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ORIGINAL RESEARCH ARTICLE

Synthesis of Substituted Phenyl-4"-thiazolidin-3"yl]-1', 3', 4'- thiadiazol-5'-yl] Coumarin Derivatives and their Antifungal Activities

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ABSTRACT

A series of 3-aminomethylene–[2'-(2"-substitutedphenyl-4-thiazolidin-3"yl-(1',3',4'-thiadia zol-5'-y'] coumarins **(7a-g)** have been synthesized by reaction of thioglycolic acid and anhydrous $ZnCl_2$ with 3-aminomethylene-(2'-substituted benzylidin-5yl)iminocoumarins **(6a-g)** and compound **(6a-g)** was formed by reaction of compound **(5)** i.e. 3-aminimethylene-(2'-amino-1',3',4'-thiadiazol-5'-yl) coumarin respectively. Compound **5** have been synthesized by reaction of H_2SO_4 and liquid ammonia with compound **(4)** 3-amino coumarino acetyl thiosemicarbazide. The structures of the compounds were established on the basis of elemental analysis and spectral studies. The newly synthesized compounds were evaluated for their antifungal activity against *Aspergillus flovus*, *A. niger* and *A. fumigatus*. *C. albicans*, *C. Albicans* ATCC, *C. parapsilosis*, *C. glabrata* H05 and *C. Krusei.*

Key words : Thiazolidinone, Thiadiazol Derivatives & antifungal Activity.

INTRODUCTION

Coumarin, a constituent of melilot and tonca beans is a simple oxygen containing heterocyclic. Use of coumarin as a perfumery chemical in industries is well known which is attributed to its odiferous principle woodruff. Coumarin possesses a large no. of important biological properties such as analgesic, [1,2] CNS depressant [3,4] antitumour [5], anti-inflammatory [6,7], analgesic. Photosensitizing antifungal, antimicrobial, tuberculostatic, psychotnopic, HIV proliferation etc. Coumarin structure also occurs in novobiocin and other more recently discovered antibiotics like coumaromfcin and charteusin. Although diverse type of heterocycles containing coumarin ring have been synthesized. The two compounds i.e. compound **7b** and **7f** were found to be the most potent compounds of the series. The structure of all the compound were established on the bases of I.R., ^1H NMR and Mass spectrometry.

CHEMISTRY

Compound 1 (3-acetylaminocoumarin) was formed by following method of Tripthy and Mukherjee, which when refluxed with ethanol and conc,. HCl, followed by the addition of $NaHCO_3$ resulted in the formation of 3-aminocoumarine (compound 2). Compound 3 i.e. 3-ethylamine coumarinoacetate was formed by the reaction of ethylchloroacetate and anhydrous K_2CO_3 in acetone. This compound 3 further on treatment with thiosemi-carbozide in methanol yielded 3-aminocoumarino acetyl thiosemi carbaxide (Compound 4), which reacted with H_2SO_4 and liquid ammonia furnished compound 5 i.e. 3-aminomethylene (2'-amino-1', 3', 4'-thiadiazol-5-yl) coumarin. Compound (6a-6g) ie.e. 3-aminomethylene [2'-(substituted benzyliodin]-5-yl) iminocoumarin was formed by reaction of compound 5 with substituted arylaldehydes. Finally compound 6a-6g on reaction with thioglycalic acid and anhydrous $ZnCl_2$ furnished the desired compound i.e. 3- aminomethylenes [2'-(2"-substituted phenyl-4"-thiazolidin-3"-yl) -1', 3', 4'-thiadiozol-5'-yl] coumarin (compound 7a-7g).

