NUSANTARA BIOSCIENCE
Vol. 3, No. 3, pp. 118-123
November 2011

ISSN: 2087-3948
E-ISSN: 2087-3956
DOI: 10.13057/nusbiosci/n030303

Synthesis and study of cholosubstituted 4-aroyl pyrazolines and isoxazolines and their effects on inorganic ions in blood serum in *albino rats*

AMOL D. BHOYAR[1,♥], GANESH N. VANKHADE[2], PRITHVISIGH R. RAJPUT[3]
[1]Department of Chemistry, P.R. Patil College of Engineering and Technology, Kathora Road, Amravati 444607, Maharashtra, India.
Tel. +91 0721 2530342, Fax. +91 0721 230341 ♥email: amolbhoyar@rediffmail.com
[2]Department of Zoology, Sant Gadge Baba Amravati University, Amravati 444602, Maharashtra, India
[3]Department of Chemistry, Vidya Bharati Mahavidyalaya, Camp, Amravati 444601, Maharashtra, India

Manuscript received: 14 March 2011. Revision accepted: 8 November 2011.

Abstract. *Bhoyar AD, Vankhade GN, Rajput PR. 2011. Synthesis and study of cholosubstituted 4-aroyl pyrazolines and isoxazolines and their effects on inorganic ions in blood serum in albino rats. Nusantara Bioscience 3: 118-123.* Condensation of 2-substituted 3,5-dichloroacetophenone **(2a-b)** obtained from the condensation of 2-hydroxy 3,5-dichloro-acetophenone **(1)** and benzoyl chloride were dissolved in NaOH, on treatment under Baker-Venkatraman transformation in presence of KOH with pyridine gives 1-(2-hydroxy-3,5-dichlorophenyl)-3-substituted-1,3-propanediones (**3a-b)**. Then converted into 3-aroyl-6,8-dichloroflavanones (**4a-d)** by using different aromatic aldehyde in ethanol containing little piperidine. The condensation of (**4a-d)** and phenylhydrazine hydrochloride, piperidine in DMF gives 3-(2-hydroxy3,5-dichlorophenyl)-4-substitution-1-phenyl-Δ^2pyrazolines **(5a-d)** and condensation of (**4a-d)** and hydroxylamine-hydrochloride gives 3-(2-hydroxy-3,5-dichlorophenyl)-4-aroyl-5-substituted isoxazolines (**6a-d).** The above compounds are screened for their activities and have been found to exhibit significant effects on inorganic ions in blood serum in *albino rats*.

Keywords: flavanone, isoxazoline, pyrazoline.

Abstrak. *Bhoyar AD, Vankhade GN, Rajput PR. 2011. Sintesis dan studi cholo-tersubtitusi 4-aroil pirazolina dan isoxazolina serta efeknya pada ion anorganik dalam serum darah tikus albino. Nusantara Bioscience 3: 118-123.* Kondensasi 2-tersubtitusi 3,5-dikloroasetofenon **(2a-b)** yang diperoleh dari kondensasi 2-hidroksi 3,5-dikloro-asetofenon **(1)** dan benzoil klorida yang dilarutkan dalam NaOH, pada perlakuan berdasarkan transformasi Baker-Venkatraman dengan keberadaan KOH dengan piridin menghasilkan 1-(2-hidroksi-3,5-diklorofenil)-3-tersubstitusi-1,3-propanedion **(3a-b).** Kemudian diubah menjadi 3-aroil-6,8-dikloroflavanone **(4a-d)** dengan aldehida aromatik yang berbeda dalam etanol yang mengandung sedikit piperidina. Kondensasi **(4a-d)** dan fenilhidrazina-hidroklorida, piperidina dalam DMF menghasilkan 3-(2-hidroksi 3,5-diklorofenil)-4-substitusi-1-fenil-Δ^2pirazolina **(5a-d)** dan kondensasi **(4a-d)** dan hidroksilamin-hidroklorida menghasilkan 3-(2-hidroksi-3,5-diklorofenil)-4-aroil-5-tersubstitusi isoxazoline **(6a-d).** Senyawa-senyawa di atas diuji untuk mengetahui aktivitasnya dan diketahui menunjukkan efek yang signifikan pada ion anorganik dalam serum darah pada tikus albino.

Kata kunci: flavanone, isoxazoline, pirazolina.

