

Synthesis and antifungal activity of some novel thiazolidinone derivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid

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Abstract: A novel series of thiazolidinone derivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid were synthesized. 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid (**1a-d**) was prepared by the reaction of corresponding Schiff base with mercaptoacetic acid. Acid chloride of prepared 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid (**2a-d**) was treated with substituted aniline in presence of ammonium thiocyanate to give thiourea derivative (**3a-h**). Thiourea derivative upon treatment with monochloro acetic acid in presence of fused sodium acetate converted to 2-(phenylimino)-3-[[4-(4-oxo-2-phenylthiazolidin-3-yl) phenyl] carbonyl]-thiazolidin-4-one (A thiazolidinone derivative (**4a-h**) of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid). The title compounds have been synthesized with several structural variations. The synthesized compounds were screened for their antifungal activity. The structure of synthesized compounds have been established on the basis of their spectral (IR, ¹H NMR and mass) data. The purity of the synthesized compounds was confirmed by TLC.

Keywords: Thiazolidinone, antifungal activity, 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid, thiourea derivatives, Schiff's bases.

Introduction

Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a very important moiety which possesses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of organic chemists to explore this skeleton to its multiple potential against biological activities.

The chemistry of heterocycles lies at the heart of drug discovery¹ 4-thiazolidinone is one of the most intensively investigated classes of five member heterocycles.^{2,3} the biological significance of this class of compounds attracted us to work on the synthesis of new thiazolidinone derivatives in the hope that synthesized compounds will be biologically active.

4-thiazolidinones are the heterocyclic compounds having nitrogen and sulfur atoms and

are known for a long time for their wide range of interesting biological activities namely anticonvulsant activity, anti-inflammatory activity, anti-tubercular activity, anthelmintic activity, antiviral activity, antifungal activity, antibacterial activity, anticancer activity and anti - HIV activity⁴⁻¹² etc. There are many protocols for the synthesis of 4-thiazolidinone.¹³⁻²² 4-thiazolidinone can be synthesized either by cyclisation of acyclic compounds or by simple condensation of thioglycolic acid with Schiff's bases. The reaction undergoes by the attack of the mercapto acetic acid upon the C = N group, with the - S - CH₂ - COOH adding to the carbon atom followed by the capture of a proton by nitrogen and subsequent cyclisation. The nucleophilic attack of mercaptoacetic acid anion on carbon of azomethine, which has got positive character while nitrogen has negative character, is evidenced. Simultaneous removal of

water as it forms in reaction helps in condensation and determination of the reaction time.

The constitution of all the products has been characterized using elemental analyses, IR, ¹H NMR and mass spectral study. All the compounds were screened for their antifungal activity.

Experimental section

All solvents and chemicals used were of commercial or LR grade, and were used without further purification. Melting points were measured on Buchi melting point apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrometer, using KBr pellets. ¹H-NMR spectra were scanned on Bruker-NMR spectrometer at 500 MHz, using TMS as an internal standard and CDCl₃ or DMSO d₆ as solvent.

General method for synthesis of 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid (1a-d)

A mixture of 4-amino benzoic acid (0.01 mole) and aromatic aldehyde (benzaldehyde, p-chlorobenzaldehyde, anisaldehyde, salicylaldehyde) (0.01 mole) was refluxed in absolute ethanol (40 ml) for 3 hrs. The excess solvent was then distilled off and the resulting solid washed with water, dried and recrystallized from ethanol to furnish 4-(benzylideneamino) benzoic acid (Schiff's base).

A mixture of 4-(benzylideneamino) benzoic acid (Schiff's base) (0.01 mole) and mercapto acetic acid (0.012 mole) in DMF (25 ml) containing a catalytic amount of anhydrous ZnCl₂ was refluxed for 8 hrs. The reaction mixture was then cooled and poured into ice-cold water. The resulting solid was filtered, washed several times with water and then crystallized from DMF to give 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid (Scheme-1).^{23, 24, 25}

Spectral data for 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid (1a) Yield: 65 %; Melting point 235°C; IR (KBr, cm⁻¹): 2926 (Ar-H), 1312 (C-N), 1690 (thiazolidinone C=O), 1421 (C-O-H), 1251(C=O), 691 (C-S); ¹H-NMR (DMSO-d₆) : 10.24 (1H, s, Ar-COOH), 5.98 (1H, s, S-CH-N), 3.50 (2H, s, CH₂-S), 7.05-8.15 (9H, m, Ar-H); MS m/z (M⁺): 300.06 (Molecular weight: 299.34).

