Volume 64, Issue 1, 2020
Journal of Scientific Research
Institute of Science,
Banaras Hindu University, Varanasi, India.

Biological Evaluation of Some Novel Chalcones and Its Derivatives

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Abstract: **CHN analysis Chalcones, (E)-N-(4-(4,6-dichloro-1,3,5 – triazin-2-ylamino) phenyl)-3-(4 methoxy-phenyl) acrylamide (4a-c) have been prepared according to Claisen-Schmidt conden-sation. Further these chalcones (4a-c) on reaction with malononitrile affords cyano-pyridines (5a-c) respectively. The constitutions of newly synthesised compounds have been characterized on the basis of their IR and 1H NMR, 13C NMR spectral data.These synthesized compounds have been screened for their antibacterial and larvicidal activity.**

Index Terms: **Chalcones, cyanopridines, Larvicidal activity, antibacterial activity.**

I. INTRODUCTION

Heterocyclic compounds are cyclic organic substances which contain at least one atom other than carbon in the ring system. The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. The chemistry of chalcones have generated intensive scientific studies throughout the world, especially interesting are their biological and industrial applications. Chalcone is a generic term given to compounds bearing the 1, 3-diphenyl-2-propen-1-one framework and it belongs to the flavonoid family. Chemically they are open-chain flavonoids in which the two aromatic rings are joined by a three carbon α, β-unsaturated carbonyl system.

Chalcones are readily synthesized in the laboratory by various synthetic methods. Structural modification of chalcone template can be readily achieved. Chalcones are unsaturated ketones containing the reactive keto and ethylenic group –CO –CH=CH – and are colored compounds because of the presence of the chromophore and auxochromes[1-3]. They are known as benzalacetophenones or benzylideneacetophenones. Kostanecki and Tambor gave the name "Chalcone"[4-5]. These are found to be effective as anti-inflammatory[6,7], anticancer[8-10], antifungal[11-13], cardiovascular[14], and antimalarial[15] agents.The well-known stepwise reaction between cyanuric chloride and aminoacetanilide is very well defined, and high yields of aminodichlorotriazines were obtained. Cyanuric chloride is definitely an excellent starting compound for the straight forward preparation of highly structured multitopic molecules. The first substitution is exothermic. Therefore, the temperature of the reaction mixture has to be maintained to 0 ºC. The substitution of the second step at room temperature, finally the third step is functionalized under reflux of the solvent. These observation led us to synthesize some new s-triazinyl based chalcones and it corresponding cyanopyridine derivatives.

II. EXPERIMENTAL MEDTHODOLOGY

Melting points were determined by Deep Vision instrument. The purity of the compounds was checked byTLC using silica gel coated plates and spots were visualized by exposing the dry plates in iodine vapours. IRSpectra were recorded in the solid state, as KBR dispersion by use of the FT-IR-Spectrometer. The ^{1}HNMR and ^{13}C NMR spectra of the compounds were carried out in Bruker AMX 400 MHZ. NMR instrument using $CDCl_3$ or DMSO as a solvent and TMS as internal reference (chemical shift in δ ppm). The mass spectra of the compounds were carried out in ESI Mass.

A. Synthesis of N-(4-(4,6-dichloro-1,3,5-triazin-2-yl amino)phenyl) acetamide (3):

4-amino acetanilide (0.01 mole) was added slowly to cyanuric chloride (0.01 mole) in acetone (30ml) with constant stirring over a period of 4 hr at 0 to 5º C Then ,sodium carbonate (0.05 mole) dissolved in water (10 ml) was added drop wise to neutralize HCl evolved during the reaction .Finally ,the contents were poured into crushed ice. The solid was separated out by filtration and washed with water. The product is dried , recrystallized from alcohol to give the product (3).

B. Synthesis of (E)-N-(4-(4,6-dichloro-1,3,5 –triazin-2-ylamino) phenyl)-3-(4-methoxyphenyl) acrylamide (4a):

Acetamide compound (3) (0.01 mole) was dissolved in Ethanol (30 ml) Then 10% NaOH solution and 4-Methoxybenzaldehyde (0.01mole) was added to the reaction mixture with constant stirring over a period of 6 hrs .The reaction mixture was poured into crushed ice. The solid was separated out by filtration and washed with water. The product (4a) is dried , recrystallized from ethanol. IR (KBR) cm^{-1} : -N,s-triazine (829.90), CN-H str (3419.04) , C─Cl (770.81).

C. Synthesis of (E)-N-(4-(4,6-dichloro-1,3,5 –triazin-2-ylamino) phenyl)-3-(4-flurophenyl) acrylamide (4b):

Acetamide compound (3) (0.01 mole) was dissolved in Ethanol (30 ml) Then 10% NaOH solution and 4-Flurobenzaldehyde (0.01mole) was added to the reaction mixture with constant stirring over a period of 6 hrs. The reaction mixture was poured into crushed ice. The solid was separated out by filtration and washed with water. The product (4b) is dried , recrystallized from ethanol .IR (KBR) cm^{-1} : C-N,s-triazine (809.95), N-H str (2926.45) , C─Cl (764.63).