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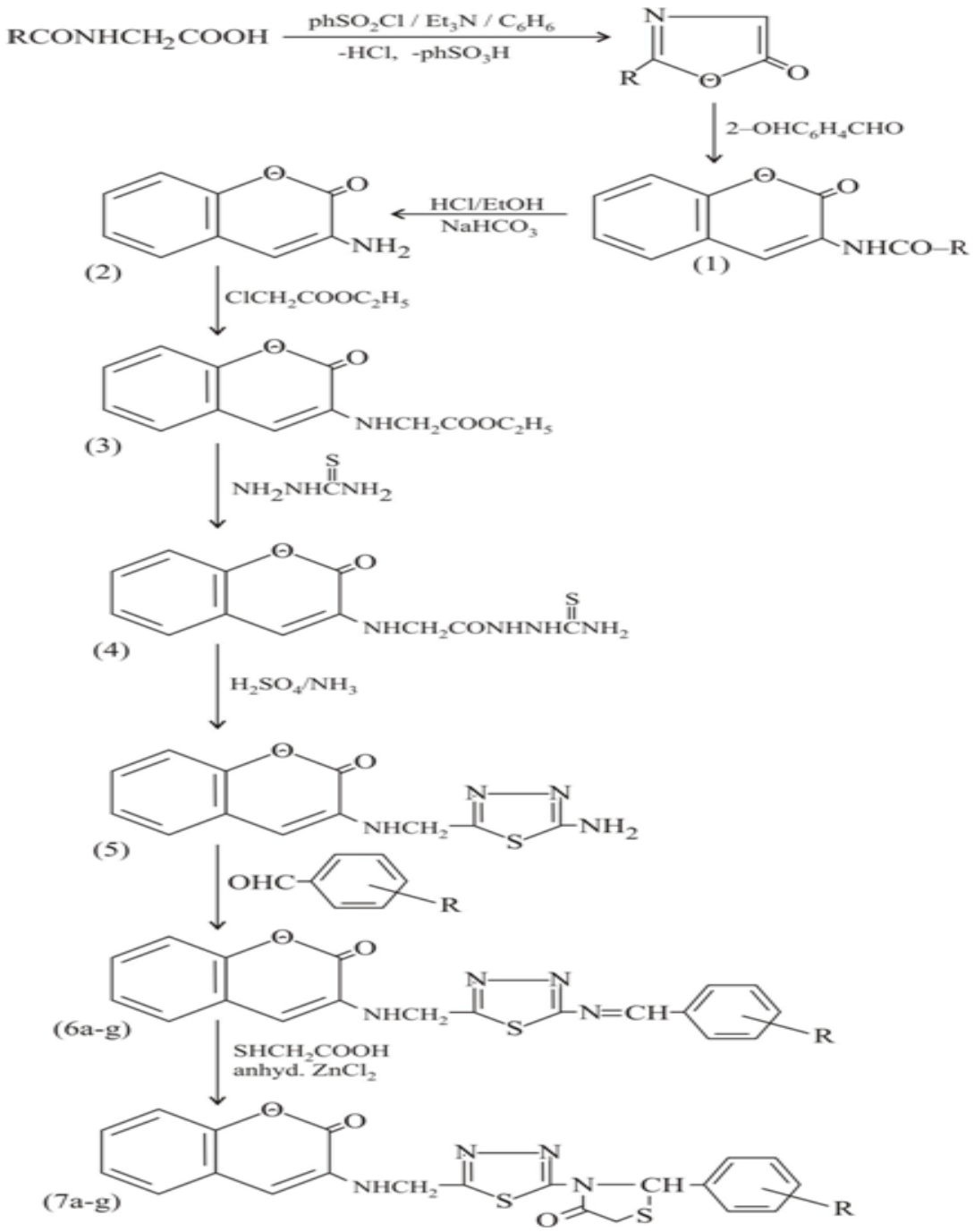


Scheme

EXPERIMENTAL

General

Melting points were taken on a thermonic melting point apparatus and are uncorrected. IR spectra were recorded in KBr on Bruker IFS-66V FI-IR spectra instrument and ν_{max} was recorded in cm^{-1}**.** ^{1}H-NMR spectras were recorded by Brucker DRX-400 FTNMR instrument using $CDCl_3$/DMSO d_6 as solvent and tetramethyl silane (TMS) as internal reference standard. Chemical shift value was recovered as S (Parts per million). Mass spectra were determined on mass spectrum E1 instrument. The homogeneity of all newly synthesized compounds was checked by TLC on silica gel G plates of 0.5 mm thickness. The elemental analysis (C, H, N,) of all compounds was performed on carlo-Ebra-1108 elemental analyzer at central Drug Research Institute at Lucknow, India.