Synthesis of 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoyl chloride (2a-d)

The mixture of 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid (0.1 mol)

and thionyl chloride (0.2 mol) was refluxed using 1,2-dichloroethane as a solvent for 3 hours. Anhydrous condition was maintained by using calcium chloride guard tube, till the HCl gas evolution was ceased. Solvent and thionyl chloride were removed by reduced pressure distillation. The solid of the title compound obtained was cooled and used in the next step.

General method for synthesis of thiourea derivatives (3a-h)

The mixture of 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoyl chloride (0.1mol) was dissolved in acetone and added to a solution of ammonium thiocyanate (0.1mol) in acetone. The reaction mixture was refluxed for one hour. A solution of suitable aniline (0.1mol) dissolved in acetone was added under stirring. The reaction was refluxed for three hours and product was isolated by pouring the mixture in cold water and purified by crystallization from ethanol.

Spectral data for 4-(4-oxo-2-phenylthiazolidin-3-yl)-N-(phenylcarbamothioyl) benzamide (3a)

IR (KBr, cm⁻¹): 2990 (Ar-H), 1611 (C=N), 1577 (Ar-C=C), 1050 (C-O-C). 1710 (thiazolidinone C=O), 1250(C=O), 685 (C-S); ¹H-NMR (DMSO-d₆ , ppm): 7.06-8.00 (m, 8H, Ar-H); 6.40-7.07 (m, 6H, Ar-H), 5.90 (s, 1H, N=CH); 3.55 (2H, s, CH₂-S); MS m/z (M⁺): 434.09 (Molecular weight: 433.54).

General method for synthesis of thiazolidinone derivatives (4a-h)

The mixture of suitable thiourea derivative (0.1mol), monochloro acetic acid (0.1mol) and fused sodium acetate (0.5mol) was refluxed in absolute ethanol for 12 hours. Progress of the reaction was monitored in thin layer chromatography, after completion of reaction excess of ethanol was removed by reduced pressure distillation, residue dissolved in dichloromethane, dichloromethane layer washed with 10% solution of sodium bicarbonate followed by washing with water. Dichloromethane layer dried over sodium sulphate and dichloromethane removed by reduced pressure distillation, recrystallization of the solid from ethanol furnished the title compound (Scheme-2).

2-(phenylimino)-3-[[4-(4-oxo-2-phenylthiazolidin-3-yl)phenyl]carbonyl]-thiazolidinone

(4a) Yield: 60 %; Melting point 215°C; IR (KBr, cm⁻¹): 2996 (Ar-H), 1712 (thiazolidinone C=O), 1523 (Ar-C=C), 1347 (C-N), 690 (C-S); ¹H-NMR (DMSO-d₆ , ppm): 7.04-8.06 (m, 14H, Ar-H), 5.94 (s, 1H, N-CH), 3.78 (s, 2H, S-CH₂ of 2-

phenylimino thiazolidinone), 3.30-3.40 (m, 2H, S-CH₂); MS m/z (M⁺): 474.09 (Molecular weight: 473.57).

2-(phenylimino)-3-[[4-(4-oxo-2-(4-chloro phenyl)thiazolidin-3-yl)phenyl]carbonyl]-thiazolidinone (4b) Yield: 60 %; Melting point 206°C; IR (KBr, cm⁻¹): 3011 (Ar-H), 1716 (thiazolidinone C=O), 1500 (Ar-C=C), 1342 (C-N), 685 (C-S); ¹H-NMR (DMSO-d₆, ppm): 7.00-8.00 (m, 13H, Ar-H), 5.90 (s, 1H, N-CH), 3.72 (s, 2H, S-CH₂ of 2-phenylimino thiazolidinone), 3.29-3.39 (m, 2H, S-CH₂); MS m/z (M⁺): 509.19 (Molecular weight: 508.01).