D. Synthesis of (E)-N-(3-(4,6-dichloro-1,3,5 –triazin-2-ylamino) phenyl)-3-(benzo [d] [1,3] dioxol-5yl) acrylamide (4c):

Acetamide compound (3) (0.01 mole) was dissolved in Ethanol (30 ml) Then 10% NaOH solution and piperonal (0.01mole) was added to the reaction mixture with constant stirring over a period of 6 hrs .The reaction mixture was poured into crushed ice. The solid was separated out by filtration and washed with water. The product is dried, recrystallized from ethanol. IR (KBR) cm^{-1} : C-N,s-triazine (809.95), N-H str (2922.59) , C─Cl (657.60).

E. Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2ylamino)phenylamino)-2-amino-4-(4-methoxyphenyl) pyridine-3-carbonitrile (5a):

A mixture of a compound (4a) (0.01 mole) dissolved in 40 ml ethanol and added malononitrile (0.01 mole), ammonium acetate (0.08 mole) was refluxed for 8 hrs. Then the mixture was cooled and poured into crused ice. The product (5a) separated out was filtered washed and recrystallized from alcohol. IR(KBR) cm^{-1} : C-Cl (834.06),Ar C-Cl (1119.48) ,Ar-N str (1383.68), primary N-H (1509.07), C=C (1570.74), C=N (1613.16), N-H str (2853.17). ^{1}H NMR($CDCl_3$) δ ppm : 3.734 ($O-CH_3$), 4. 311 to 4.349 (S,1H,s-triazine, Ar-C-NH) , 6.986-7.437 (d, 4H,Ar-CH),7.688 (Ar-H), 9.896 (2-Py-Ar-1H). ^{13}C NMR($CDCl_3$) δ ppm: Aliphatic-CH_3 (55.51), Ar-CH (119.52 to 121.12), 2-Py (134.85), 1-imine (166.10), S- triazine (168.3).

F. Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2ylamino)phenylamino)-2-amino-4-(4-flurophenyl) pyridine-3-carbonitrile (5b):

A mixture of a compound (4b) (0.01 mole) dissolved in 40 ml ethanol and added malononitrile (0.01 mole),ammonium acetate (0.08 mole) was refluxed for 8 hrs. Then the mixture was cooled and poured intocrused ice .The product (5b) separated out was filtered washed and recrystallized from alcohol. IR(KBR) cm^{-1}: C-Cl (776.208),Ar C-Cl (1129.12) ,Ar-N str (1380.78), primary N-H (1509.07), C=C (1626.66), N-H str (2918.73).^{1}H NMR($CDCl_3$) δ ppm : 4.296 to 4.314 (S,1H,s-triazine Ar-C-NH) , 4.331 (S,1H,Ar-C-NH_2), 6.986-7.437 (d, 4H,Ar-CH),7.588 (Ar-H), 9.898 (2-Py-Ar-1H).^{13}C NMR($CDCl_3$) δ ppm: Ar-CH (119.40to 121.02), 2-Py-CH (134.15 to135.28), S- triazine (168.20).

G. Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2ylamino)phenylamino)-2-amino-4-(benzo [d] [1,3] dioxol 4-yl pyridine-3-carbonitrile (5c):

A mixture of a compound (4c) (0.01 mole) dissolved in 40 ml ethanol and added malononitrile (0.01 mole),ammonium acetate(0.08 mole) was refluxed for 8 hrs. Then the mixture was cooled and poured into crused ice .The product (5c) separated out was filtered washed and recrystallized from alcohol. C=C (1578.45), IR(KBR) cm^{-1} : C─Cl (813.61), C-O-C (1032.69), Ar C-Cl (1108.87) Ar-N (1334.50), primary N-H (1508.06), C=N (1616.06), N-H str (2922.59), O-H str (3784.62).^{1}H NMR($CDCl_3$) δ ppm : 4.427(S,1H,s-triazine Ar-C-NH) , 5.276(S,1H,Ar-C-NH_2), 6.672 (d,1H,Ar-Py), 6.983-7.469 (d, 4H,Ar-CH), ^{13}NMR($CDCl_3$) δ ppm: Ar-CH (108.82 to121.53),2-Py-CH(134.65 to148.38), 1-imine (166.01), S- triazine (166.24).

III. RESULT AND DISCUSSION

The interest of organic chemistry in 2,4,6-trichloro-1,3,5-triazine as a starting material is due to temperature dependent reactivity of one chlorine atom that allow a sequential introduction of various substituents. In the present artical we have reported the synthesis, characterization and antibacterial and Larvicidal activity of some novel s-triazine based cyanopyridine derivatives.

A. Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion methodagainst S. aureus and E.faecalis (Gram positive bacteria) and E.coli, S.Typi (Gram negative bacteria) by using agar medium.Ciprofloxacin was used as standard drugs for the comparison of antibacterial activity by visualizing activity data it could be observed that compounds (5a-c) were found to be active or inactive against all bacterial strain. (Table No. 2)

B. Larvicidal Activity

For the bioassay test, larvae were taken in five batches of 20 in 249 ml of water and 1.0 ml of the desired chemical extract concentration. The numbers of dead larvae were counted after 24 h of exposure and the percentage of mortality was reported from the average of five replicates.