Synthesis of 3-acetyl amino Coumarin (1)

To the suspension of aceturic acid (0.05 mol) in dry benzene (100 ml) containing triethylamine (0.125 mol), benzene sulphonyl chloride (0.05 mol) was added and mixture was stirred continuously at room temperature, until the

crystals of aceturic acid disappeared. Triethylamine salts thus separated out were filtered and then washed with benzene (50ml) to give the intermediate compound salicylaldchycel was added to the benzene filtrate of formed compound. The resultant mixture was refluxed for 2 hours. The solution was then concentrated up to dryness and the residue thus obtained was treated with aqueous ethanol and filtered. The solid separated out was recrystallised from aqueous ethanol to given compound **(1).** M.P. 208^0 C, yiled 70%
Reported 205-206

Synthesis of 3-aminocoumarin (2)
The compound 3- Acetyl amino coumarin was treated with ethanol, conc. HCl and the mixture obtained was refluxed for 15-20 min. the solution thus formed was concentrated on steam bath, diluted with water, and to the clear solution thus obtained, $NaHCO_3$ was added until the solution becomes alkaline. The resultant solid was filtered, washed with water and recrystallised with aqueous ethanol. Compound 2 M.P. 133^0 C reported 130-131 yield - 65% IR (KBr) 1110, 1715, 3250 Cm^{-1}; 1H -NMR ($CDCl_3$ +DMSO-d_6) δ (ppm); 7.78 (bs, 2H, NH_2, exchangeable with D_2O), 7.25 – 8.00 (m,5H, Ar-H), MS: $[M]^+$ at m/z 161.

Synthesis of 3- Ethylaminocoumarinoacetate (3)
To the mixture of compound 3-aminocoumarin **2** (0.1 mol) and ethylchloroacetate (0.1 mol), anhydrous K_2CO_3 (5.0 g) in acetone (80 ml) was added. The reaction mixture was then refluxed for about 15-18 hours. The excess of acetone was distilled off under reduced pressure and the solid mass left out was poured into ice cold water, filtered and recrystallised from methol-water to give compound 3.
M.P. 90 ^{0}C. yield 49%, IR (KBr) 1115 (C-O-C), 1720 (C-O), 2835 (CH_2), 3260 (NH) cm^{-1} **;** ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (PPM): 1.30 (t, 3H, CH_3), 4.21 (q, 2H, $COOCH_2$ CH_3), 4.39 (d, 2H, $NHCH_2$), 9.68 (ss, 1H, $NHCH_2$, exchangeable with D_2O), 7.30-8.05 (m, 5H, Ar-H) Elemental Analysis: Calculated % C, H, N,- 61.27, 5.53, 5.95 Found 61.48, 5.73, 5.60, MS: $[M]^+$ m/z 235.

Synthesis of 3-aminocoumarino acetyl thiosemicarbazide (4)
Compound **3** (0.02 mol) and thiosemicarbazide (0.02 mol) in methanol (50 ml) was refluxed for 10-12 hours. Excess of methanol was distilled off under reduced pressure and the viscous mass left out was poured over ice water, filtered and finally recrystallied from ethanol-water to furnish compound 4.