INTRODUCTION

Pyrazole is a five-membered heterocyclic azole containing two nitrogen atoms in 1,2-position, and its dihydro derivative is pyrazolines (Stokes and Ridgway 1980). Last five decades, the pyrazolines ring shows spectacular presence as it has fairly accessible and shows diverse properties. Recently, numbers of derivatives of pyrazolines are reported to have anesthetic properties (Sinha 1939; Mandal et al. 1986). Along with the traditional interest, pyrazoline is a base of number of dyes and drugs. They show bleaching, luminescent and fluorescent (Orlov et al. 1977; Krasovitskii 1994; Archana et al. 2002; Mulwad and Choudhari 2005; Li et al. 2007). properties and are reported to be useful intermediates in the synthesis of pyrazoles. The use in the development of cine-films opened a new area of applicability based on easier oxidation of 1-phenyl-3-aminopyrazolines.

Several pyrazolines and isoxazolines derivatives have been found to be posses considerable activity such as antimicrobial (Ramlingham et al. 1977), antibacterial (Azarifar and Maseud 2002), 5-α reductase inhibitor (Amr et al. 2006), antiproliferative (Chimichi 2006), central nervous system (Brown and Shavrel 1972) and immunosuppressive stimulant (Lombardino et al. 1981), Antispermatogenic (Raji et al. 2005), hypoglycemic and antidiabetic (Adeneye et al. 2008; Ettarh et al. 2004), Hepatotoxicity, nephro-toxicity (Shri 2003), they can also help in predictive toxicology (Rahman et al. 2001; Sahni et al. 2001; Hodgson et al. 2004; Paliwal et al. 2009), Hepatoprotective (Itoh et al. 2009), 2-pyrazoline seems to be mostly among the frequently studied of all pyrazolines and isoxazoline type compound. Numerous chlorinated organic compounds have various bioactivities which render them valuable active ingredient of medicine or plant protecting agents. Taking into consideration the possible beneficial effect of the presence of chlorine atom(s) in an organic compound, it appears expedient to synthesize a series of systematically chlorinated 2-pyrazolines and isoxazolines.

Toxicology is a very old concern to humans from the time of Stone Age to modern era. Now it is a separate branch of science and has its own importance. Toxicology deals with toxicity by any chemical or compound by intention or accidental exposure to living organisms. Excess of any compound will be harmful to life and considered under toxicity studies. In the modern era, use of chemicals and compounds that will accumulate or daily exposed to humans, are harmful in many ways. Pesticides are used for welfare of human beings but by the time, they will challenge us by showing their toxicity. They can be directly exposed to us or indirectly through food chain. Indiscriminate use of pesticides is on increase. India is one of the largest users of agricultural pesticides such as organophosphates, carbamates, etc. Pesticides are toxic compounds to all living organisms however effects vary with species to species. But excessive use of these pesticides creates many problems for all of us. These days, synthetic chemical pesticides are in practice because of their active and best results. But their excessive use causes serious damage to ecosystem-terrestrial as well as aquatic and consequently the flora and fauna of surrounding. Nowadays synthetic pyrethroids have become an economically and environmentally friendly group of insecticides as these possess low mammalian toxicity, rapid decomposition in soil, leave no residue in biosphere and are stable in sunlight. The persistence and continuous application of these synthetic pyrethroids may create a problem directly or indirectly in the higher tropical level of the ecosystem. Accidental exposure at the workplace and their presence in the environment has aroused concern over their possible adverse effects on human health.

MATERIALS AND METHODS

2-hydroxy-3,5-dichloroacetophenone (**1**) on treating with different aromatic acid in the presence of pyridine and NaOH gives a compound containing aromatic group, The structures are possible for these compounds (**2a, 2b**). The IR spectrum of these compounds consist of an ester stretching band at 1790 cm-^{1}, thereby suggested that there is reaction between hydroxyl group and benzoyl chloride (**2a**). However (**2b**) shows a PMR peak at δ2.60 of Ar-OCH_3.

The acetophenones (**2a-b**) was formulated by the reaction of pyridine in KOH gives 1-(2-hydroxy-3,5-dichloro-phenyl)-3-aryl-1,3-propane-dione (**3a-b**) which on reaction with different aldehyde gives 3-aroyl-flavanones (**4a-d**). These flavanones on treatment with phenylhydrazine-hydrochloride in DMF medium containing small amount of piperidine gives 4-aroyl-3,5-diaryl-1-phenyl-pyrazolines (**5a-d**) which was confirmed by its spectral analysis. In a similar fashion 3-aroyl-flavanone (**4a-d**) were treated with hydroxylamine hydrochloride in DMF medium containing small amount of piperidine gives 3,5-diaryl-4-aroyl-isoxazolines (**6a-d**) which was characterized by spectral analysis. All melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on a Perkin Elmer Infra-Red Spectrophotometer 1310 using KBr disc. ^{1}H NMR was recorded in $CDCl_3$ on a DRX 300 spectrometer (Figure 1; Table 1).