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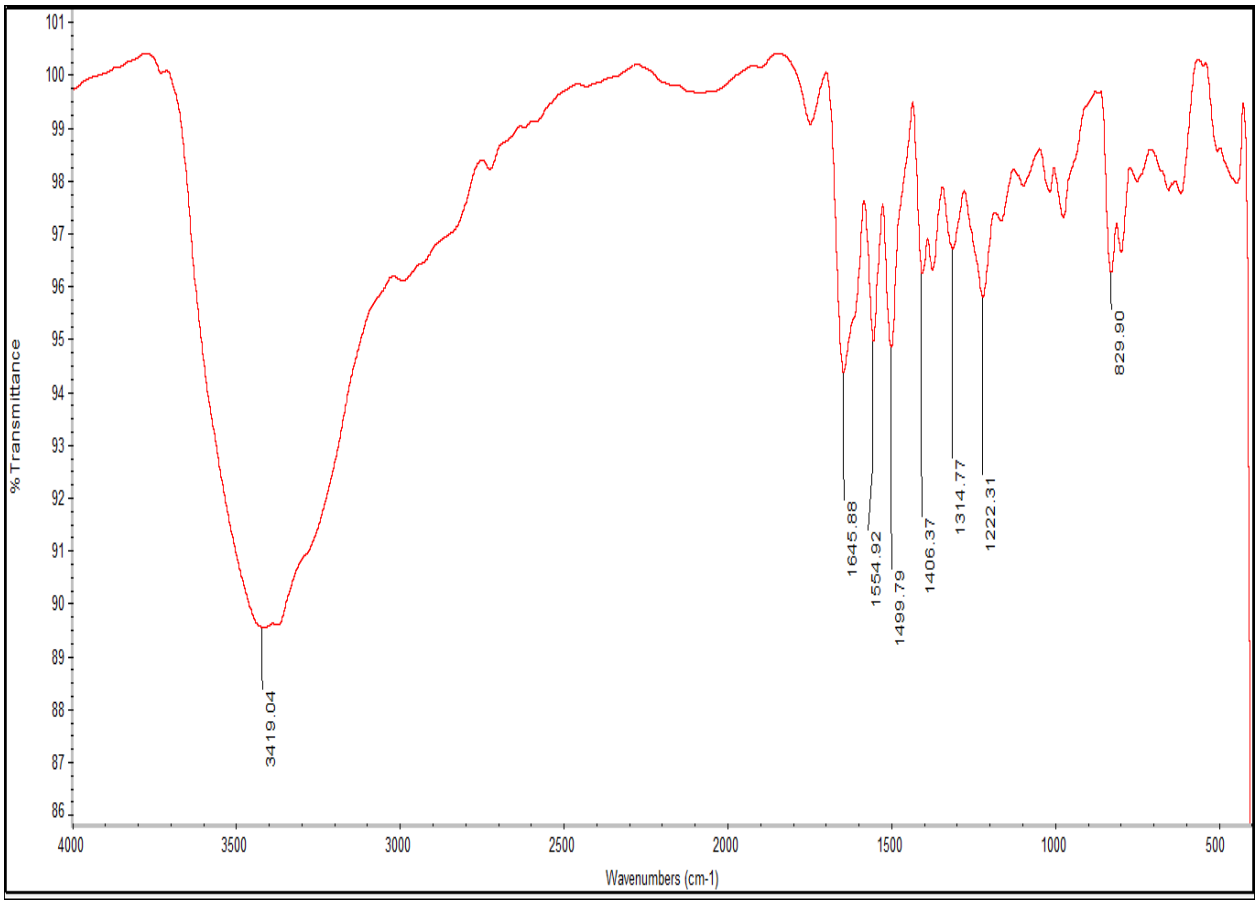