2-(phenylimino)-3-[[4-(4-oxo-2-(4-methoxy phenyl)thiazolidin-3-yl)phenyl]carbonyl]-thiazolidinone (4c) Yield: 58 %; Melting point 212°C; IR (KBr, cm⁻¹): 3010 (Ar-H), 1710 (thiazolidinone C=O), 1521 (Ar-C=C), 1339 (C-N), 680 (C-S); ¹H-NMR (DMSO-d₆, ppm): 6.60-8.01 (m, 13H, Ar-H), 5.88 (s, 1H, N-CH), 3.77 (s, 2H, S-CH₂ of 2-phenylimino thiazolidinone), 3.70 (s, 3H, OCH₃), 3.29-3.39 (m, 2H, S-CH₂); MS m/z (M⁺): 504.41 (Molecular weight: 503.59).

2-(phenylimino)-3-[[4-(4-oxo-2-(2-hydroxy phenyl) thiazolidin-3-yl) phenyl] carbonyl]-thiazolidinone (4d) Yield: 62 %; Melting point 218°C; IR (KBr, cm⁻¹): 3030 (Ar-H), 1715 (thiazolidinone C=O), 1510 (Ar-C=C), 1347 (C-N), 688 (C-S); ¹H-NMR (DMSO-d₆, ppm): 6.61-7.95 (m, 13H, Ar-H), 5.90 (s, 1H, N-CH), 3.70 (s, 2H, S-CH₂ of 2-phenylimino thiazolidinone), 3.29-3.40 (m, 2H, S-CH₂); MS m/z (M⁺): 490.29 (Molecular weight: 489.57).

2-(p-tolylimino)-3-[[4-(4-oxo-2-phenylthiazolidin-3-yl) phenyl] carbonyl]-thiazolidinone (4e) Yield: 64 %; Melting point 199°C; IR (KBr, cm⁻¹): 3030 (Ar-H), 1712 (thiazolidinone C=O), 1520 (Ar-C=C), 1347 (C-N), 690 (C-S); ¹H-NMR (DMSO-d₆, ppm): 7.05-8.00 (m, 13H, Ar-H), 5.92 (s, 1H, N-CH), 3.76 (s, 2H, S-CH₂ of 2-tolylimino thiazolidinone), 3.30-3.41 (m, 2H, S-CH₂); MS m/z (M⁺): 488.44 (Molecular weight: 487.59).

2-(p-tolylimino)-3-[[4-(4-oxo-2-(4-chlorophenyl) thiazolidin-3-yl)phenyl]carbonyl]-thiazolidinone (4f) Yield: 62 %; Melting point 201°C; IR (KBr, cm⁻¹): 2990 (Ar-H), 1710 (thiazolidinone C=O), 1533 (Ar-C=C), 1342 (C-N), 688 (C-S); ¹H-NMR (DMSO-d₆, ppm): 7.00-7.89 (m, 12H, Ar-H), 5.90 (s, 1H, N-CH), 3.71 (s, 2H, S-CH₂ of 2-tolylimino thiazolidinone), 3.33-3.42 (m, 2H, S-CH₂), 2.33 (s, 3H, CH₃); MS m/z (M⁺): 488.44 (Molecular weight: 487.59).

2-(p-tolylimino)-3-[[4-(4-oxo-2-(4-methoxy phenyl)thiazolidin-3-yl)phenyl]carbonyl]-thiazolidinone (4g) Yield: 58 %; Melting point 181°C; IR (KBr, cm⁻¹): 2996 (Ar-H), 1711 (thiazolidinone C=O), 1520 (Ar-C=C), 1340 (C-N), 688 (C-S); ¹H-NMR (DMSO-d₆, ppm): 6.60-8.00 (m, 12H, Ar-H), 5.93 (s, 1H, N-CH), 3.76 (s, 2H, S-CH₂ of 2-tolylimino thiazolidinone), 3.71 (s, 3H, OCH₃), 3.32-3.42 (m, 2H, S-CH₂), 2.35 (s, 3H, CH₃); MS m/z (M⁺): 518.52 (Molecular weight: 517.62).

