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Synthesis and Biological Evaluation of Some New Chalcones and Their Derivatives

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Some new chalcones have been prepared by the Claisen-Schmidt condensation between ketone and different aldehydes. Further chalcones on cyclocondensation with phenylhydrazine hydrochloride and thiourea in presence of alkali give pyrazolines and pyrimidinethiones respectively. The constitution of the synthesized products have been characterized by elemental analysis, IR and PMR spectral data. The products have been screened for their *in vitro* biological assay like antibacterial activity.

Key Words: Synthesis, Chalcones, Pyrazolines, Pyrimidinethiones, Antibacterial activity.

INTRODUCTION

The chemistry of chalcones has been recognized as a significant field of study. Chalcones[1,2] are useful intermediates in the synthesis of various heterocyclic compounds such as pyrazolines, isoxazolines pyrimidines, flavones and flavonols. Chalcones have been associated with diverse biological activities, *e.g.*, cardiovascular[3], antiviral[4], anticancer[5], etc. The literature survey reveals that pyrazolines are found to possess many biological activities and have variety of industrial applications[6]. Pyrazolines have also been found to possess antiinflammtory[7], antidiabetic[8] and anaesthetic[9] properties. Pyrimidinethiones[10–12] also play a vital role in many biological processes. Pyrimidinethiones have been found to possess antitubercular[13], antifungal and antibacterial[15] activities.

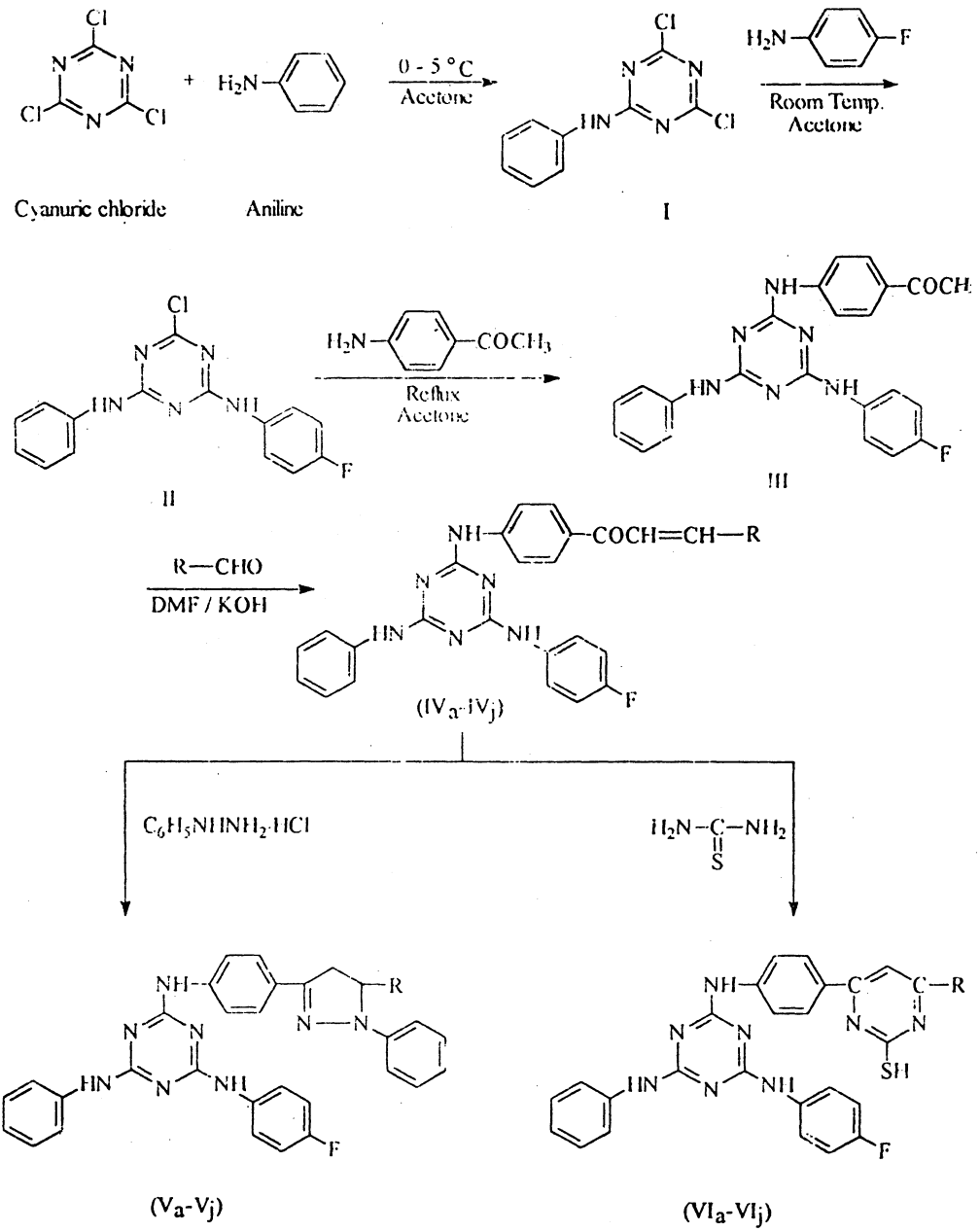
In the present work chalcones have been prepared according to Claisen-Schmidt condensation by condensing ketone with different aldehydes. Further, these chalcones on cyclocondensation with phenylhydrazine hydrochloride and thiourea in presence of alkali give pyrazolines and pyrimidinethiones respectively.

