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Synthesis of *p*-N-substituted Tertiary Aminophenyl-4′-substituted Phenyl Ketone and Their Derivaties as Potent Antifungal Agents

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Several new *p*-N-substituted tertiary aminostyryl-4′-substituted phenyl ketone and some of their derivatives have been prepared. The structures have been supported by analysis and spectral data. Some of the compounds have been screened for their antifungal activity against *F. oxysporum*, *P. italicum*, *H. sativum* and *C. lunata*.

INTRODUCTION

In view of the significant antifungal activities of thiosemicarbazone, hydantoin derivatives of carbonyl compounds[1, 2] creates an interest to carry out research in this field. The present paper is to report the synthesis of a new set of complex chalcones and to investigate their use as a starting material for the synthesis of some new antifungal agent.

The required *p*-N-substituted tertiary amino styryl-4′-substituted phenyl ketones were prepared from the corresponding tertiary aminobenzaldehyde and *p*-substituted acetophenone by base catalysed condensation[3]. This complex chalcones were subjected to condensation reaction with thiosemicarbazide in presence of small amount of acetic acid to give the corresponding thiosemicarbazones. In presence of piperidine this ketone condenses with cyanoacetamide to form the corresponding cyanoacetamide derivatives and with hydantoin in presence of ammonium acetate and acetic acid to afford the corresponding merocyanines.

EXPERIMENTAL

All melting points reported are uncorrected. UV-spectra (ethanol) were recorded on Schmaduzu du-spectrophotometer and IR spectra (KBr) on Perkin Elmer Spectrophotometer.

p-N-methyl, N-acetyl-tertiary aminostyryl-4′-fluorophenyl ketone

This compound was prepared by the preparative method of Rout[4] and co-workers with some modifications suggested by previous workers[5]. Equimolar amounts of *p*-fluoroacetophenone and *p*-N-methyl, N-acetyl tertiary aminobenzaldehyde were dissolved in the minimum quantity of methanol and to the

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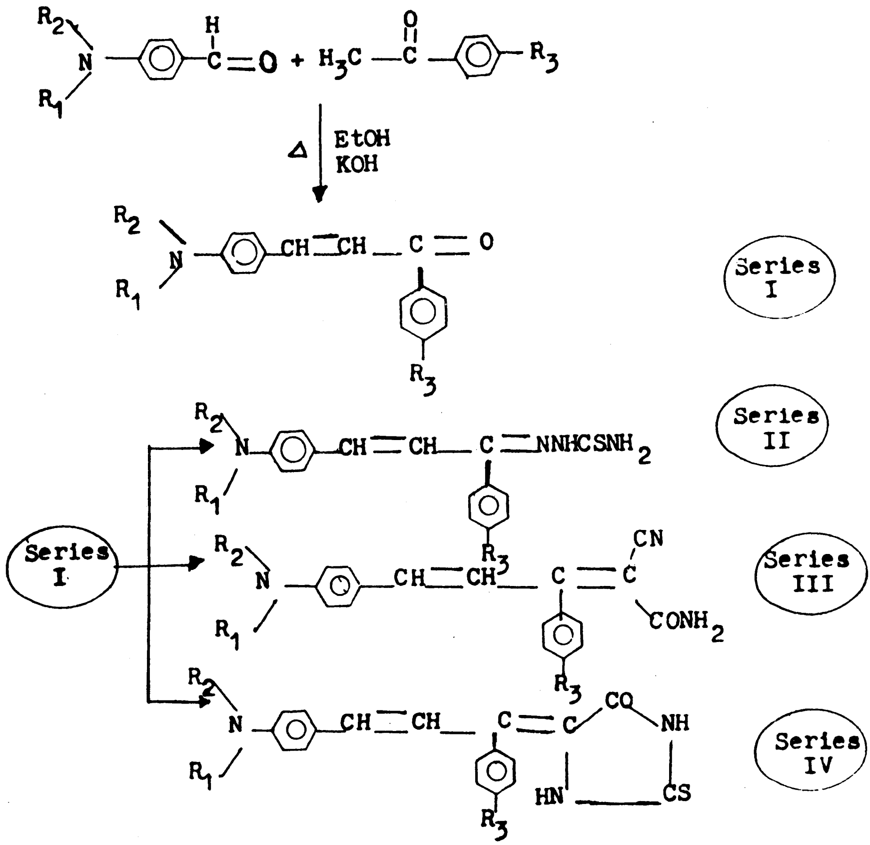
SCHEME-1



R_3	Series I		Series II		Series III		Series IV	
	$R_1=C_2H_5$ $R_2=C_2H_5$ Compd. Nos.	$R_1=CH_3$ $R_2=COCH_3$ Compd. Nos.	$R_1=C_2H_5$ $R_2=C_2H_5$ Compd. Nos.	$R_1=CH_3$ $R_2=COCH_3$ Compd. Nos.	$R_1=C_2H_5$ $R_2=C_2H_5$ Compd. Nos.	$R_1=CH_3$ $R_2=COCH_3$ Compd. Nos.	$R_1=C_2H_5$ $R_2=C_2H_5$ Compd. Nos.	$R_1=CH_3$ $R_2=COCH_3$ Compd. Nos.
Me	1	4	7	10	13	16	19	22
F	2	5	8	11	14	17	20	23
Br	3	6	9	12	15	18	21	24

solution were added dry pulvarised caustic alkali. This mixture was shaken briskly for 0.5 h and left for 1 h at room temperature. The separated product was filtered washed, dried and recrystallised from petroleum ether as shining yellow needles.

