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Biological evaluation of some novel chalcones and their derivatives

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Chalcones, (E)-N-(4-(4,6-dichloro-1,3,5 –triazin-2-ylamino) phenyl)-3-(4 methoxy-phenyl) acrylamide **4a-c** have been prepared by employing Claisen-Schmidt condensation. Further, these chalcones **4a-c** on reaction with malononitrile afford cyano-pyridines **5a-c** respectively. The constitution of newly synthesised compounds have been characterized on the basis of their IR, ^{1}H and ^{13}C NMR spectral data. These synthesized compounds have been screened for their antibacterial and larvicidal activity.

Keywords: Chalcones, cyanopridines, larvicidal activity, antibacterial activity

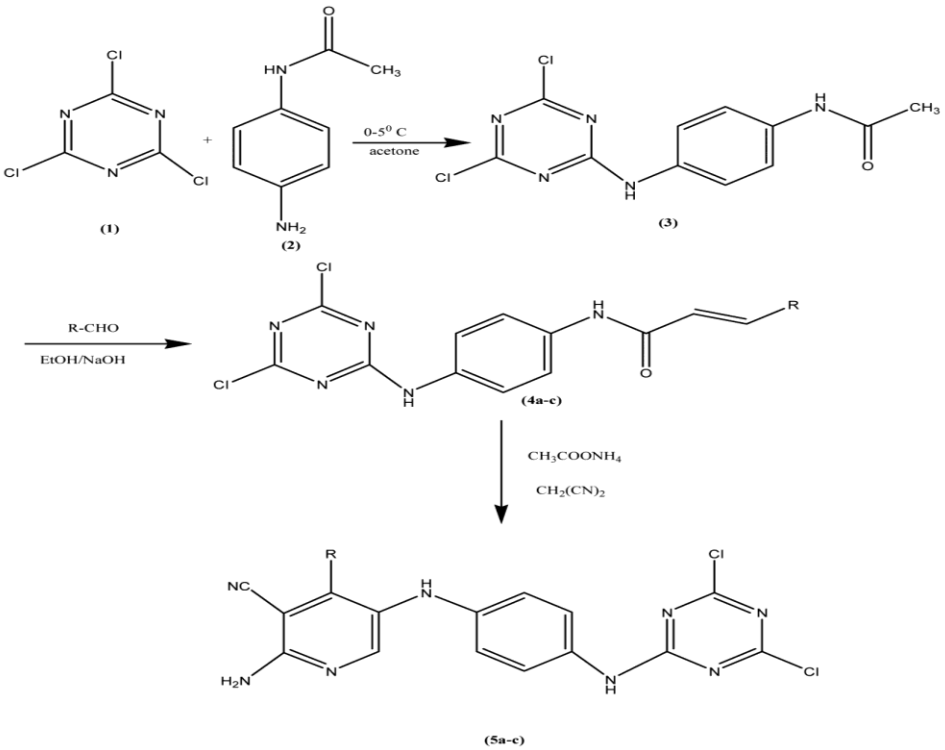
Heterocyclic compounds are cyclic organic substances which contain at least one atom other than carbon in the ring system. The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. A practical method for the synthesis of such compounds is of great interest in synthetic 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 (Scheme I).

Experimental Section

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. IR spectra 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.

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

4-Amino acetanilide (0.01 mol) was added slowly to cyanuric chloride (0.01 mol) in acetone (30ml) with constant stirring over a period of 4 hr at 0 to 5ºC Then,sodium carbonate (0.05 mol) 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



Scheme I

filtration and washed with water. The product is dried, recrystallized from alcohol to give the product (3).

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 mol) was dissolved in Ethanol (30 ml) Then 10% NaOH solution and 4-Methoxybenzaldehyde (0.01mol) 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): -N,s-triazine (829.90), CN-H str (3419.04), C─Cl (770.81 cm^{-1}).

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 mol) was dissolved in Ethanol (30 ml) Then 10% NaOH solution and 4-Flurobenzaldehyde (0.01mol) 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): C-N,s-triazine (809.95), N-H str (2926.45), C─Cl (764.63).

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 mol) was dissolved in Ethanol (30 ml) Then 10% NaOH solution and piperonal (0.01mol) 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): C-N,s-triazine (809.95), N-H str (2922.59), C─Cl (657.60).

Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2ylamino) phenylamino)-2-amino-4-(4-methoxy-phenyl) pyridine-3-carbonitrile, 5a

A mixture of a compound **4a** (0.01 mol) dissolved in 40 ml ethanol and added malononitrile (0.01 mol),ammonium acetate (0.08 mol) 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): 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 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 Aliphatic-CH_3 (55.51), Ar-CH (119.52 to 121.12), 2-Py (134.85), 1-imine (166.10), S-triazine (168.3).

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 mol) dissolved in 40 ml ethanol and added malononitrile (0.01 mol), ammonium acetate (0.08 mol) 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): 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 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 Ar-CH (119.40to 121.02), 2-Py-CH (134.15 to135.28), S-triazine (168.20).

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 mol) dissolved in 40 ml ethanol and added malononitrile (0.01 mol),ammonium acetate (0.08 mol) 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. IR (KBr): C=C (1578.45), 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 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 Ar-CH (108.82 to121.53), 2-Py-CH (134.65 to 148.38), 1-imine (166.01), S-triazine (166.24).

Results 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 (Table I and Table II) and antibacterial and Larvicidal activity of some novel s-triazine based cyanopyridine derivatives.