The reactions were monitored on TLC on Silica gel G and the solvent system used was benzene.

2-Aroyloxyacetophenone (2a-b)

2-hydroxy-3,5-dichloroaceto-phenone(0.04mol.)and benzoyl chloride (0.05mol.) were dissolved in NaOH (10%) 30 mL, (**2a**), 2-hydroxy-3,5 dichloroaceto-phenone (0.04 mol) and anisic acid (0.05mol) were suspended in dry pyridine (30 mL) with $POCl_3$ 3 mL, (**2b).** All the above reaction mixture was kept for overnight and then worked up by dilution and acidification with ice cold HCl (50%) to neutralize pyridine. The solid product was filtered washed with water followed by sodium-bicarbonate (10%) washing finally again with water it crystallized from ethanol to obtained 2-Aroyloxyaceto-phenones (**2a-b**).

1-(2-hydroxy-3,5-dichlorophenyl)-3-aryl-1,3-propane-diones (3a-b)

When 2-Aroyloxyacetophenone (**2a-b**) (0.05 mol) was dissolved in dry pyridine 40 mL .The solution was warmed up to 60^{0}C and pulverized KOH (15 g) were added slowly with constant stirring. After 4 hours the reaction mixture was acidified by adding ice cold dil. HCl (1:1) The product thus separated was filtered washed with sodiumbicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol-acetic acid mixture to get 1-(2-hydroxy-3,5-dichloro-phenyl)-3-aryl-1,3-ropanedione (**3a-b**) respectively.

3b-IR spectrum recorded in KBr (cm^{-1}) 3030, (v),-OH; 1600, (s), >C=O;1170, (s), >C-O; 790,(s), C-Cl. PMR spectrum recorded in δ $CDCl_3$ 3.69,(s), 3H, Ar-O-CH_3; 4.56,(s), 2H,-CO-CH_2-CO-(Keto); 6.6, (s), 1H,-C=CH-; 6.92-8.08, (m), 6H, Ar-H; 12.75, (s), 1H, Ar-OH; 15.71, (s), 1H, -CHOH=C(enol). TLC: solvent (benzene) height: 2.7 cm, solute height: 2.3 cm; Rf value: 0.85, m.p.112^{0}C, yield 78%.

3-Aroylflavanone (4a-d)

1-(2-hydroxy-3,5-dichlorophenyl)-3-(4'-methoxyphenyl)-1,3-propanedione **3a** (0.01 mol) and benzaldehyde, anisaldehyde (0.012 mol) separately was refluxed in ethanol (25 mL) and piperidine (0.5 mL) for 15-20 min. yield 3-arylflavanone (**4a-b**) resp. 1-(2-hydroxy-3,5-dichloro-phenyl)-3-phenyl-1,3-propanedione**3b** (0.01mol) and benzaldehyde, anisaldehyde (0.012 mol) separately was refluxed in ethanol (25 mL) and piperidine (0.5 mL) for 15-20 min. yield 3-aroylflavanone **(4 c-d)** resp**.** 1-(2-hydroxy-3,5-dichlorophenyl-3-(2'-hydroxyphenyl)-1,3-proponedione. All above reaction after refluxing, cooling the reaction mixture was acidified with dil. HCl (1:1). The product thus separated was filtered washed with sodium bicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol-acetic acid mixture.

4c IR spectrum recorded in KBr (cm^{-1}) 1637, (s), >C=O; 1562, (s), >C=O; 1213,(s), C-O-C; 825, (s), C-Cl PMR spectrum recorded in δ $CDCl_3$ 3.89, (s), 3H, Ar-OCH_3; 5.36, (dd), 1 H, CH_A-CH; 5.76 (dd), 1H, CH-CH_B; 6.7-8.1, (m), 11H,-Ar-H. TLC: solvent (benzene) height: 2.0 cm; solute height: 1.7 cm; Rf value: 0.85, m.p.178^{0}C, yield 72%.

