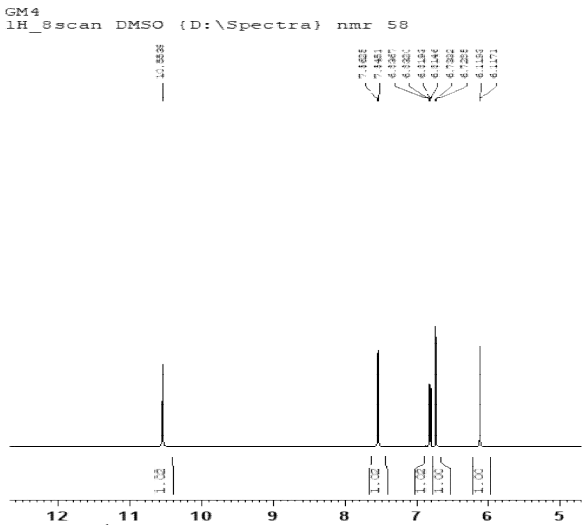
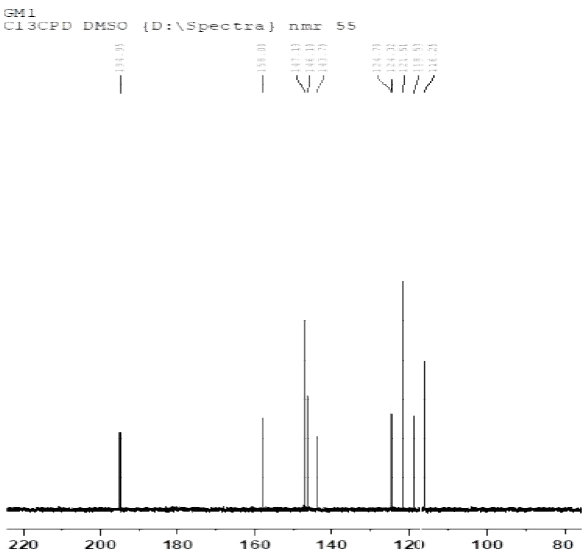


Fig-12: ^{1}H- spectrum 7-hydroxy-4-methyl-3-acetyl-2H-chromen-2-one (HMAC)

Table No.4-^{13}C-NMR spectral data (ppm) of substituted derivatives of 3-acetyl 2-*H*-chromene-2-one

Coumarin Compound		^{13}C(δ in ppm 500MHz DMSO-d_6)
MAC	($C_{12}H_{10}O_4$)	29.90(CH_3),194.95(C=O acetylenic),158(C=O lactone),124 (C3), 143(C4), 121(C5), 124(C6), 116(C7) ,147(C8), 118(C9), 143(C10), 56.05 (C11, C13).
DAC	($C_{15}H_{17}O_3N$)	159.78(C2 lactone),132.32(C3),147(C4),132(C5),111.8(C6),152(C7), 107(C8),147(C9),110(C10),44.31(C11),12.23(C12),44.31(C13),12.23(C14),194.09 (C15, C=O ketone),30.04(C16)
HAC	($C_{11}H_8O_4$)	161.19(C2, C=O lactone),129.59(C3),144(C4),111.29 (C6), 160(C7,C-OH), 102.05(C8,Ar-C),113(C9, Ar-C), 155(C10,Ar-C).
HMAC	($C_{12}H_{10}O_4$)	160(C2,C=O,lactone),126.36(C3),159(C4),126.36(C5,Ar-C), 110(C6,Ar-C),161.11(C7,Ar-C), 111.93(C8,Ar-C),102.14(C9,Ar-C),153.30.14(C10,Ar-C),18.01(C13-CH_3).



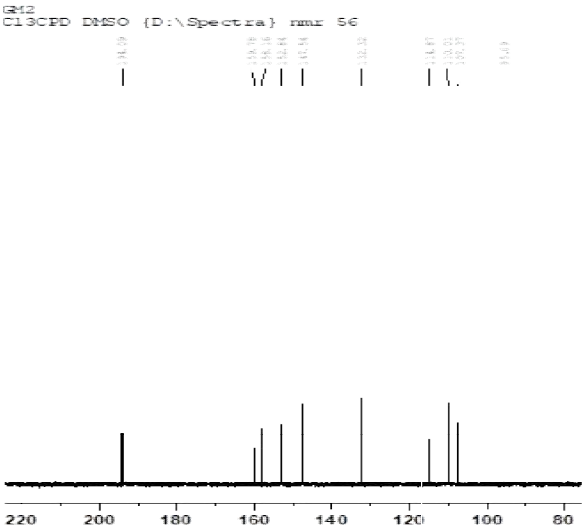


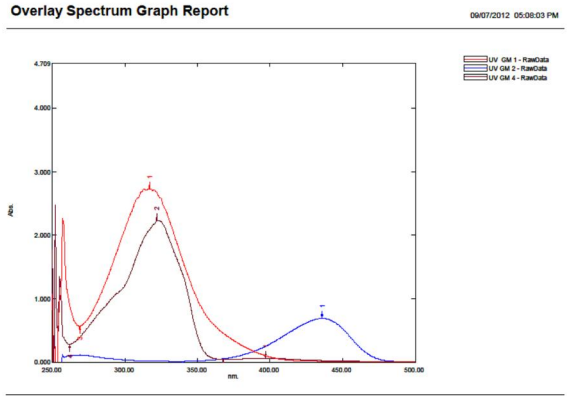
Table No.5- Mass spectral data (ESI) m/z of substituted derivatives of 3-acetyl 2-*H*-chromene-2-one

Coumarins	Molecular Mass m/e	Mass fragmentation $[M]^{+1}$
MAC	218.20	219
DAC	259.30	260
HAC	204.17	205
HMAC	218.20	2019

Electronic Spectra–The attachment of substituent group on basic chromophores changes the position and intensity of absorption band of the chromophores. The substituents increases the intensities of absorption due to auxochromses >C=O , $O=CCH_3$ and >C=C< , -OH ,Amino groups profoundly shows important transition occurs shown in Table No.6 and fig.13,14.