M.P. 222^0C , yield 65% IR (KBr); 1115 (C-O-C), 1178 (C=O), 1715 (C=O), 2840 (CH_2), 3270 (NH_2), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 4.40 (d, 2H, NH CH_2), 8.89 (m,4H, NH NH CS NH_2) 9.70 (SS, 1 H, NH CH_2, exchangeable with D_2O), 7.35-8.15 (m, 5H, Ar-H), Elemental Analysis: Calculated % C; H, N, - 47.14, 4.28 20.00, Found 47.05, 4.45, 20.09, MS: $[M]^+$ m/z 280.

Synthesis of 3-aminomethylene-(2'-amino-1',3',4'- thiadiazol-5'-yl) coumarin (5)
Conc. H_2SO_4 (20 ml) was added to compound **4** (0.05 mol). The reaction mixture as kept overnight at room temperature, poured in to ice cold water, neutralilzed with liquid ammonia and then filtered. The solid mass thus obtained was recrystallised to yield compound 5.
M.P. 201^0C, yield 68%, IR (KBr): 687 (C-S-C), 1110 (C-O-C), 1250 (C-N), 1530 (N-N), 1575 (C=C of Ar,) 1624 (C-N), 1718 (C=O), 2845 (CH_2), 3015 (Ar-CH), 3265 (NH_2), 3349 (N-H), ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 4.38 (d, 2H, $NHCH_2$), 7.30-8.10 (m, 5H, Ar-H), 8.26 (S, 2H, NH_2, exchangeable with D_2O), 9.45 (SS, 1H, $NHCH_2$, exchangeable with D_2O), Elemental analysis; - Calculated % C, H, N,- 50.38, 21.37, Found 50.05, 3.50, 21.69 MS: $[M]^+$ m/z 262.

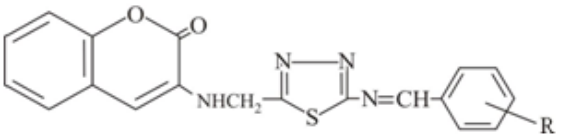
Synthesis of 3-aminomethylene-(2'-substitutedbenzylidin-5'-yl)imino coumarins (6a-g).
A solution of compound **5** in methanol was refluxed with m-methoxyaryl aldehyde (0.01 mol) in presence of few drops of 2% NaoH solution for 10-12 hours. The process of reaction towards completion was monitored by TLC. The excess of solvent was distilled off and the solid thus separated out was poured into crushed ice and then filtered finally the solid mass was recrystallised form ethanol-water to give compound. Compound 6b.

M.P. 170^0 C, yield 62% IR (KBr), 680 (C-S-C), 1100 (C-O-C), 1255 (C-N), 1525 (N-N), 1585.56 (C….C Ar-CH), 1580 (C=N), 1710 (C=O), 2910 (CH_2), 3033 (Ar-CH), 3335 (NH), 3558 (OH), ^{1}H-NMR ($CDCl_3$ + DMSO+d_6) δ (ppm) 4.32 (d, 2H, NH CH_2), 4.95 (d, 1 H, N=CH -Ar), 8.24 (m, 9H, Ar-H), 9.65 (SS, 1H, NHCH_2 , exchangeable with D_2O) 12.35 (SS, 1H, OH-Ar. exchangeable

with D_2O) Elemental analysis: Calculated % C, H, N,- 60.31, 3.70, 14.81, Found 60.05, 3.50, 14.69, MS: $[M]^+$ m/z 378.

All the spectral data of compound (6a-6g) shown in (**Table 1**).