IR Spectra (KBr) ν_{max} (cm^{-1}); 1620 (νC=N); 980 (phenylene ring); 3070 (CH aromatic); 1590 (νC=C aromatic); 3200 (νNH); 1200 (νC=S).

p-N-methyl, N-acetyl-tertiary amino styryl-4′-fluorophenyl thiosemicarbazone:

To a mixture of ketone (0.01 mol.) and thiosemicarbazide (0.01 mol.) in dil ethanol were added a few drops of acetic acid and the mixture was refluxed for 3 h then cooled, filtered and recrystallised from methanol as glistening yellow flakes.

IR Spectra (KBr) ν_{max} (cm^{-1}) 3200 (νNH); 3070 (CH: aromatic) 1620 (νC=N); 1590 (νC=C aromatic); 980 (Phenylene ring) ; 1200 (νC=S).

3-p-N-methyl, N-acetyl-t-aminophenyl 1-4′-fluorophenyl prop-2-ene-1-ylidene cynoacetamide:

To an equimolar mixture of *p*-N-methyl, N-acetyl-t-aminostyryl-4′-fluorophenyl ketone and cyanoacetamide in ethanol were added few drops of piperidine and the mixture was refluxed for 3 h left overnight, filtered and recrystallised from ethanol as reddish brown crystals.

IR Spectra ν_{max} (cm^{-1}): 3200 (νNH); 3070 νCH: (aromatic); 1620 (νC = N); 1590 (νC=C aromatic); 1200 (νC=S); 980 (phenylene ring)

3-p-N-methyl, N-acetyl, t-aminophenyl 1- -4′-fluorophenyl prop-2-ene-1-ylidine hydantoin:

A mixture of ketone, hydantoin and ammonium acetate in equimolar proportion in benzene solution together with acetic acid (2 mL) was refluxed under $CaCl_2$ guard tube for 3 h. The mixture was allowed to keep overnight and the crystal so separated was filtered, dried and recrystallised from ethanol as wine red crystals.

IR Spectra ν_{max} (cm^{-1}): 3200 (NH); 3070 νCH: (aromatic); 1680 (ν–CONH); 1620 (νC=N); 1590 (νC=C aromatic); 1200 (νC=S); 980 (phenylene ring) .

Antifugal Activity

The highly purified and screened samples are tested for their *in vitro* and *in vivo* fungitoxicity. The *in vitro* fungitoxicity were tested on ED_{50} index by inhibition of mycelial growth of *F. oxysporum, P. italica, A. alternata* and *C. lunata* and *H. sativum*. A methanolic solution of desired concentration were used alongwith seerite PDA (potato dextrose agar) culture. The culture plates were inoculated with fungus and the fungitoxicity were recorded on ED_{50} index.[6–8]

Keeping in view the encouraging report *in vitro* analysis the *in vivo* fungitoxicity of the compounds were examined on *F. oxysporum* and *P. italicum.* Orange rind discs of the size 3 × 3 cm were obtained from orange fruits. The discs were surface sterlised by immersing in 75% ethanol and then treated with compound solution under investingation. The treated discs dried and inoculated

with spores of *F. oxysporum* and *P. italicum*. Commercial thiobenzazol-2-(4-thiazolyl) benzimidazole (TBZ) were taken as a standard to control citrus disease.

