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Synthesis and Antimicrobial Study of Triazolo Pyrazolines and Isoxazoline Derivatives

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2,4-Bis-anilino-6-(2′-acetyl 4′-chlorophenyl phenyloxy)triazines have been converted into chalcones by condensing with aromatic aldehydes. These chalcones on treatment with hydrazine hydrate and hydroxyl amine hydrochloride give pyrazolines and isoxazolines respectively. The synthesized compounds have been tested for their antimicrobial activity.

Key Words: S-triazine, Pyrazolines, Isoxazoline, Chalcone.

INTRODUCTION

S-triazine[1] nucleus has a potential therapeutic agent for diseases due to bacteria and protozoa[2], African sleeping sickness[3,4], malaria[5,6] and cancer[7]. Nitrogen heterocyclic compounds like pyrazolines and isoxazolines have received considerable attention in recent years due to their biological and physiolcgical activities. Several pyrazoline derivatives have shown considerable promise as chemotherapeutic agents[8]. Some derivatives of isoxazoline have been reported for their bacteriostatic, herbicidal, antiinflammatory and analgesic activities. 2,4-Dimethyl-5-sulphanilamido isoxazolines[9] (gastrin) is known as therapeutically active drug. These observations prompted us to synthesise some pyrazolines and isoxazolines incorporating S-triazine moiety and to study their biological activity.

EXPERIMENTAL

All melting points were taken in open capillary in liquid paraffin bath and are uncorrected. Purity of all compounds was checked by TLC. IR spectra were recorded in nujol on Perkin-Elmer 1420 spectrophotometer while PMR spectra in $CDCl_3$ on Bruker AC-300 spectrophotometer using TMS as an internal standard.

2,4-Bisanilino-6-[2′(3″-phenyl pyrazolin-5″-yl)-4′-chlorophenyloxy]triazine (1): Chalcone (1) (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (50 mL) containing acetic acid (7.0 mL) was refluxed for 4 h. The reaction mixture was concentrated, cooled and pured into ice-cold water. The solid separated was filtered, washed and crystallized from ethyl alcohol. Yield 70%, m.p. 205°C.

IR nujol (cm^{-1}): 3300–3320 ν(—NH), 1590 ν(C=N), 1230–1225 ν(C–O–C). PMR: 3.3–3.5 δ(S, 3H forming on ABX system corresponding to —CH—CH_2 group n of pyrazoline ring), 6.7 δ(d, 1H, —NH pyrazoline), 7.0–7.5 δ(m, 16H, Ar—H), 7.8 δ (S, 2H, —NH).

Similarly, other compounds of the series (**2–15**) were synthesized. The analytical data of these compounds are recorded in Table-1.