Table 1: Physical and analytical data of 3-aminomethylene-(2'substitutedbenzyliden-5'yl-imino) coumarin (6a-6g)



Compd No	X	R	M.P. (^{0}C)	Yield (%)	Recrystallisation solvent	Molecular Formula	Elemental Analysis (%) Calculated/Found		
							C	H	N
6a.	-	H	155	60	Ethanol	$C_{19}H_{14}N_4O_2S$	62.98 / 62.68	3.86/3.54	15.46/15.72
6b.	-	m-OH	172	54	Acetone	$C_{19}H_{14}N_4O_3S$	60.31 / 60.05	3.70/3.50	14.81/14.69
6c.	-	m-OH	200	50	Methanol	$C_{19}H_{14}N_4O_3S$	60.31 / 60.06	3.70/3.92	14.81/14.55
6d.	-	m-$N(CH_3)_2$	188	57	DMG	$C_{20}H_{19}N_5O_2S$	61.06 / 61.37	4.83/4.58	17.81/17.54
6e.	-	p-OH o-OCH_3	193	60	Acetone	$C_{19}H_{16}N_4O4S$	57.58 / 57.75	4.04/3.92	14.14/14.00
6f.	-	p-OCH_3	194	56	Ethanol/Water	$C_{19}H_{16}N_4O3S$	60.00 / 60.28	4.21/4.00	14.73/14.99
6g.	-	m-OCH_3	211	58	Benzene	$C_{19}H_{16}N_4O_3S$	60.00 / 60.38	4.21/4.05	14.73/15.02

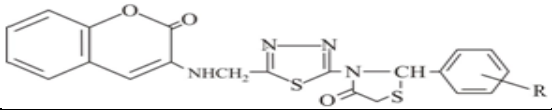
Synthesis of 3-aminomethylene-[2'(2"-substituted phenyl-4"-thiazolidin-3"yl]-1', 3', 4'- thiadiazol-5'-yl] coumarins (7a-g).

Compound **6** was stirred property. To this well stirred compound (0.01 mol) as small amount of anhydrous $zncl_2$ and thioglycolic acid (0.02 mol) were added. This reaction mixture was then refluxed in dry DMF (80 ml) for 18-20 hours. The reaction mixture was cooled and then poured into ice cold water. The solid thus separated out was filtered, washed and finally recrystalised from ethanol-benzene to give the product.

Compound (7b)- M.P. 183^{0}C, yield 58% , IR (KBr): 685 (C-S-C), 1110 (C-O-C), 1245 (C-N), 1520 (N-N), 1585 (C……C of Ar), 1610 (C-N), 1755 (C=O of β- thialactum), 1700 (C-O of coumarin), 2910 (CH_2), 3330 (NH), 3562 (OH) 1H- NMR ($CDCl_3$ + DMSO-d_6) δ (PPM): 3.55 (δ, CH_2 of thiazolidinone , 4.35 (d,2H, NCH_2), 6.28 (S.1H. CH-Ar), 7.45 -8.05 (m, 9 H, Ar-H), 9.45 (SS, 1H, $NHCH_2$ exchangeable with D_2O), 12.50 (SS, 1H, OH – Ar, exchangeable with D_2O) Elemental analysis: Calculated % C, H, N,- 55.75; 3.53, 12.38 Found 55.53, 3.29, 12.53, MS: $[M]^+$ m/z 452.

All the spectral data of compounds (7a-7g) shown in (**Table 2**).

Table 2: Physical and analytical data of 3-aminomethylene-(2'-(2"substituted benzyliden-4''-thiazolidin-3"-yl)-1',3',4'-thiadiazol-5'-yl] coumarin (7a-7g)



Compd No	X	R	M.P. (^{0}C)	Yield (%)	Recrystallisation solvent	Molecular Formula	Elemental Analysis (%) Calculated/Found		
							C	H	N
7a.	-	H	151	60	Benzene	$C_{21}H_{16}N_4SO_3$	62.80 / 62.58	4.13/4.29	15.42/15.07
7b.	-	m-OH	183	8	Ethanol/Water	$C_{21}H_{16}N_4SO_4$	55.75 / 55.53	3.53/3.29	12.38/12.53
7c.	-	m-OH	202	55	Acetic-acid	$C_{21}H_{16}N_4SO_4$	60.00 / 59.95	3.81/3.62	13.33/13.59
7d.	-	m-$N(CH_3)_2$	204	57	Methanol	$C_{23}H_{21}N_5SO_3$	61.74 / 61.95	4.69/4.41	15.65/15.87
7e.	-	p-OH o-OCH_3	214	55	Hexane	$C_{22}H_{18}N_4SO5$	58.66 / 58.75	4.00/3.82	12.44/12.10
7f.	-	p-OCH_3	196	59	DMG	$C_{22}H_{18}N_4SO4$	60.82 / 60.63	4.14/4.05	12.90/12.33
7g.	-	m-OCH_3	205	60	Methanol	$C_{22}H_{18}N_4SO4$	60.82 / 61.02	4.14/4.03	12.90/12.69

