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Synthesis and Antifungal Activity of 2-Ketophenyl-3-substituted aryl-1-thiazolidin-4-ones

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Abstract: A new series of 2-ketophenyl-3-substituted aryl-1- thiazolidin-4-ones were synthesized by cyclocondensation of ketoazomethines and thioglycolic acid. Ketoazomethines were synthesized by condensation of phenyl glyoxal (prepared by partial oxidation of acetophenone) and various *para*-substituted anilines. Their structures were elucidated by elemental analysis, IR and H^1 NMR; they were screened for their antifungal activity against hazardous fungi namely *Fusarium Oxysporum, Pythium, Sclerotium* and *Alternaria brassicola.*

Keywords: Synthesis, 2-Ketophenyl-3-substituted aryl-1-thiazolidin-4-ones, Antifungal activity.

Introduction

4-Thiazolidinones are most popular, probably owing to their high versatility in exhibiting diverse potent biological properties *viz.*, antiprotozoa[1], analgesic[2-5], anti-inflammatory[6-9] anti-HIV[10], CFTR-inhibitor[11], anticonvulsant[12-13], SHP-inhibitor[14], antimicrobial[15,16] and fungicidal[17] *etc*. Although plenty of thiazolidinones and their derivatives have been synthesized by condensation of Schiff bases[18-20], halo acetanilide[21], thiosemicarbazone[22], thiamide[23], with thiocyanates, halo fatty acid and aldehydes *etc.* This project includes synthesis of these compounds and their elemental, spectral studies and screening for antifungal activity against hazardous fungi *i.e. Fusarium Oxysporum, Alternaria Brasssicola, Sclerotium and Pythium* which cause harm to crops like tomato, onion and cauliflower.

Experimental

All the chemicals used were either E-Merck or Qualigens. Melting points of all the compounds determined in open glass capillaries were uncorrected. Elemental analysis of

samples was carried out on Euro EA Elemental Analyzer. Infrared spectra were recorded in KBr medium on Thermo Nicolet Nexus FT-IR spectrophotometer and 300 MHz NMR spectra were recorded in dimethylsulphoxide medium on Varian C-13 NMR spectrometer using TMS as internal standard. Column chromatography was carried out using silica gel (finer than 200#).Characterization data is presented in Table 1 and spectral data in Table 2.

Table 1. Characterization data of compounds (**6a-f**).

Compds	M.F.	Colour	Yield %	m.p. °C	Elemental analysis, % Cald.(found)			
					S	C	H	N
6a	$C_{16}H_{12}NO_2SCl$	Pink	67.4	223	7.6 (7.8)	60.37 (60.44)	3.77 (3.18)	4.40 (4.76)
6b	$C_{16}H_{12}NO_2SBr$	Yellow	78.5	245	9.2 (9.1)	53.35 (53.39)	3.31 (3.35)	3.86 (3.15)
6c	$C_{20}H_{22}N_2O_2S$	Light brown	63.6	235	8.0 (7.8)	67.79 (67.83)	6.21 (6.35)	7.90 (7.65)
6d	$C_{17}H_{15}NO_2S$	Brown	71.5	218	8.9 (9.1)	68.68 (68.65)	5.75 (5.86)	4.71 (4.23)
6e	$C_{16}H_{12}N_2O_4S$	Light green	65.6	228	8.6 (8.5)	58.53 (58.74)	3.65 (3.46)	8.53 (8.32)
6d	$C_{16}H_{13}NO_2S$	Orange	69.5	210	8.3 (8.4)	67.84 (67.73)	4.59 (4.13)	4.96 (4.12)

Table 2. IR, H^1 NMR Spectral data of the compounds (**6a-f**).

Compds.	IR, cm^{-1} (KBr)	H^1 NMR (δ ppm)
6a	560, 700, 750,818, 1241,1324,1486, 1542, 1605,1651,3061	7.48-7.50(6H,m),6.89(4H,m), 5.11(1H,s),3.98(2H,s)
6b	660, 752 , 822, 1326, 1489,1549, 1609, 1648,3066	7.51-7.72(6H,m), 6.78(4H,m), 5.15(1H,s),3.82(2H,s)
6c	692,778,1407,1594,1680,1684, 2970,3032	7.56-7.73(6H,m),7.11(2H,d) 6.92(2H,d), 3.89(2H,s), 2.75(3H,m),5.21(1H,s)
6d	694,756,1238,1316,1496,1543, 1595,1670,3052	7.48-7.51(6H,m),4.02(2H,s),4.31(2H,s), 2.75(3H,s,Ar-CH_3),5.43(1H,s)
6e	683,771,888,1286, 1569,1652, 1713, 3045	7.33-7.36(6H,m), 4.05(2H,S),4.28(2H,s),5.34(1H,s)
6f	648,700,748,813,1257,1458, 1515,1682,1726,3056	7.35-7.54(5H,m),7.51-7.64(4H,m),4.25(2H,s),5.32(1H,s)

Preparation of phenyl glyoxal

Phenyl glyoxal was prepared by the partial oxidation of acetophenone with selenium dioxide. Reaction mixture containing acetophenone (1,0.2 mol) and selenium dioxide (0.4 mol) was taken in a round bottom flask containing 300 mL of 95% ethyl alcohol and refluxed for 4-6 h. Orange yellow reaction mixture was decanted and concentrated over water bath and dissolved in ether to remove selenium from the product.