EXPERIMENTAL

Melting points of the synthesized compounds have been taken in open capillaries and are uncorrected. Purity of the compounds is checked on TLC using Silica Gel-G. IR spectra have been taken on Perkin-Elmer-283 spectrophotometer using KBr pellets. NMR spectra have been run on Bruker Avance DPX 200 MHz

spectrophotometer and chemical shifts (δ in ppm) have been reported relative to TMS as an internal standard. The C and N analyses have been done on Carlo-Erba-1108 analyzer. All synthesized compounds have been screened for their antibacterial activity. All the physical and analytical data are given in Table-1.

Reaction



I

II

III

(IV_a-IV_j)

(V_a-V_j)

(VI_a-VI_j)

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS (IVa – VIj)

Compd.	R	m.f.	m.p. (°C)	% Elemental analysis			
				C		N	
				Found	Calcd.	Found	Calcd.
IVa	3-Chlorophenyl	$C_{30}H_{22}FClN_6O$	152	67.08	67.01	15.60	15.65
IVb	2-Nitrophenyl	$C_{30}H_{22}FN_7O_3$	110	65.80	65.81	17.90	17.91
IVc	4-Nitrophenyl	$C_{30}H_{22}FN_7O_3$	148	65.79	65.81	17.99	17.91
IVd	4-Methylphenyl	$C_{31}H_{25}FN_6O$	106	72.00	72.09	16.22	16.28
IVe	3-Methoxypheyl	$C_{31}H_{25}FN_6O$	120	69.82	69.92	15.71	15.79
IVf	2,4-Dichlorophenyl	$C_{30}H_{21}FCl_2N_6O$	155	63.00	63.04	14.70	14.71
IVg	2,5-Dimethoxyphenyl	$C_{32}H_{27}N_6FO_3$	115	68.29	68.22	15.00	14.90
IVh	3,4,5-Trimethoxyphenyl	$C_{33}H_{29}FN_6O_4$	147	66.86	66.89	14.22	14.18
IVi	2-Furanyl	$C_{28}H_{21}FN_6O_2$	144	68.25	68.29	17.00	17.07
IVj	3-Pyridinyl	$C_{29}H_{22}FN_7O$	121	69.23	69.18	19.50	19.48
Va	3-Chlorophenyl	$C_{36}H_{28}FClN_8$	149	68.93	68.95	17.99	17.87
Vb	2-Nitrophenyl		123	67.87	67.81	19.70	19.78
Vc	4-Nitrophenyl	$C_{36}H_{28}FN_9O_2$	132	67.93	67.26	19.88	19.78
Vd	4-Methylphenyl	$C_{37}H_{31}FN_8$	94	73.23	73.26	18.42	18.48
Ve	3-Methoxyphenyl	$C_{37}H_{31}FN_8O$	97	71.33	71.38	18.11	18.00
Vf	2,4-Dichloropheneyl	$C_{36}H_{27}FCl_2N_8$	111	65.34	65.35	16.85	16.94
Vg	2,5-Dimethoxyphenyl	$C_{38}H_{33}FN_8O_2$	109	69.89	69.93	17.00	17.17
Vh	3,4,5-Trimethoxyphenyl	$C_{39}H_{35}FN_8O_3$	121	68.51	68.62	16.41	16.42