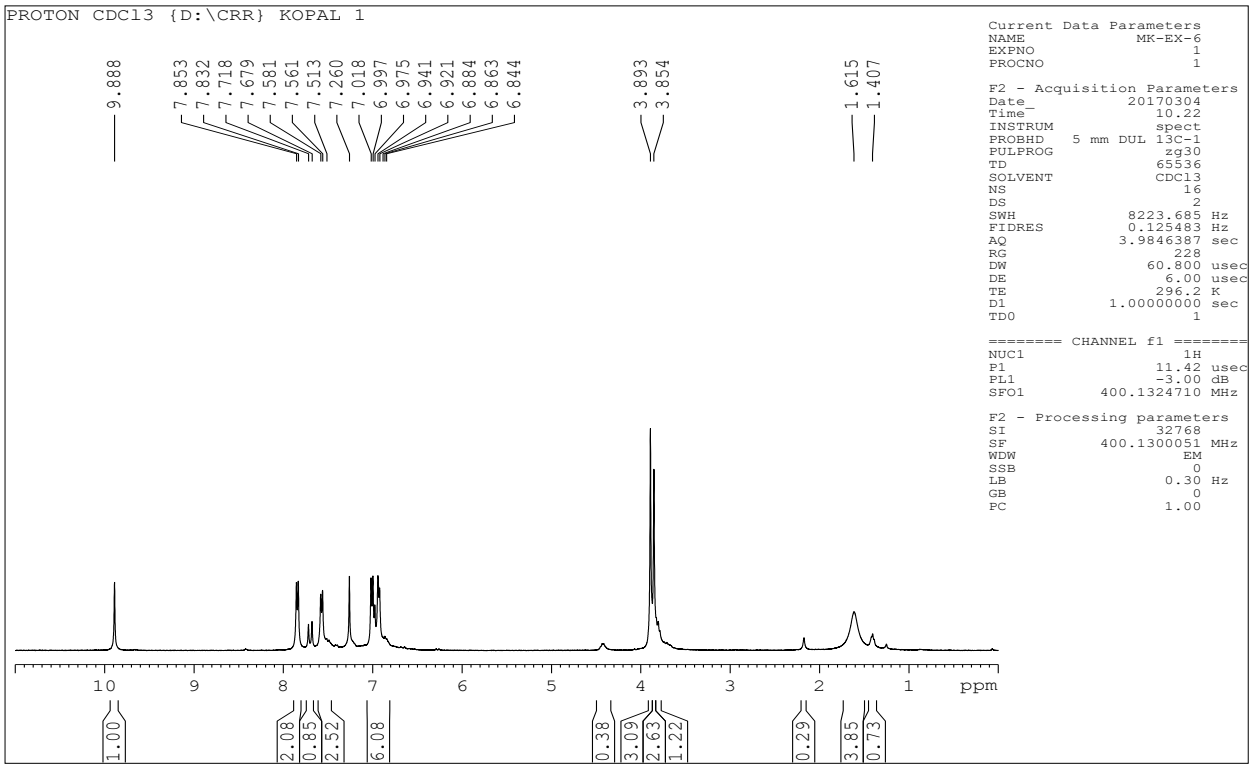
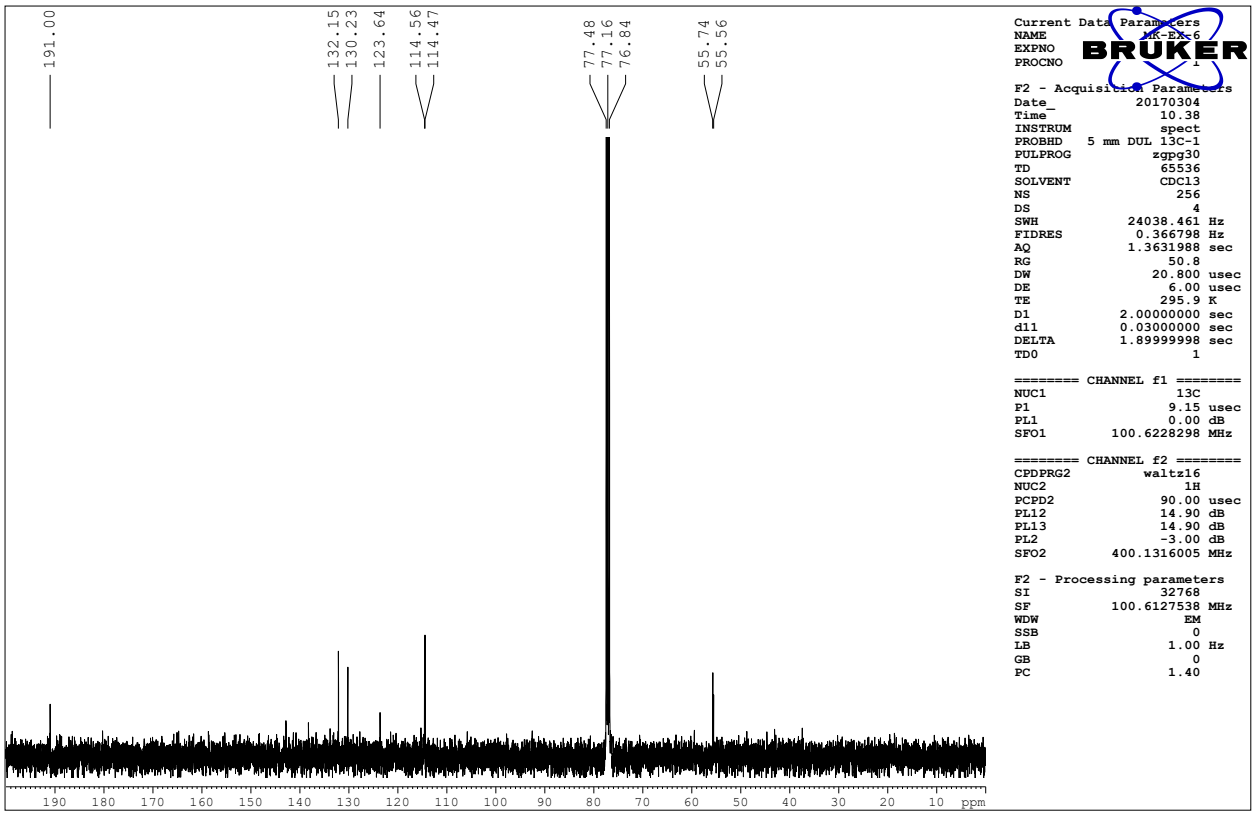
C. Spectral Data