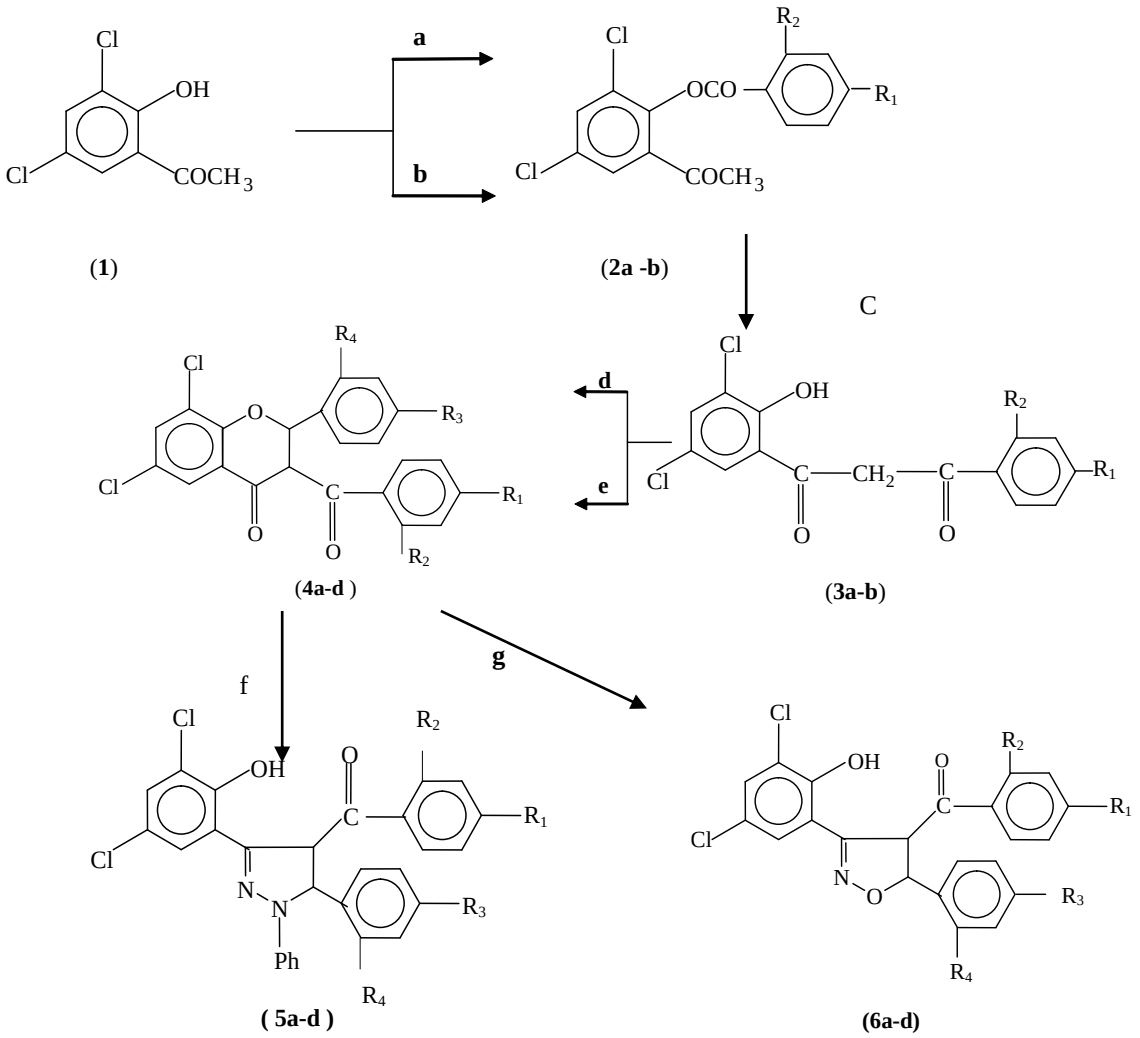

Figure 1. Stepwise reaction of compounds from starting material to final product. **a**. C_6H_5 COCl, NaOH (10%), **b**. Anisic Acid, $POCl_3$, Pyridine, **c**. Pyridine, KOH, **d**. Benzaldehyde, Piperidine, ethanol, **e**. Anisaldehyde, Piperidine, ethanol, **f**. $PhNHNH_2$.HCl, Piperidine DMF, **g**. NH_2OH.HCl, Piperidine DMF

Table 1. Physical and Analytical characterization data of newly synthesized compounds