TABLE-1
CHARACTERIZATION DATA OF PYRAZOLINES AND ISOXAZOLINES

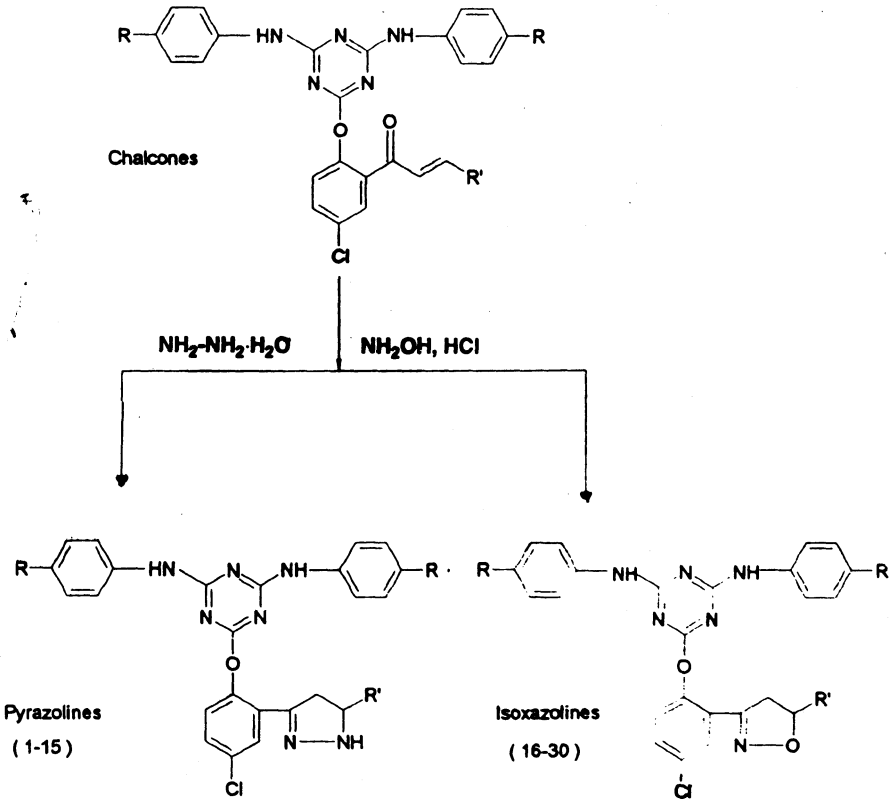
Compound	R	R′	Yield (%)	m.p. (°C)	m.f.	N%	
						Calcd.	Found
1	Cl	C_6H_5	70	205	$C_{30}H_{22}N_7Cl_3$	16.7	16.4
2	Cl	2-ClC_6H_4	73	208	$C_{30}H_{21}N_7OCl_4$	15.3	15.0
3	Cl	3-ClC_6H_4	71	182	$C_{30}H_{21}N_7OCl_4$	15.3	14.9
4	Cl	4-ClC_6H_4	74	216	$C_{30}H_{21}N_7OCl_4$	15.3	15.1
5	Cl	4-$NO_2C_6H_4$	77	202	$C_{30}H_{21}N_8O_2Cl_3$	17.7	17.3
6	CH_3	C_6H_5	73	188	$C_{32}H_{28}N_7Cl$	18.4	18.2
7	CH_3	2-ClC_6H_4	75	230	$C_{32}H_{27}N_7Cl_2$	17.3	17.0
8	CH_3	3-ClC_6H_4	72	202	$C_{32}H_{27}N_7Cl_2$	17.3	16.9
9	CH_3	4-ClC_6H_4	76	170	$C_{32}H_{27}N_7Cl_2$	17.3	17.2
10	CH_3	4-$NO_2C_6H_4$	73	208	$C_{32}H_{27}N_8O_2Cl$	18.9	18.5
11	OCH_3	C_6H_5	69	220	$C_{32}H_{28}N_7O_2Cl$	16.9	16.5
12	OCH_3	2-ClC_6H_4	74	204	$C_{32}H_{27}N_7O_2Cl_2$	16.0	15.6
13	OCH_3	3-ClC_6H_4	70	198	$C_{32}H_{27}N_7O_2Cl_2$	16.0	15.8
14	OCH_3	4-ClC_6H_4	72	184	$C_{32}H_{27}N_7O_2Cl_2$	16.0	15.7
15	OCH_3	4-$NO_2C_6H_4$	75	214	$C_{32}H_{27}N_8O_4Cl$	17.9	17.6
16	Cl	C_6H_5	73	224	$C_{30}H_{21}N_6OCl_3$	14.2	13.9
17	Cl	2-ClC_6H_4	71	157	$C_{30}H_{20}N_6OCl_4$	13.5	13.3
18	Cl	3-ClC_6H_4	76	178	$C_{30}H_{20}N_6OCl_4$	13.5	13.1
19	Cl	4-ClC_6H_4	73	117	$C_{30}H_{20}N_6OCl_4$	13.5	13.3
20	Cl	4-$NO_2C_6H_4$	69	158	$C_{30}H_{20}N_7O_3Cl_3$	15.4	15.1
21	CH_3	C_6H_5	71	222	$C_{32}H_{27}N_6OCl$	15.3	15.0
22	CH_3	2-ClC_6H_4	72	168	$C_{32}H_{26}N_6OCl_2$	14.4	14.1
23	CH_3	3-ClC_6H_4	78	218	$C_{32}H_{26}N_6OCl_2$	14.4	14.2
24	CH_3	4-ClC_6H_4	71	204	$C_{32}H_{26}N_6OCl_2$	14.4	14.0
25	CH_3	4-$NO_2C_6H_4$	69	217	$C_{32}H_{26}N_7O_3Cl$	18.8	18.5
26	OCH_3	C_6H_5	72	205	$C_{32}H_{27}N_6O_3Cl$	14.5	14.2
27	OCH_3	2-ClC_6H_4	75	209	$C_{32}H_{26}N_6O_3Cl_2$	13.7	13.4
28	OCH_3	3-ClC_6H_4	71	219	$C_{32}H_{26}N_6O_3Cl_2$	13.7	13.3
29	OCH_3	4-ClC_6H_4	70	228	$C_{32}H_{26}N_6O_3Cl_2$	13.7	13.5
30	OCH_3	4-$NO_2C_6H_4$	68	198	$C_{32}H_{26}N_7O_5Cl$	15.7	15.3