4a-^{1}H NMR

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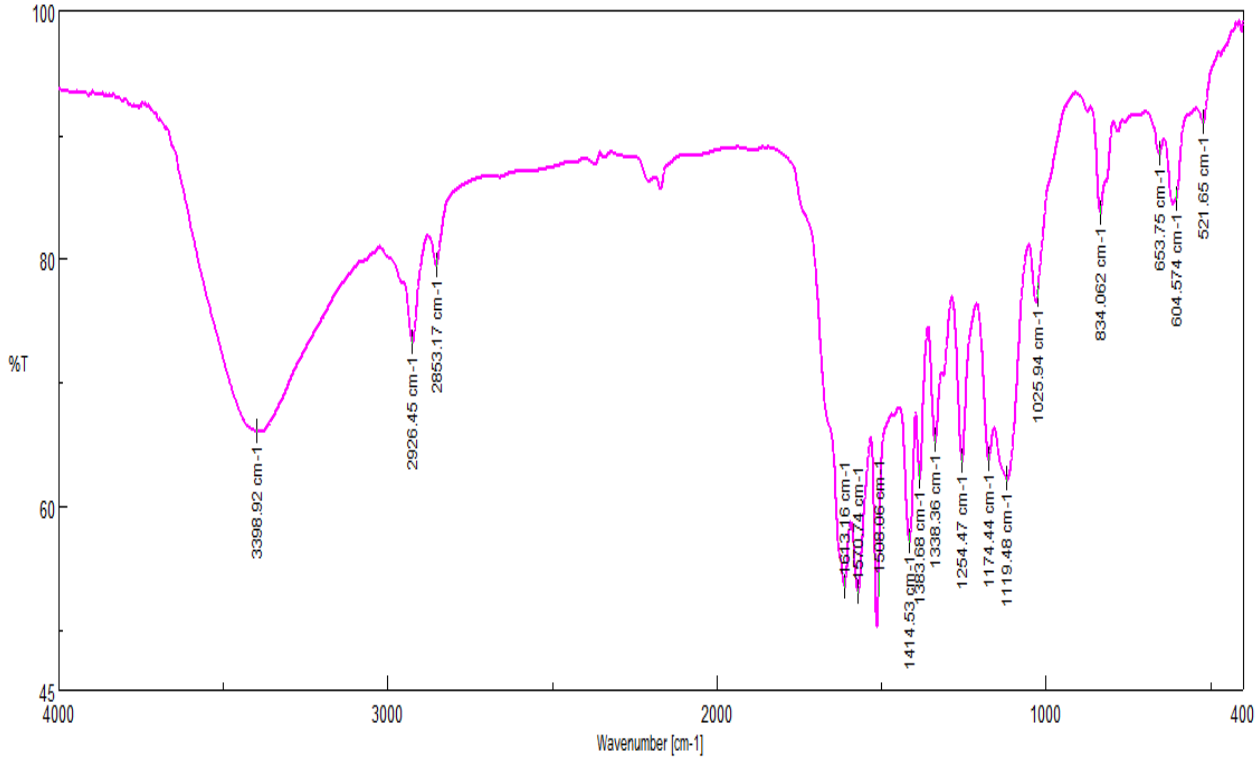
5A-I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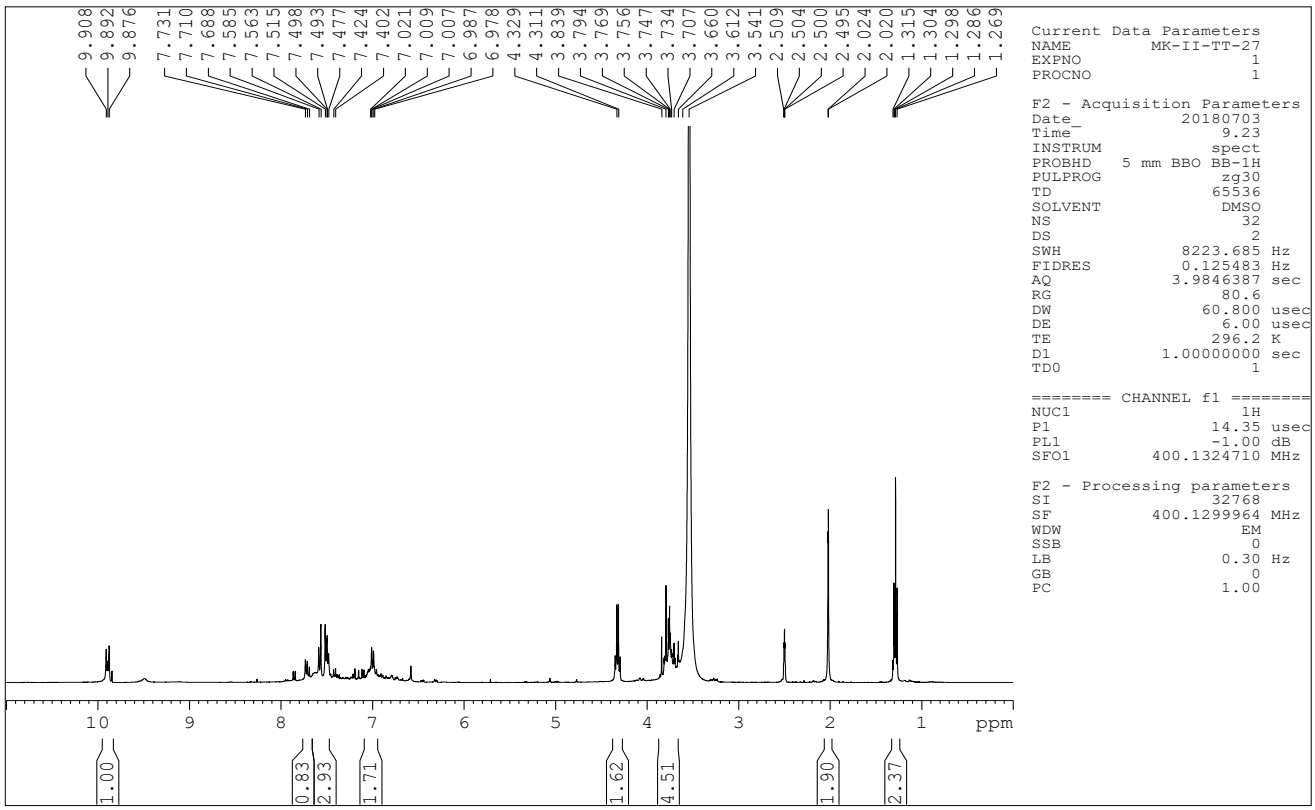
521.65 cm-1