General procedure for preparation of 4- thiazolidinones

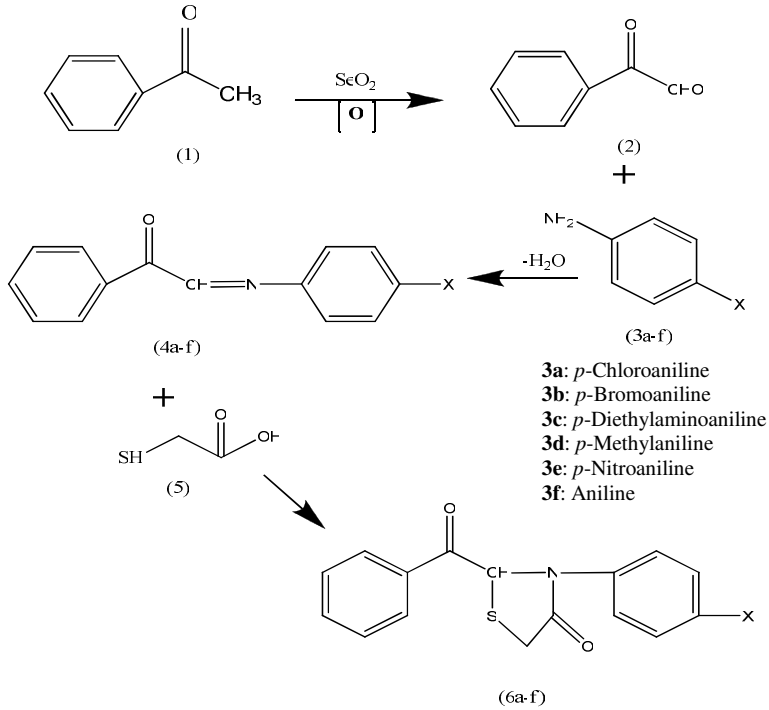
*Preparation of ketoazomethines (**4a-f**)*

Phenyl glyoxal (2, 0.2 mol) and aniline (**3a-f,** 0.2 mol) were taken in a round bottom flask containing 100 mL of ethanol and refluxed on water bath for 8 h. Excess of ethanol was

removed from reaction mixture and cooled at room temperature. Then it was poured in ice cold water and filtered. Solid obtained were collected and recrystallized with ethanol. Similarly, other ketoazomethines of *p*-chloro, *p*-bromo, *p*-nitro, *p*-methyl and *p*-diethylaminoaniline were prepared.

*Preparation of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-one (**6a-f**)*

Ketoazomethines (0.2 mol, **4a-f**) and thioglycolic acid (0.3 mol,5) were refluxed in dry benzene for ~ 15 h. The reaction mixture was concentrated to half of its volume over water bath and then neutralized with sodium bicarbonate solution. The contents were cooled and poured in ice cold water and filtered. The solid obtained was collected and purified by recrystallization (Scheme l).



Scheme l

Antifungal activities

Preparation of medium and sample solutions

For the preparation of PDA (Potato Dextrose Agar) medium 250 g potato pieces boiled in water were filtered and filtrate was made up to 1 litre. To this solution 20 g dextrose powder was added followed by heating to a syrupy viscous consistency. Standard solutions of all the samples were prepared by dissolving known quantity of compounds in known volume of DMSO (dimethylsulphoxide).

The synthesized thiazolidinones were screened for their antifungal activity against hazardous fungi namely *Fusarium Oxysporum, Pythium, Alternaria brassicola* and *Sclerotium* by paper disc method[24] using Diethane-M45 as reference fungicide and DMSO as control showing no inhibition, incubation periods of 72 h at 25-30 ^{0}C for the growth of fungi were measured in triplicates and the results of inhibition were noted in Table 3.

Table 3. Antifungal activity of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-one.

Compound	M.F.	Incb. Time, days	S.	P.	F.O.	A.B.
6a	$C_{16}H_{12}NO_2SCl$	3	++	++	+	++
6b	$C_{16}H_{12}NO_2SBr$	3	++	++	++	++
6c	$C_{20}H_{22}N_2O_2S$	3	-	+	-	-
6d	$C_{17}H_{15}NO_2S$	3	-	+	-	+
6e	$C_{16}H_{22}N_2O_4S$	3	++	-	-	+
6f	$C_{16}H_{13}NO_2S$	3	++	-	-	++
Ref.	Diethane-M45	3	+	++	-	++

Sample 10 mg/mL, S.-Sclerotium, P.-Pythium, F.O.-Fusarium Oxysporum, A.B - Alternaria Brasssicola -ve=1-7 mm, +ve= 10-15 mm and ++ve=15-18 mm.