Vi	2-Furanyl	$C_{34}H_{27}FN_8O$	93	70.19	70.10	19.25	19.24
Vj	3-Pyridinyl	$C_{35}H_{28}FN_9$	113	70.89	70.82	21.20	21.24
VIa	3-Chlorophenyl	$C_{31}H_{22}FClN_8S$	156	62.75	62.78	18.87	18.90
VIb	2-Nitrophenyl	$C_{31}H_{22}FN_9O_2S$	113	61.64	61.69	21.00	20.89
VIc	4-Nitrophenyl	$C_{31}H_{22}FN_9O_2S$	140	61.63	61.69	20.76	20.89
VId	4-Methylphenyl	$C_{32}I_{25}FN_8S$	139	67.12	67.13	19.50	19.58
VIe	3-Methoxyphenyl	$C_{32}H_{25}FN_8OS$	105	65.29	65.30	19.00	19.04
VIf	2,4-Dichlorophenyl	$C_{31}H_{22}FCl_2N_9O_9S$	150	59.39	59.33	18.00	17.86
VIg	2,5- Dimethoxyphenyl	$C_{33}H_{27}FN_8O_2S$	130	64.00	64.07	18.10	18.12
VIh	3,4,5-Trimehoxyphenyl	$C_{34}H_{29}FN_8O_3S$	143	62.91	62.96	17.23	17.28
VIi	2-Furanyl	$C_{29}H_{21}FN_8OS$	105	63.42	63.50	20.33	20.43
VIj	3-Pyridinyl	$C_{30}H_{22}FN_9S$	142	64.43	64.40	22.44	22.54

Preparation of 2-phenylamino-4,6-dichloro-s-triazine (I): Aniline (0.01 mol) was added slowly to cyanuric chloride (0.01 mol) in acetone (30 mL) with constant stirring within 4 h at 0°C. Sodium carbonate solution was added to neutralize HCl evolved during the reaction. Finally the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol, m.p. 196°C.

Preparation of 2-phenylamino-4-(4′-fluorophenylamino)-6-chloro-s-triazine (II): 4-Fluoro aniline (0.01 mol) was added solowly to compound **I** (0.01 mol) in acetone (35 mL) with constant stirring within 4 h at room temperature. Sodium carbonate solution was added to neutralize HCl evolved during the reaction. Finally the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallized from alcohol, m.p. 170°C.

Preparation of 2-phenylamino-4-(4′-fluorophenylamino)-6-(4′-acetylphenylamino)-s-triazine III: 4-Amino acetophenone (0.01 mol) and compound **II** (0.01 mol) were dissolved in acetone (40 mL). The reaction mixture was refluxed for 4 h. Periodically sodium carbonate solution was added to neutralize HCl evolved during the reaction. Finally the reaction mixture was cooled and poured into crushed ice. The solid separated out was filtered, washed with water and recrystallized from alcohol, m.p. 190°C.