5a-^{1}H-NMR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5A-^{13}C-NMR

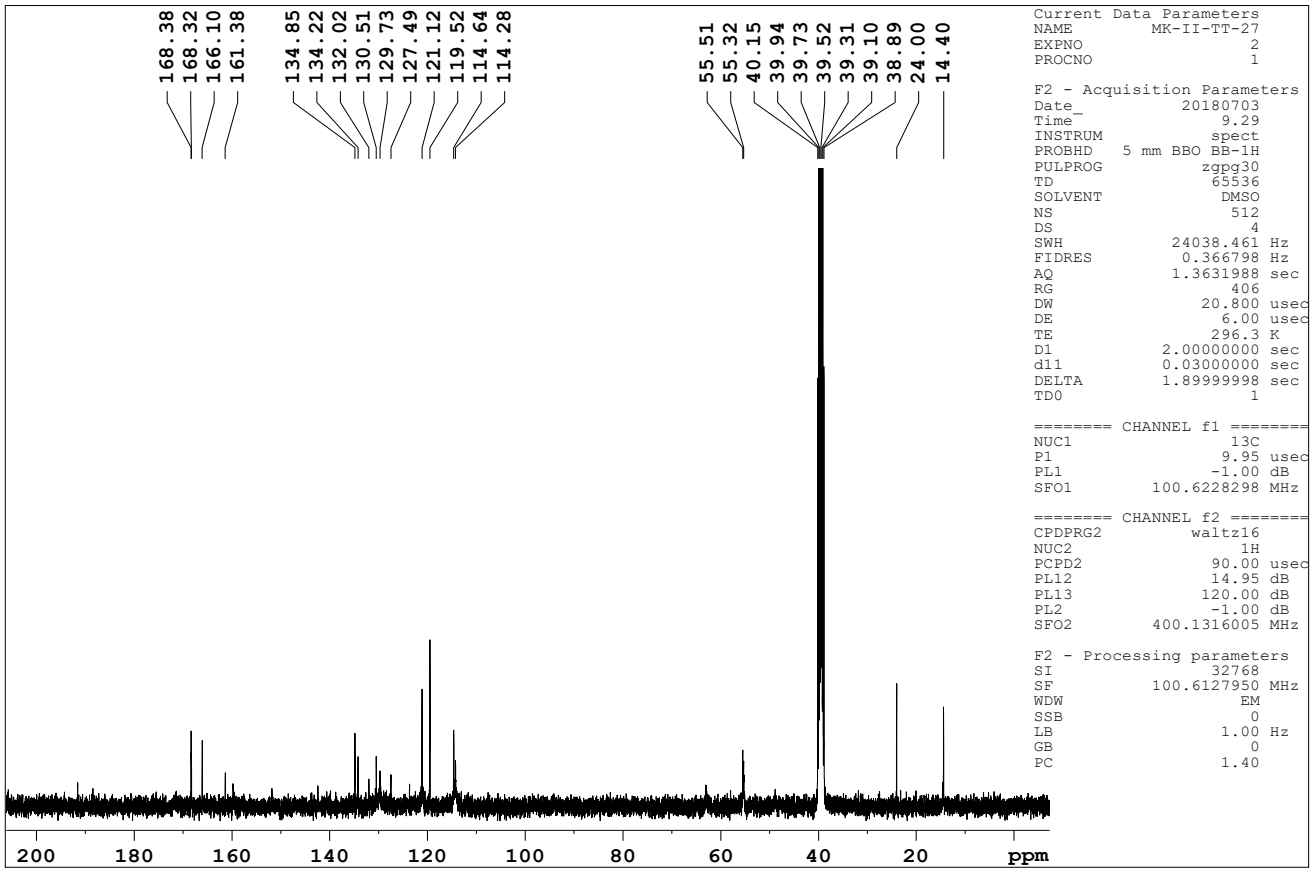
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Table- 1: Physical data of the synthesized compounds (4a-c) and (5a-c)