Results and Discussion

The antifungal studies of the compounds were tested by paper bit method against hazardous fungi namely *Fusarium Oxysporum, Alternaria Brassicola, Pythium* and *Sclerotium* and were compared with reference fungicidal Diethane-M45, 2-ketophenyl-3-(4-bromoaryl)-1-thiazoldin-4-one (**6b**) and 2-ketophenyl-3-(4-chloroaryl)-1-thiazolidin-4-one (**6a**) showed highest inhibition against *Fusarium Oxysporum, Alternaria Brassicola, Sclerotium* and *Pythium.* 2-ketophenyl-3-(4-nitroaryl)-1-thiazolidin-4-one (**6e**) showed highest inhibition against *Sclerotium*, 2-ketophenyl-3-aryl-1-thiazolidin-4-one (**6f)** was effective against *Alternaria brassicola* and *Sclerotium*. Therefore, from the results it is evident that compounds having electronegative groups are responsible for antifungal activity.

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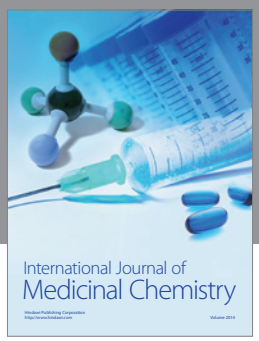

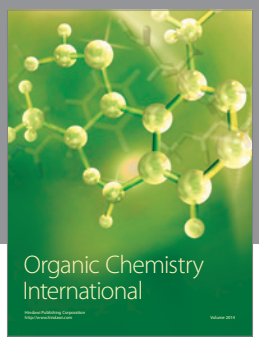

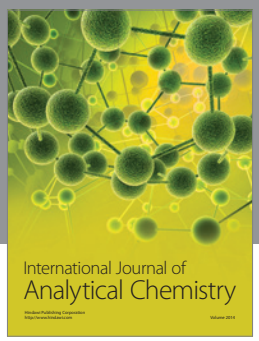

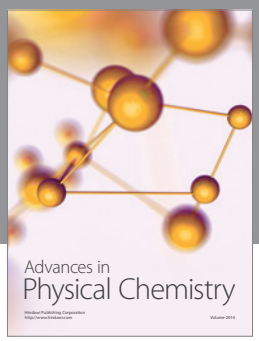

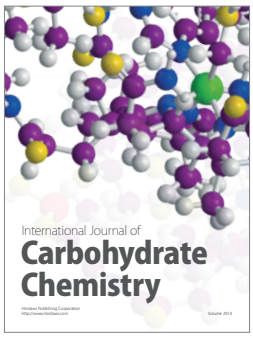

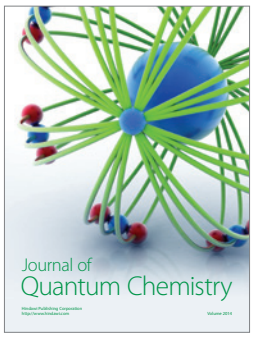

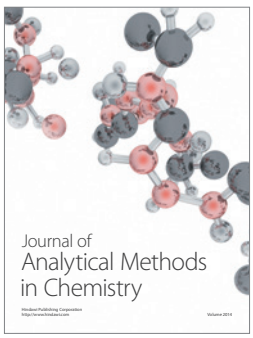

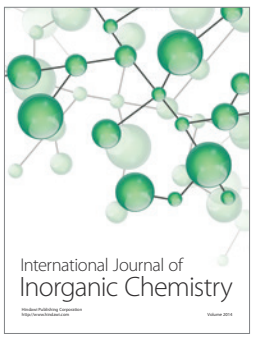

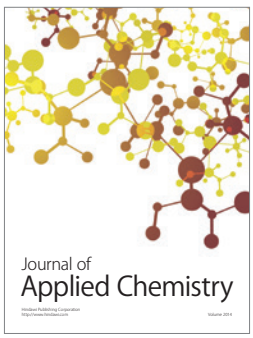

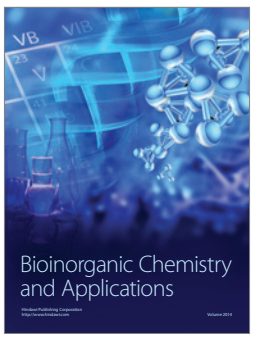

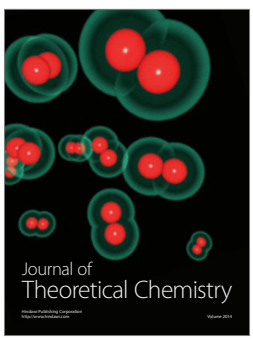

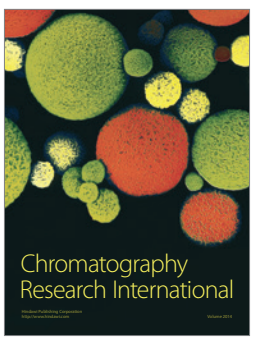

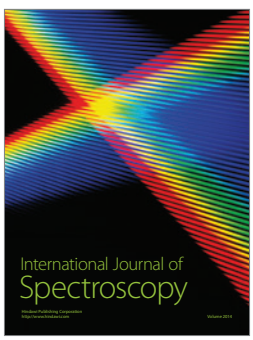

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