Compound	Molecular formula	Molecular weight	R1	R2	R3	R3	M.P.	Yield (%)	Rf	Cal. (Found) C	N
2a	$C_{15}H_{10}O_3Cl_2$	309	H	H	-	-	69^0C	72	0.71	58.14 (58.25)	-
2b	$C_{16}H_{12}O_4Cl_2$	339	OCH_3	H	-	-	119^0C	77	0.82	56.41 (56.43)	-
3a	$C_{15}H_{10}O_3Cl_2$	309	H	H	-	-	122^0C	82	0.76	58.18 (58.25)	-
3b	$C_{16}H_{12}O_4Cl_2$	339	OCH_3	OCH_3	-	-	112^0C	78	0.85	56.48 (56.63)	-
4a	$C_{22}H_{14}O_3Cl_2$	417	H	H	H	H	161^0C	87	0.42	61.17 (61.53)	-
4b	$C_{23}H_{16}O_4Cl_2$	447	H	H	OCH_3	H	178^0C	72	0.85	64.55 (64.63)	-
4c	$C_{23}H_{16}O_4Cl_2$	447	OCH_3	H	H	H	167^0C	75	0.61	64.46 (64.63)	-
4d	$C_{24}H_{18}O_5Cl_2$	477	OCH_3	H	OCH_3	H	156^0C	62	0.44	62.99 (63.01)	-
5a	$C_{28}H_{20}O_2N_2Cl_2$	473	H	H	H	H	169^0C	85	0.70	68.62 (68.99)	5.35 (5.47)
5b	$C_{29}H_{22}O_3N_2Cl_2$	503	H	H	OCH_3	H	165^0C	82	0.82	67.24 (67.31)	5.32 (5.41)
5c	$C_{29}H_{22}O_3N_2Cl_2$	503	OCH_3	H	H	H	172^0C	68	0.73	67.22 (67.31)	5.32 (5.41)
5d	$C_{30}H_{24}O_4N_2Cl_2$	533	OCH_3	H	OCH_3	H	170^0C	75	0.44	65.67 (65.81)	5.01 (5.11)
6a	$C_{22}H_{15}O_3NCl_2$	412	H	H	H	H	193^0C	86	0.73	64.01 (64.07)	3.31 (3.39)
6b	$C_{23}H_{17}O_4NCl_2$	442	H	H	OCH_3	H	188^0C	84	0.79	62.33 (62.44)	3.07 (3.16)
6c	$C_{23}H_{17}O_4NCl_2$	442	OCH_3	H	H	H	195^0C	71	0.88	62.38 (62.44)	3.10 (3.16)
6d	$C_{24}H_{19}O_5NCl_2$	472	OCH_3	H	OCH_3	H	180^0C	82	0.83	60.96 (61.01)	2.81 (2.96)

4-Aroyl-Δ^2-Pyrazolines (5a-d)

When 3-aroylflavanone (**4a-d**) and phenyl-hydrazine-hydrochloride (0.02mol) were refluxed in 20 mL DMF containing a few drops of piperidine for 1.5 hrs separately, after cooling the mixture was diluted with water HCl (1:1). The product thus separated was filtered washed with sodium bicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol-acetic acid mixture to yield 4-Aroyl-Δ^2-pyrazolines **(5a-d)** respectively.

5c IR spectrum recorded in KBr cm^{-1} 3076, (w,b),-OH; 1598, (s), > C=O; 1502, (s), >C=N;1176, (m), Ar-O-C; 837, (s), C-Cl; PMR spectrum recorded in δ $CDCl_3$ 3.89, (s), 3H, Ar-OCH_3; 5.27, (dd), 1H, CH_A-CH; 5.65, (dd), 1H, CH-CH_B; 6.6-8.1, (m), 16 H, Ar-H; 12.08, (s), 1H, Ar-OH. TLC: solvent (benzene) height: 3.1cm; solute height: 2.6 cm; Rf value: 0.83; m.p. 165^{0}C, yield 82%.

3,5-diaryl-4-aroylisoxazoline (6a-d)

When 3-aroylflavanone (0.01 mol) **6a-d** and hydroxylaminehydrochloride (0.02 mol) were refluxed in 20 mL DMF containing few drops of piperidine for 1.5 hrs. Separately, after cooling the mixture was diluted with water HCl (1:1). The product thus separated was filtered washed with sodium bicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol-acetic acid mixture to yield 3,5-diaryl-4-aroylisoxazoline (**6a-d**)

6c IR spectrum recorded in KBr cm^{-1} 3377, (w,b),-OH; 3012, (s), C-H;1691, (s),>C=O; 1599, (s), >C=N; 1382, (m), Ar-O-C; 812, (s), C-Cl PMR spectrum recorded in δ$CDCl_3$ 2.35, (s),3H,Ar-OCH_3; 5.21, (dd), 1H, CH_A-CH; 5.63, (dd), 1H, CH-CH_B; 7.26-8.14, (m), 10H, Ar-H; 9.94, (s), 1H, Ar-OH. TLC: solvent (benzene) height: 2.4 cm; solute height: 1.7 cm; Rf value: 0.79, m.p. 188^{0}C, yield 89%