Entry	Maxi. absorbs at λ nm conc. 10^{-4}M in DMSO	Auxo chromophores Substituents	Important Transitions
MAC	228, 269,317	>C=O,O=CCH_3 and >C=C<	$\pi \rightarrow \pi^*$, n $\rightarrow \pi^*$ $\pi \rightarrow \pi^*$.
DAC	340, 436,581	ArN<, >C=O, O=CCH_3 , >C=C<	$\pi \rightarrow \pi^*$, n $\rightarrow \pi^*$, $\pi \rightarrow \pi^*$.
HAC	215,315	Ar-OH, >C=O, >C=C<	n $\rightarrow \sigma^*$, $\pi \rightarrow \pi^*$, n $\rightarrow \pi^*$
HMAC	322, 368, 397.	Ar- OH, >C=O,>C=C<	n $\rightarrow \sigma^*$,$\pi \rightarrow \pi^*$, n $\rightarrow \pi^*$

Table No.6- Electronic spectral data of subtd. 3-acetyl 2-H-chromene-2-one chromophores



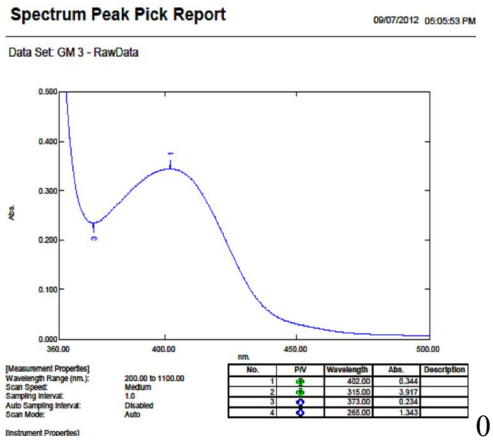


Figure.13- Overlay Electronic spectrum MAC, DAC, HMACFig.14. Electronic spectrum of HAC

Biological Screening-Mono microbial sensitivity disc to evaluate the invitrosusceptibility of antimicrobial agents of rapidly growing bacteria and several difficult species by an agar diffusion method asper **"WHO"**[23].

Principle- The disc diffusion method to the MIC of the strain being tested. AMC susceptibility testing with of testing bacterial sensitivity to maximum antibiotics and chemotherapeutic agents.

Material Required – Trypticase Soya Broth, 5 ml, Potato Dextrose Agar, sterile Normal Saline, discs stability $+2^0$ to $+8^0$. Disc Size 10 mm.

Procedure-

1) Preparation of Plates- The Potato dextrose agar pH 7.3 was poured into plates kept on a levelled surface. The depth of medium should be approx. 4mm. After the medium was solidified dry the plate for 30 min. in incubator $+35^0$ to $+37^0$ to remove excess moisture from surface.

2) Preparation of Inoculum- Used pure culture for Gram staining before preparing an inculum. Selected 4-5 similar colonies were transferred them into a tube containing 5 ml of Trypticase soya broth. Colonies directly suspended into a small volume of saline.

3) Inoculation - Dipped a sterile cotton swab into diluted culture inoculum and rotated inside wall of tube. A sterile cotton swab was dipped in diluted culture inoculum and on the entire disc surface was spread the agar surface of the plate.

4) Incubation- The plates were incubated at temperature $+35^0$ to $+37^0$ for 16 to 18 hours.

5) Reading of Zones- Measured the diameterof zoneofinhibition at last of incubation period.

6) Interpretation of Result- The zone of inhibition and susceptibility of organism to antibiotic, i.e. density of inoculum, depth, diffusion of antibiotic. The size of inhibition zone was considered resistivity and intermediate or sensitive was given in the zone size interpretative chart as per literatures represented in table no7.

Compounds	GRAM -VE BACTERIA		GRAM + VE BACTERIA	
	Escherichia *coli* (mm)	Salmonella *typhi* (mm)	Staphylococcus*aures*(mm)	Bacillus*substillis* (mm)
MAC	14	20	11	----
DAC	15	25	10	10
HAC	20	15	11	10
HMAC	15	10	----	----
Reference Antibiotic	30 mm (Ofloxacin)	30 mm (Ofloxacin)	15 mm (Azithromycin)	20 mm (Azithromycin)

Table No.7- Zones of Inhibition of Growth of Microorganism

Conclusion

The 3-acetyl derivatives of coumarin was synthesized using convenient method without solvent and characterized by different techniques. These coumarin consist of auxochromophore have strong absorption indicates the solvatochromics. The biological screening of coumarin shows potent againstbacterial colonies of Escherichia *coli* Salmonella *typhi,* Staphylococcus aures Bacillus *substillis.*

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