ANTIFUNGAL ACTIVITY

Poisened food technique (Gehlot and Vohra, 1998) was performed to evaluate the antifungal propery of the test compounds and standard drugs i.e. fluconazole and griseofulvin Iagainst *Aspergillus jlavus, A. niger,* and *A. fumigatus.*

10% solution of DMSO in methanol was prepared. 100 mg of test compound as well as the reference drugs i.e fluconazole and griseofulvin were dissolved in sufficient amount of this solution (5 ml). This solution (5 ml) was added to 995 ml Czapex Dox Agar medium so as to obtain 100 mg /L concentration of the compound in the medium. 5ml of 10% DMSO in methanol solution (without any test compound or the standard drug) added to 995ml Czapex Dox Agar medium served as control. Diameter of the fungal colony in mm

in the control medium. The resultant solutions were thoroughly mixed and approximately 20 ml of the solution was poured into 9cm sterile glass Petridishes and allowed to set. The resulting agar plates were inoculated with 5mm plugs, of fungal mycelia cut from freshly prepared, actively growing cultures. The plates were then incubated at 25 $\pm^0$C in the dark for eight days. The diameter of each colony was measured after eight days of incubation. Three replicates were taken for each test compound and for each organism test cultures. The average inhibition of test compound was calculated using the equation:

Inhibition % = (C-T) 100 / C

Where;

C = Diameter of the fungal colony in mm in the control medium.

T = Diameter of the fungal colony in mm in the test medium, containing the given test compound or the reference drug.

STANDARD AGAR DISC DIFFUSION METHOD (Pai and Platt, 1995)

All the cultures were maintained of Sabouraud Dextrose Agar medium and incubated at 30 ^{0}C. In order to prepare homogenous suspension or" these fungi for disc assays, they were grown overnight in Sabouraud broth, centrifuged to collect the pellet and resuspended in sterile phosphate buffered saline. The fungal pellet was homogenized in sterile hand held homogenizer. This suspension was then plated on a Sabouraud Dextrose Agar medium using a bacterial spreaded to obtain an even growth. Sterile 6 mm whattmann filter paper disc were impregnated with 100mg/L of various test compounds and standard drugs. These discs were then placed in the centre of quadrent of Sabauroud Dextrose Agar medium plate. These plates have one control disc impregnated with 10% DMSO in methanol. The plates were incubated at 30 ^{o}C. Three replicates were used for each test compound as well as for each standard drug used. After 48 hours the plates were removed and radious of inhibition zones were measured and calculated the average.

RESULTS

All the pharmacological results of the present study are shown in (**Table 3 & 4**). Screening of compounds **5**, **6a-6g** and **7a-7g** and the reference drug i.e. fluconazole and griseofulvin were performed at concentration of 100 mg/L for antifungal activity against different strains of candida and Aspergillus spp. Two compound i.e. compound **7b** and **7f** were found to be the most potent compounds of the series. Compound **7b** with ortho-hydroxyphenyl group showed remarkable activity (even more than the reference drugs) against C. albicons, C. albicans ATCC, A. niger, and A flavus, It was equipotent to the standards against C. Krusei GO3, and C. parapsilosis 22019.Compond **7f** on the other land showed better activity as compared to fluconazole and griseofulvin against C.albicans, C. Krusei GO3, A. niger, and A flavus and was equipotent C. parapsilosis 22019. These two compounds showed better anti-fungal activity then the reference drugs.