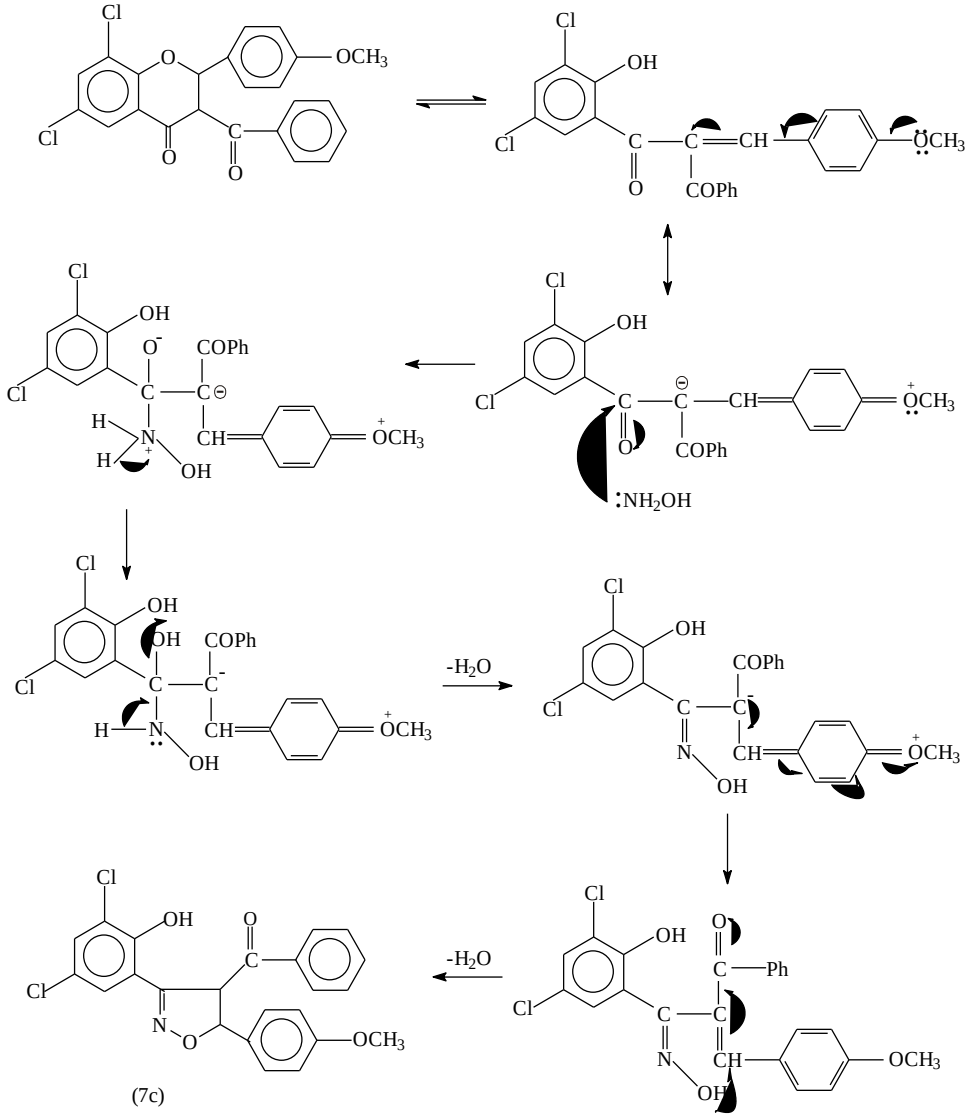

Figure 2. A possible mechanism with NH_2OH for the conversion of 3-aroylflavanone into 3, 5-diaryl-4-aroylisoxazoline

Table 2. Serum sodium, potassium, calcium and magnesium ions changes on exposure to cythion and chlorosubstituted heterocycles in *albino rats*.