Preparation of 2-phenylamino-4-(4′-fluorophenylamino)-6-(4′-{3″-(3‴,4‴, 5‴-trimethoxyphenyl)-2″-propenon-1″-yl}-phenylaminol-s-triazine (IVh): Compound **III** (0.01 mol) was dissolved in DMF (20 mL) and 3,4,5-trimethoxy benzaldehyde (0.01 mol) was added to it. Then 40% KOH (1 mL) was added to the reaction mixture with constant stirring at room temperature. After 24 h the reaction mixture was poured into crushed ice and neuralized with HCl. The yellow colour solid separated out was filtered, washed withe water and recrystallized from alcohol. m.p. 147°C.

Similarly other compounds (**IVa–j**) were prepared by the same method as discussed above.

IR spectra (cm^{-1}) (KBr): 810 ν(C—N) (s-triazine), 3315 ν(—NH) (secondary amine), 1670 ν(C==O) (chalcone moiety), 1580 ν(—CH=CH—) (chalcone moiety), 1350 ν(C—N) (aromatic) and 1070 ν(C—F). **NMR spectra ($CDCl_3$):** 3.8 (s, 6H, *m*-OCH_3), 3.9 (s, 3H, *p*-OCH_3), 6.8 (d, 1H, —CO—CH=), 8.1 (d, 1H, Ar—CH=) and 7.0 to 7.75 (m, 18H, Ar—H + NH).

Preparation of 2-phenylamino-4-(4′-fluorophenylamino)-6-[4′-{1″-phenyl-5″-(2‴,5‴- dimethoxyphenyl)-pyrazolin-3″-yl}-pheylamino]-s-triazine (Vg): A mixture of chalcone (**IVg**) (0.01 mol) and phenylhydrazine hydrochloride in 25 mL dioxane was refluxed for 10 h in presence of alkali. Then the reaction mixture was cooled and poured into crushed ice and neutralised with diluted HCl. The solid separated out was filtered, washed with water and recrystallized from alcohol, m.p. 109°C.

Similarly other compounds (**Va–j**) were prepared by the same method as discoussed above.

IR spectra (cm^{-1}) (KBr): 810 ν(C—N) (s-triazine), 3315 ν(—NH) (secondary amine), 1350 ν(—CH_2) (pyrazoline ring), 1580 ν(C=N) (pyrazoline ring)

and 1070 ν(C—F). **NMR spectra ($CDCl_3$)** 2.9 (dd, 1H, CH—CH_a), 3.5 (dd, 1H, CH—CH_b), 3.8 (s, 3H, *o*-OCH_3), 3.9 (s, 3H, *m*-OCH_3), 5.2 (t, 1H, CH_2—CH) and 6.75 to 7.75 (m, 20H, Ar—H + NH).

Preparation of 2-phenyl amino-4-(4′-fluorophenylamino)-6-[4′-{2″-mercapto-6″-(3‴-chlorophenyl)-pyrimidin-4″-yl}-phenylamino]-s-triazine (VIa): A mixture of chalcone (**IVa**) (0.01 mol) and thiourea in 25 mL dioxane was refluxed for 10 h in presence of alkali. Then the reaction mixture was cooled, poured into ice and neutralized with diluted HCl. The solid separated out was filtered, washed and recrystallised from alcohol, m.p. 156°C.

Similarly other compounds (**VIa – j**) were prepared by the method as discussed above.

IR spectra (cm^{-1}) (KBr) of compound VIa: 810 ν(C—N) (s-triazine), 3320 ν(NH) (secondary amine), 1580 ν(C=N) (pyrimidine ring), 2560 ν(—SH) (pyrimidine ring), 1075 ν(C—F) and 750 ν(C—Cl). **NMR spectra ($CDCl_3$):** 3.2 (s, 1H, —CH), 4.8 (s, 1H, —SH) and 6.8 to 8.1 (m, 20H, Ar—H + NH).