TABLE-1
PHYSICAL DATA OF COMPOUNDS

Compound No.	Mol. Formula	Yield (%)	m. p. (°C)	% of N	
				Found	Calcd.
1.	$C_{20}H_{23}NO$	78	111	4.67	4.77
2.	$C_{19}H_{20}NOF$	85	120	4.69	4,71
3.	$C_{19}H_{20}NOBr$	76	115	3.89	3.92
4.	$C_{19}H_{19}NO_2$	93	105	4.67	4,77
5.	$C_{18}H_{16}NO_2F$	45	125	4.69	4.71
6.	$C_{18}H_{16}NO_2Br$	70	138	3.89	3.92
7.	$C_{21}H_{26}N_4S$	85	160	15.10	15.30
8.	$C_{20}H_{23}N_4SF$	75	164	15.00	15.13
9.	$C_{20}H_{23}N_4SBr$	80	170	12.97	13.02
10.	$C_{20}H_{23}N_4OS$	56	177	15.10	15.30
11.	$C_{19}H_{19}N_4SOF$	81	169	15.00	15.13
12.	$C_{19}H_{19}N_4SOBr$	55	175	12.97	13.02
13.	$C_{23}H_{25}N_3O$	82	165	11.56	11.69
14.	$C_{22}H_{22}N_3OF$	90	171	11.47	11.57
15.	$C_{22}H_{22}N_3OBr$	72	181	9.89	9.92
16.	$C_{22}H_{21}N_3O$	68	160	12.12	12.24
17.	$C_{21}H_{18}N_3OF$	51	184	11.98	12.10
18.	$C_{21}H_{18}N_3OBr$	64	165	10.21	10.31
19.	$C_{23}H_{25}N_3OS$	79	225	10.54	10.74
20.	$C_{22}H_{22}N_3OSF$	59	204	10.53	10.63
21.	$C_{22}H_{22}N_3OSBr$	65	215	9.13	9.23
22.	$C_{22}H_{21}N_3OS$	72	207	11.00	11.20
23.	$C_{21}H_{19}N_3OSF$	73	235	10.99	11.05
24.	$C_{21}H_{19}N_3OSBr$	51	220	9.34	9.54

TABLE-2
ANTIFUNGAL ACTIVITY OF COMPOUNDS TOXICITY INDEX*

Compd. No.	*F. oxysporum*	*C. lunata*	*P. italicum*	*H. sativum*
7.	1	0	2	0
8.	2	0	3	0
9.	2	1	3	0
10.	4	1	3	1
11.	5	2	6	4
12.	4	1	5	2
13.	1	0	1	0
14.	1	1	2	1
15.	2	0	2	1
16.	2	0	3	1
17.	4	1	4	2
18.	5	2	5	1
19.	3	0	3	0
20.	3	1	4	1
21.	4	2	4	2
22.	4	1	5	1
23.	5	2	5	2

*Estimated ED – 50 scale – 0 = 100 μg ml^{-1} 1 = 50 – 100; 2 = 20 – 50; 3 = 10 – 20; 4 = 5 – 10; 5 = 5

TABLE-3
EFFECT OF COMPOUNDS ON RIND DISCS (μg ml^{-1})

Compd. No.	*F. oxysporum*			*P. italicum*		
	100	1000	4000	100	1000	4000
7.	100.00	100.00	100.00	100.00	100.00	100.00
8.	80.00	70.00	60.00	75.00	60.00	40.00
9.	50.00	40.00	30.00	50.00	40.00	30.00
10.	100.00	100.00	100.00	100.00	100.00	100.00
11.	60.00	43.30	36.30	60.00	40.00	35.00
12.	100.00	100.00	100.00	100.00	100.00	100.00
13.	70.00	60.00	50.00	60.00	40.00	40.00
14.	75.00	50.00	45.00	80.00	70.00	60.00
15.	100.00	100.00	100.00	100.00	100.00	100.00
16.	100.00	100.00	100.00	100.00	100.00	100.00
17.	100.00	100.00	100.00	100.00	100.00	100.00
18.	95.00	75.00	65.00	90.00	70.00	50.00
19.	100.00	100.00	100.00	100.00	100.00	100.00
20.	30.00	20.00	10.00	20.00	15.00	5.00
21.	60.00	40.00	30.00	70.00	50.00	40.00
22.	40.00	20.00	10.00	30.00	20.00	10.00
23.	20.00	10.00	5.00	20.00	10.00	5.00
24.	20.00	10.00	0.00	20.00	10.00	0.00
TBZ	20.00	0.00	0.00	20.00	0.00	0.00

RESULT AND DISCUSSION

The antifungal activity of some of the screened compounds evaluated through toxicity index ED-50 values (Table-2) reveals some interesting generalisations. *F. oxysporum* and *P. italicum* were found densitiveto the compounds followed by *H. sativum* but with *C. lunata* no significant response were noticed. Only compounds 11, 14, 21, 23, 24 shows feeble activity against *C. lunata*. The high fungi toxicity of compounds 11, 12, 17, 18, 23, 24 were attributed to the presence of electron withdrawing group present in the phenyl nucleus. Furthermore the chalcone derivatives were found to be more toxic than the parent chalcone. The merocyanines 21, 22, 23, 24 shows encouraging results over other derivatives. Probably cyclisation and the presence of S atom in the hydantoin nucleus is significant in causing such effect. Fluorine substitution in the phenyl nucleus records significant fungitoxicity *e.g.*, compound no. 11, 17, 23, *p*-bromo derivaties though found more effective against *P. italicum* but less in case of *F. oxysporum.*

From effect of compounds on prevention of disease development on rind discs it appears that compounds no. 23, 24 gave a good control especially at 4000 ng ml^{-1} level followed by compound no. 9, 11, 20, 21, 22. However, it has been found that some compounds with same value of ED-50 or higher did not prevent the decay at all concentration.

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