Compound code	R	Mol. Formula	Mol. weight	MP(ºC)	Yield(%)	Rf value
4a	**$C_6H_4OCH_3$**	**$C_{19}H_{15}C1_2N_5O_2$**	**416.26**	**190-191 ºC**	**89%**	**0.61**
4b	**C_6H_4F**	**$C_{17}H_{13}Cl_2FN_5O$**	**404.23**	**194-196 ºC**	**75%**	**0.70**
4c	**$C_7H_5O_2$**	**$C_{19}H_{13}Cl_2N_5O_3$**	**430.24**	**206-208º C**	**83%**	**0.53**
5a	**$C_6H_4OCH_3$**	**$C_{22}H_{16}Cl_2N_8O$**	**479.32**	**115-120 ºC**	**70 %**	**0.55**
5b	**C_6H_4F**	**$C_{17}H_{13}Cl_2FN_8$**	**467.29**	**138-140º C**	**75%**	**0.65**
5c	**$C_7H_5O_2$**	**$C_{22}H_{14}Cl_2N_8O_2$**	**493.30**	**123-125º C**	**62 %**	**0.61**

Table 2: Elemental analysis of the synthesized compounds (4a-c) and (5a-c)

Compound code	Mol. Formula	Appearance	Elemental Analysis		
			% C Calcd (found)	% H Calcd (found)	% N Calcd (found)
4a	$C_{19}H_{15}C1_2N_5O_2$	Light yellow	54.82 (54.80)	3.63 (3.60)	16.82 (16.21)
4b	$C_{18}H_{12}C1_2N_5OF$	Half white	53.48 (53.46)	2.99 (2.97)	17.83 (17.80)
4c	$C_{19}H_{13}Cl_2N_5O_3$	Pale yellow	53.04 (53.03)	3.05 (3.03)	16.28 (16.26)
5a	$C_{22}H_{16}Cl_2N_8O$	Greenish yellow	55.13 (55.10)	3.36 (3.33)	23.38 (23.35)
5b	$C_{21}H_{13}Cl_2FN_8$	Dark brown	53.98 (53.95)	2.80 (2.78)	23.98 (23.97)
5c	$C_{22}H_{14}Cl_2N_8O_2$	Brown	53.67 (53.66)	2.86 (2.84)	22.75 (22.73)

Table 3: Larvicidal activity

S.No.	Chemical name with concentration	Effectiveness after 24 Hrs in % of killing
1	5a	**79%**
2	5b	**80%**
3	5c	**72%**