Antbacterial Activity

The synthesized compounds were assayed against human pathogens like gram positive *S. aureus*, *B. subtilis* and gram negative *E. coli*, *S. paratyphi-A* by agar cup plate method[16] at concentration of 40 μg/mL in solvent DMF using nutrient agar medium. The zone of inhibition was measured in mm. Under similar conditions control experiment was carried out using Chloramphenicol, Streptomycin and Penicillin. The results are shown in Table-2.

From the experimental data it has been observed that the compounds **IVb** and **IVf** bearing R = 2-nitrophenyl and 2,4-dichlorophenyl respectively are found to be moderately active against *S. aureus*. The remaing compounds are found to be less active or inactive against the same bacteria.

In case of gram negative bacteria *E. coli* compound **IVe** bearing R = 3-methoxyphenyl shows good activity, whereas the remaining compounds are found to be less active or inactive against the same bacteria.

Compound **IVa** bearing R = 3-chlorophenyl shows very good activity against *S. paratyphi-A*, whereas compound **IVh** bearing R = 3,4,5-trimethoxyphenyl is found to be active against the same bactria. Compounds **IVc**, **IVd**, **IVr** and **IVb** baring R = 4-nitrophenyl, 4-methylphenyl, 2,4-dichlorophenyl and 2-nitrophenyl respectively are found to be moderately active against *S. paratyphi-A*, While the remaining compounds are less active or inactive against the same bacteria.

In case of gram positive bacteria *B. subtilis* compound **IVd** bearing R = 4-methylphenyl shows very good activity whereas compound, **IVa**, **IVb** and **IVh** bearing R = 3-chlorophenyl, 2-nitrophenyl and 3, 4, 5-trimethoxyphenyl respectively are found to be moderately active against the same bacteria. The remaining compounds are poorly active or inactive against *B. subtilis*.

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS (IVa–VI)

Compd.	R	Diameter of zone of inhibition (in mm)			
		S. aureus	*E. coli*	*S. paratyphi-A*	*B. subtilis*
IVa	3-Chlorophenyl	–	–	19	14
IVb	2-Nitrophenyl	13	12	10	14
IVc	4-Nitrophenyl	12	9	14	10
IVd	4-Methylphenyl	–	–	14	18
IVe	3-Methoxypheyl	–	15	–	9
IVf	2,4-Dichlorophenyl	13	–	14	–
IVg	2,5-Dimethoxyphenyl	–	–	–	–
IVh	3,4,5-Trimethoxyphenyl	–	–	16	15
IVi	2-Furanyl	10	–	–	–
IVj	3-Pyridinyl	9	12	–	–
Va	3-Chlorophenyl	–	11	–	–
Vb	2-Nitrophenyl	10	–	8	–
Vc	4-Nitrophenyl	10	–	8	–
Vd	4-Methylphenyl	–	12	11	10
Ve	3-Methoxypheyl	9	9	9	–
Vf	2,4-Dichloropheneyl	–	–	–	–
Vg	2,5-Dimethoxyphenyl	9	8	9	–
Vh	3,4,5-Trimethoxyphenyl	9	9	9	8
Vi	2-Furanyl	9	9	9	8
Vj	3-Pyridinyl	8	10	10	9
VIa	3-Chlorophenyl	–	11	8	10
VIb	2-Nitrophenyl	8	11	13	–
VIc	4-Nitrophenyl	–	9	10	11
VId	4-Methylphenyl	–	12	9	–
VIe	3-Methoxyphenyl	8	8	10	–
VIf	2,4-Dichlorophenyl	8	10	10	9
VIg	2,5-Dimethoxyphenyl	8	9	10	–
VIh	3,4,5-Trimethoxyphenyl	–	9	9	–
VIi	2-Furanyl	9	11	10	–
VIj	3-Pyridinyl	9	–	10	11

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