2,4-Bisanilino-6-[2′(5″-phenyl isoxazolin-3″-yl)-4′-chlorophenyloxy] triazine (16)

Chalcone (1) (0.01 M), hydroxylamine hydrochloride (0.02 M) and KOH (0.02 M) methanol (50 mL) was refluxed for 4 h. The reaction mixture was cooled and acidified with acetic acid. The solid obtained was filtered, washed with water and crystallized from ethanol to give compound **16.** Yield 73%, m.p. 224°C.

IR (nujol, cm^{-1}): 3320–3300 ν(—NH), 1590 ν(C=N), 1230–1225 ν(C—O—C); PMR = 3.3–3.5 δ(S, 3H, ABX pattern of isoxazoline ring corresponding to —CH—CH_2, 7.0–7.5 δ(m, 16H, Ar—H), 7.8 δ(S, —NH).

Similarly, other compounds of the series (**17–30**) were synthesized. The analytical data of these compounds is recorded in Table-2.



Scheme-1

RESULTS AND DISCUSSION

Few of the representative compounds from the synthesized series were tested for their antifungal activity against *Alternaria brassicicola* and *Fusarium udam* while antibacterial activity was tested against *Staphylococcus* and *Lactobacillus* (Table-2). The activity of these compounds was tested using filter paper disc method[10] at 500 ppm concentration using 5 mm disc of filter paper. At similar conditions the standard drugs, *i.e.*, controls used were carbendazim and streptomycine.

From the activity data (Table-2) it may be concluded that the compound number **2, 4, 5, 16** and **19** showed good activity against fungi and bacteria. It was also observed that the pyrazolines and isoxazolines containing —Cl and —NO_2 group are showing good antimicrobial activity, while substituents such as —OCH_3 and —CH_3 are showing moderate to low activity.

TABLE-2
ACTIVITY DATA

Compound	R	R'	*Alternaria brassicicola*	*Fusarium-udam*	*Staphylo-coccus*	*Lactobacillus*
1	Cl	C_6H_5	11	10	12	+11
2	Cl	2-ClC_6H_4	14	14	15	+14
4	Cl	4-ClC_6H_4	15	14	15	+15
5	Cl	4-$NO_2C_6H_4$	13	12	12	+13
6	CH_3	C_6H_5	9	10	11	10
8	CH_3	3-ClC_6H_4	12	11	12	11
9	CH_3	4-ClC_6H_4	11	12	11	11
10	CH_3	4-$NO_2C_6H_4$	10	9	10	10
11	OCH_3	C_6H_5	11	12	11	11
12	OCH_3	2-ClC_6H_4	12	10	13	12
14	OCH_3	4-ClC_6H_4	13	11	12	12
16	Cl	C_6H_5	13	12	11	13
19	Cl	4-ClC_6H_4	14	14	15	14
21	CH_3	C_6H_5	9	10	10	9
23	CH_3	3-ClC_6H_4	8	9	11	10
25	CH_3	4-$NO_2C_6H_4$	9	10	10	8
26	OCH_3	C_6H_5	10	9	9	8
28	OCH_3	3-ClC_6H_4	11	10	10	11
30	OCH_3	4-$NO_2C_6H_4$	9	8	8	10
Carbendazim			15	14	—	—
Streptomycine			—	—	16	15

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