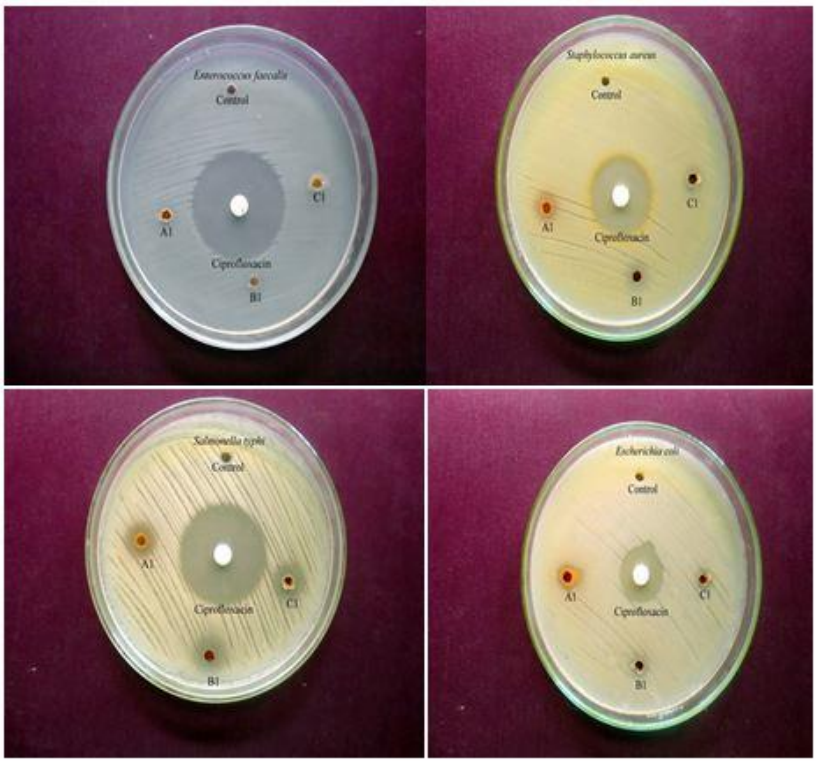
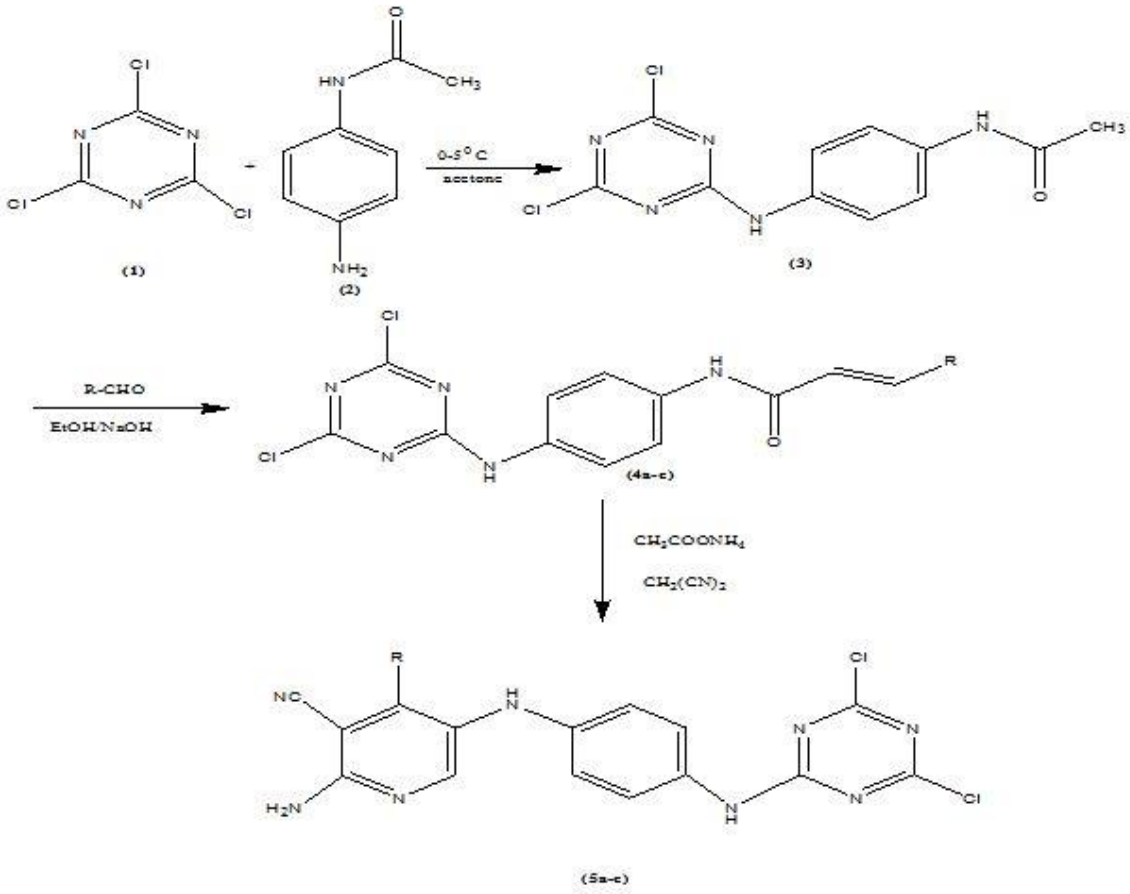


Figure 1. In vitro antibacterial activity data of s-triazine derivatives against tested organisms.

Standard = Ciprofloxacin

A1- Compound 5a B1- Compound 5b, C1- Compound 5C,



CONCLUSION

We have successfully synthesizes a new series of chalcone derivatives and moreover, some compounds contains bioactive heterocyclic moiety. The antibacterial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested organism. The compounds showed good Larvicidal activity.

ACKNOWLEDGEMENT

The author's wishes to express their thanks to, Department of chemistry, Thiruvalluvar university for providing laboratory facilities and also pondicherry university for spectral and Larvicidal studies.

REFERENCES

[1]. Dhar DN. Chem. Review 1981.
[2]. Bardia R, Rao JT. Asian. J. chem. 2004,16,1194.
[3]. Hussian MA. Indian J. Chem. 2001,40A, 324.
[4]. Ishida S, Matsuda A, Kawamura A. Chemotherapy.1960, 146.
[5]. Salvie D, Richard F, John A. Bio Org. Med. Chem. Lett.1998, 9, 8.
[6]. Vanstone AE , Maile GK, Nalbantoglu LK. Ger. Offen. DE. 1986, 3, 537, 207.
[7]. Prescott . Int. J. Clin. Pharmacol. Bio. Pharm.,1975,11(4), 332.
[8]. De vincenzo R, Seambla G, Panici P, Benedess, Remelletti FO. Anticancer. Drug Des. 1995, 10(6), 481-490.
[9]. Ahluwalia VK, Nayal L, Kaila N, Bala S, Tahim AK. India. J. Chem.1987, 26B, 384.
[10]. Modzelewska A, Pettit C, Achanta G, Davidson NE, Hunag P, Khan SR. Anticancer activities of novel chalcone and bischalcone. Bioorg. Med. chem. 2006, 14:10, 3491-3495.
[11]. Mehta KJ, Patel VS, Parikh AR. J. Indian chem. Soc.1978, 50, 241.
[12]. Pedersen AK, Fitzgereald GA, J. Pharm. Sci. 1985,74(2), 188.
[13]. Mishra SS, Kowhwaha CS. Indian. J.Chem. Soc.1977, 64, 640.
[14]. Brzozowski z, Kaminski Z. And Angielski S, Acta Pol. Chem. Abstr. 1980,93, 204525e.
[15]. Tomcufak AS, Wilkson RG, Child RG. German Patent .1975, 2502490.

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