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

Table I — Physical characterization data of the synthesized compounds **4a-c** and **5a-c**

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

Table II — Elemental analysis of the synthesized compounds **4a-c** and **5a-c**

Compd	Mol. Formula	Appearance	Elemental Analysis		
			C	H	N
			Calcd % (Found)	Calcd % (Found)	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)

of dead larvae were counted after 24 h of exposure and the percentage of mortality was reported from the average of five replicates (Table III).

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method against *S. aureus* and *E. faecalis* (Gram positive bacteria) and *E. coli*, *S. typhi* (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 IV, Figure 1).

Table III — Larvicidal activity of compounds **5a**, **5b** and **5c**

S. No.	Compd	Effectiveness after 24 hr (% of larvae killed)
1	**5a**	79
2	**5b**	80
3	**5c**	72

Table IV — Antibacterial activity data of compounds **5a-c**

S.No	Microorganism	Control	**5a**	**5b**	**5c**	Ciprofloxacin
1	*Enterococcus faecalis*	–	16	15	19	35
2	*Staphylococcus aureus*	–	18	16	15	18
3	*Salmonella typhi*	–	10	10	8	30
4	*Escherichia coli*	–	10	13	9	15

Standard = Ciprofloxacin

A1- Compound **5a** B1- Compound **5b**, C1- Compound **5c**,

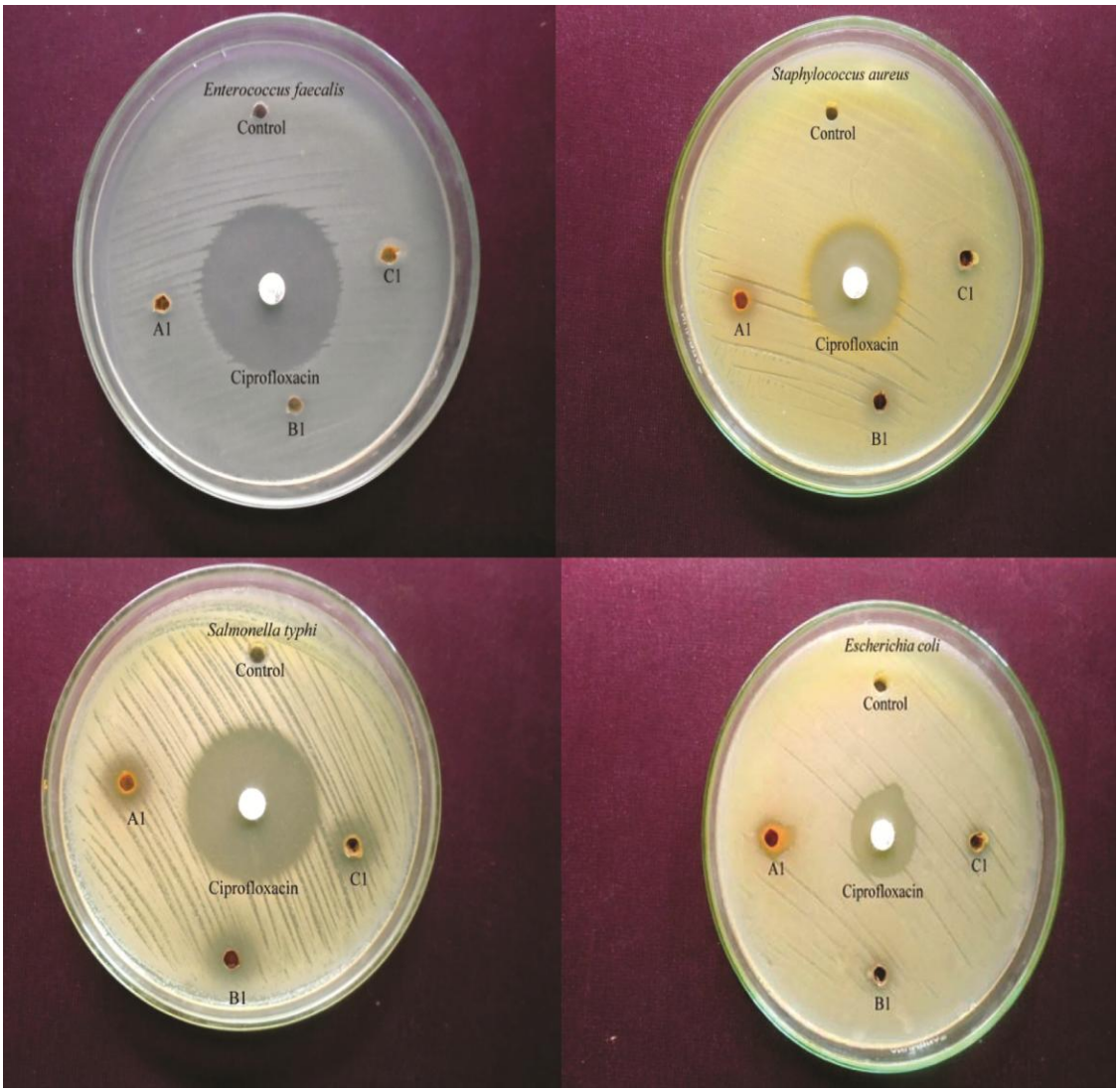


Figure 1 — *In vitro* antibacterial activity data of s-triazine derivatives against tested organisms

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.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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