Weeks	Inorganic ions	Control	Induced	Chlorosubstituted heterocycles	
				5d	6d
2	Sodium	1.36 ± 0.17	1.41± 0.18	1.37± 0.17	1.36± 0.17
	Potassium	6.08± 0.18	6.95± 0.20	6.10± 0.20	6.22± 0.17
	Calcium	6.30± 0.20	8.7± 0.29	7.38± 0.20	7.49± 0.29
	Magnesium	3.5± 0.17	3.8± 0.19	3.6± 0.17	3.72± 0.18
4	Sodium	1.36± 0.17	1.39± 0.18	1.35± 0.17	1.36±0.18
	Potassium	6.18± 0.17	7.37± 0.20	6.38± 0.17	6.25± 0.18
	Calcium	6.30± 0.29	11.2± 0.34	7.35± 0.34	7.42± 0.21
	Magnesium	3.5± 0.17	4.7± 0.18	3.62± 0.17	3.78± 0.19
6	Sodium	1.36± 0.17	1.48± 0.17	1.39± 0.18	1.42± 0.18
	Potassium	6.18± 0.20	8.27± 0.17	7.28± 0.18	7.40± 0.20
	Calcium	6.30± 0.20	13.8± 0.29	7.39± 0.20	7.35± 0.20
	Magnesium	3.5± 0.18	4.2± 0.18	3.58± 0.19	3.72± 0.19
8	Sodium	1.36± 0.17	1.55± 0.18	1.40± 0.17	1.39± 0.18
	Potassium	6.18± 0.18	8.84± 0.17	7.32± 0.18	7.25± 0.18
	Calcium	6.30± 21	15.82± 0.34	7.42± 0.20	7.38± 0.21
	Magnesium	3.5± 0.19	3.9± 0.19	3.62± 0.17	3.57± 0.18
10	Sodium	1.36± 0.17	1.58± 0.17	1.42± 0.18	1.45± 0.17
	Potassium	6.18± 0.18	9.40± 0.20	7.40± 0.20	7.36± 0.17
	Calcium	6.30± 10.20	16.96± 0.21	7.39± 0.29	7.51± 0.29
	Magnesium	3.5± 0.17	4.1± 0.17	3.58± 0.17	3.71± 0.18

Effect on Inorganic Ions in blood serum in Albino rat

Albino rats of either sex weighing between 80-120 gms were divided into three groups viz (A, B and C). Animals in each group maintained on specific diet . The animals of group A were fed on stock diet used as *control*. Animals of group B were given cythion intravenously (40 SD) body weight/day for one week. Animals from group C were given newly synthesized heterocycles. Synthesized drug doses were administered orally and pesticide cythion was injected 0.2 to 0.3 mL/100 g body weight. Intravenous injections were given in the tail vein using 12.7 mm 24 gauge needle. The animals were restrained in a plastic holder with the tail protruding. Anesthetic ether was used as anesthetic reagents to sacrifice test animals without pain and discomfort. For inducing alteration of liver functions cythion pesticide was selected. The doses were prepared on the basis of lethal toxicity method and injected intravenously by a sterile syringe of about 12.7 mm 24 gauge.

Blood samples were collected from normal as well as insecticide-treated animals and left to clot at room temperature for at least 30 minutes then centrifuged at 2000 r.p.m. to remove clot and cell debris. Equal amounts of serum from experimental and control animals were pooled in order to have sufficient material to perform all the analysis. Effects of chlorosubstituted heterocycles on induced (cythion treated) hepatotoxicity with special reference to serum inorganic ions in *albino rats* are tabulated in Table 2, no. from 2.

In the present study, it is evident from Table 1 that a large decrease in the level of circulating serum inorganic ions was found in *albino rats* due to the cythion intoxication.

CONCLUSION

When we analyzed the results obtained from newly synthesized chlorosubstituted heterocycles treated animals it was found that the decreasing trend in the levels of circulating serum inorganic ions was prevented and consequently protected the liver from cythion intoxication. During hepatic concentration of sodium, potassium, calcium, magnesium, and phosphate get significantly increased. Increased in this concentration may be due to histopathological changes in kidney. Increased potassium concentration may be due to cellular necrosis which has already been reported in many tissues during hepatitis. Dehydration during hepatics has also been reported. These cations may be present into the circulation only for excretion. Decrease SDH activity in liver and kidney might because of reduction in stored energy and activity of sodium pump. The peroxidation of membranes lipid during hepatics indicate the loss of membrane integrity and membrane-bound enzyme activity which in turn brought about disturbance in cellular homeostasis. Increase calcium in serum could be due to its release from bones. The level of calcium and phosphate ion in extracellular fluid rise markedly, instead of falling. Because kidney cannot excrete rapidly enough as phosphorus being reabsorbed from bones. Since cythion cause nephrotoxicity. From table 1 it is evident that the two heterocyclic compounds viz 5d and 6d were effectively helpful in restoring the increased concentration of sodium, potassium, calcium, magnesium, and phosphate to normalcy. Thus these drugs may protect liver function from cythion damage.

ACKNOWLEDGEMENTS

The authors express their sincere thanks to the Principal Vidya Bharati Mahavidyalaya, Amravati, India and Head Department of Zoology, Sant Gadge Baba Amravati University, Amravati, India for providing necessary laboratory facilities.

REFERENCES

Adeneye AA, Agbaje EO. 2008. Pharmacological evolution of oral hypoglycemic and antidiabetic effect of fresh leaves. Ethanol extract of Morinda lucida Benth in Normal and Alloxan Induced diabetic rats. Afr J Biomed Res 11 (1): 65-71.