Table 3: Pharmacological data of compounds 5, 6a-6g and 7a-7g

Compounds	Antifungal activity# [diameter of inhibition zone (mm)]				
	Candida albicans	*Candida albicans ATCC*	*Candida krusei GO3*	*Candida glabrata HO5*	*Candida parapsiolsis 22019*
@Control	0	0	0	0	0
Fluconazole*	29	25	19	15	20
Griseofulvin*	25	26	18	16	22
5.	13	-	-	11	-
6a.	14	-	-	13	-
6b.	21	-	13	-	13
6c.	18	-	9	-	-
6d.	17	-	-	-	10
6e.	16	-	10	-	-
6f.	20	-	1	10	12
6g.	15	-	8	-	-
7a.	17	-	-	17	-
7b.	31	31	19	-	22
7c.	21	11	17	-	18
7d.	20	12	-	-	-
7e.	19	-	7	-	-
7f.	31	-	22	11	22
7g.	21	-	7	7	17

Concentration was 100 mg/L. ; 10% DMSO in methanol.

- = No. inhibition zone.

- = Standard drugs used for comparison.

Table 4: Pharmacological data of compounds 5, 6a-6g, and 7a-7g

Compounds	Antifungal activity# [Inhibition in percentage]		
	Aspergillus fumigates	*Aspergillus niger*	*Aspergillus flavus*
@Control	0	0	0
Fluconazole*	-	90	84
Griseofulvin*	80	88	82
5.	-	49	-
6a.	-	48	29
6b.	-	65	45
6c.	-	59	39
6d.	-	-	-
6e.	-	53	-
6f.	-	56	40
6g.	-	54	37
7a.	-	55	-
7b.	62	95	91
7c.	56	86	-
7d.	-	47	-
7e.	-	53	-
7f.	-	95	88
7g.	-	82	48

Concentration was 100 mg/L. ; 10% DMSO in methanol.
- = No. inhibition zone.
= Standard drugs used for comparison.

DISCUSSION

Compound **5** possessing thiadiazole ring showed minimum fungal inhibition among all the Compounds which were screened for antifungal activity. Structure activity relationship of the tested Compounds reveled the conversion of Compound **5** to various arylidine derivatives (Compound 6a-6g) increases the antifungal activity in all the derivatives. Among theses seen aryl dine derivatives, Compound 6b with o-hydroxyphenyl ring and Compound 6c with o-methoxyphenyl ring enhanced the antifungal activity more than rest of the derivatives. Further cyclisation of arylidine derivatives (6a-6g) into their corresponding thiazolidinones (7a-7g) increased the antifungal activity in addition to widening the antifungal spectra of the Compounds. This increase in the activity of these Compounds may be due to the presence of thiazolidinone ring. It is interesting to point out that the Compounds having ortho or para hydroxyphenyl or methoxyphenyl group as a substituent, elicited a remarkable increase in antifungal activity. Moreover, it has also been observed that o-derivatives (7b and 7f) exhibited more potent antifungal activity than the para isomers. Hence, it seems that substitution with an orthomethoxyphenyl group or orthohydroxyphenyl group at 2-positon of thiazolidinone ring is beneficial for antifungal activity.

CONCLUSION

1. Compound 5 with thiadiazole ring exhibited minimum antifungal activity.
2. The differently substituted benzylildines (6a-6g) shows mild to moderate antifungal activity. Cyclisation of these benzylildine congeners (6a-6g) into their corresponding thiazolidinone congeners (7a-7g) enhances the antifungal activity.
3. Compound with a phenyl ring having a hydroxyl group or methoxy group at ortho or para position show promising antifungal activity. Ortho derivatives possess the better antifungal activity.
4. Compounds 7b and 7f are more active Compounds than the standard drugs.

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