Amr AG, Abdel-Latif NA, Abdalla MM. 2006. Synthesis of some new testosterone derivatives fused with pyrazoline as promising 5alpha-reductase inhibitors. Acta Pharm 52 (2): 203-218.

Archana VK, Shrivastava RC, Kumar A. 2002. Synthesis of potential quinazolinyl pyrazolines and quinazolinyl isoxazolines as anticonvulsant agents. Indian J Chem 41B: 2371.

Azarifar D, Maseud S. 2002. Synthesis and characterization of new 3,5-dinaphthyl substituted-2-pyrazolines and study of their antimicrobial activity. Molecules 7: 885-895.

Brown RE, Shavrel Jr, J. 1972. US Patent. 1972, 3, 624, 102. Chem Abstr 76: 59618.

Chimichi S, Boccalini M, Hassan MM, Viola G, Dall'Acqua F, Curini M. 2006. Synthesis, structural determination and photo antiproliferative activity of new 3-pyrazolyl or isoxazolyl substituted 4-hydroxy-2(1H)-quinolinones. Tetrahedron 62: 90-96.

Ettarh RR, Emeka P. 2004. Morinda lucida extract induces endothelium-dependent and independent relaxation of rats aorta. Fitoterapia 75 (3-4): 332-336.

Hodgson E. 2004. A Textbook Of Modern Toxicology.3rd Edition. John Wiley and Sons, Inc, New Jersey.

Itoh A, Isoda K, Kondoh M (et al). 2009. Hepatoprotective effect of syringic acid and vanillic acid on concanavalin A-induced liver injury. Biol Pham Bull 32: 1215-1219.

Krasovitskii BM, Afanasiadi LSh, Lysova IV, Vinetskaya. 1994. Luminescence properties of 5-oxazoles derivatives containing a pyrazoline ring. Chem Heterocycl Comp 30 (3): 358-360.

Li JF, Guan B, Li DX, Dong C. 2007. Study on the fluorescence properties of a new intramolecular charge transfer compound 1,5-diphenyl-3-(N-ethylcarbazole-3-yl)-2-pyrazoline. Spectrochimica Acta Part A 68 (2): 404-408.

Lombardino IG, Otterness IGI. 1981, Novel immunosuppressive agents potent immunological activity of some benzothiopyran [4,3-C]pyrazole-3-ones. J Med Chem. 24: 830

Mandal NK, Sinha R, Banerjee KP. 1986. Synthesis and biological activity of some haloanilido pyrazoline and isoxazoline. Chem Abstr 104: 34034v.

Mulwad VV, Choudhari BP. 2005. Synthesis and antimicrobial screening of N[coumarin-6-ylamino] thiazolidinone and spiroindolthiazolidinone derivatives. Indian J Chem 44B: 1074.

Orlov VD, Roberman AI, Rybachenko AI, Lavrushin VF. 1977. 1,3,5-triaryl-Δ^2-pyrazolines with a nitro or amino group in the N-phenyl ring. Chem Heterocycl Comp 13 (11): 1230-1234.

Paliwal A, Gurjar RK, Sharma HN. 2009. Analysis of liver enzymes in albino rat under stress of λ-cyhalothrin and nuvantoxicity. Biol Med 1 (2): 70-73.

Rahman MF, Siddiqui MKJ, Jamil K. 2001. Effects of vepacide (*Azadirachta indica*) on aspartate and alanine aminotransferase profiles in subchronic study with rats. Human Exp Toxicol 20: 243-249.

Raji Y, Akinsomisoye OS, Salman TM. 2005. Antispermatogenic activity of Morinda lucida extract in male rats. Asian J Androl 7 (4): 405-410.

Ramlingham K, Thyvekikakath GX, Berlin KD, Chestnut RW, Brown RA, Durhum NN, Ealick AE, Vander Helm D. 1977. Synthesis and biological activity of some derivatives of thiochroman-4-one and tetrahydrothipyron-4-one. J Med Chem 20: 847.

Sahni K, Saxena Y. 2001. Toxic effects of diefethialone on the liver of Swiss albino mice *Mus musculus.* U.P. J Zool 21 (1): 47-52.

Shri JNM. 2003. Ginger: Its role in Xenobiotic metabolism. ICMR Bulletin 33 (6): 57-63.

Sinha HK. 1939. The local anesthetic action of certain pyrazoline compounds. J Pharm Exp Ther 66 (1): 54-59.

Stokes EJ, Ridgway GL. 1980. Clinical Bacteriology, 5th ed. Edward Arnold, London.