2-(p-tolylimino)-3-[[4-(4-oxo-2-(2-hydroxyphenyl)thiazolidin-3-yl)phenyl] carbonyl]-thiazolidinone (4h) Yield: 64 %; Melting point 198°C; IR (KBr, cm⁻¹): 3011 (Ar-H), 1712 (thiazolidinone C=O), 1540 (Ar-C=C), 1347 (C-N), 690 (C-S); ¹H-NMR (DMSO-d₆, ppm): 6.60-8.00 (m, 12H, Ar-H), 5.94 (s, 1H, N-CH), 3.75 (s, 2H, S-CH₂ of 2-tolylimino thiazolidinone), 3.30-3.40 (m, 2H, S-CH₂), 2.33 (s, 3H, CH₃); MS m/z (M⁺): 504.52 (Molecular weight: 503.59).

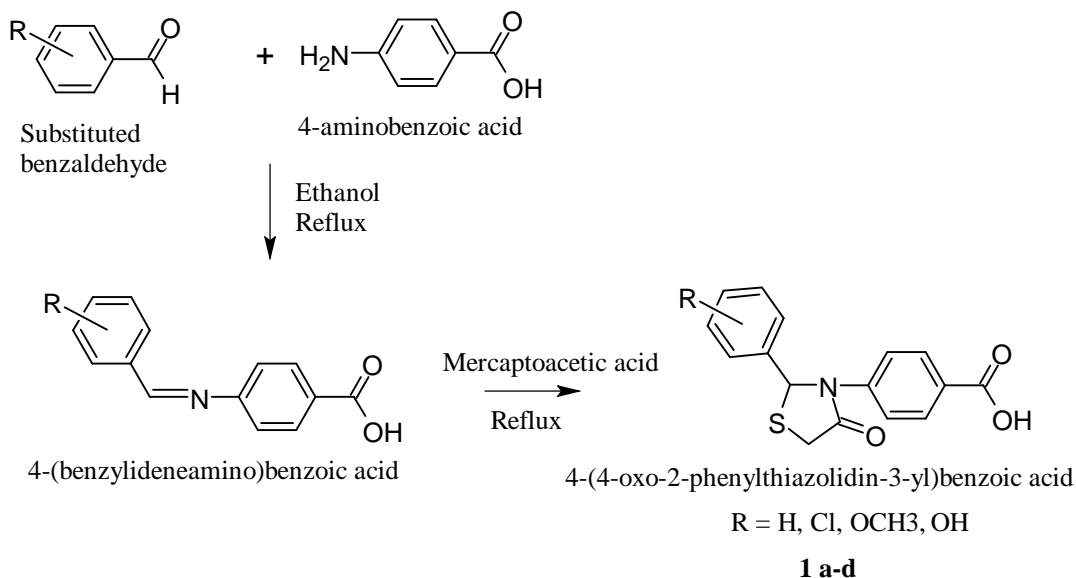
Antifungal activity study of compounds synthesized

The antifungal activities of compounds were assayed *in vitro* against selected fungi, *Aspergillus flavus*, *Aspergillus niger* and *Candida albicans* strains. The inhibition zones (mm) of compounds were determined using the filter paper disc diffusion method²⁶ at two concentrations of 50 and 100 ppm and the percentage activity of compounds were determined using conventional method.

Results and discussion

Chemical synthesis

The chemical synthesis started with the synthesis of schiff's by the reaction of 4-amino benzoic acid and aromatic aldehyde, four aromatic aldehydes were used namely benzaldehyde, p-chlorobenzaldehyde, anisaldehyde and salicylaldehyde to synthesize Schiff's bases namely 4-(benzylideneamino) benzoic acid, 4-[(4-chlorobenzylidene) amino] benzoic acid, 4-[(4-methoxybenzylidene) amino] benzoic acid and 4-[(2-hydroxybenzylidene) amino] benzoic acid. Schiff's bases upon reaction with mercaptoacetic acid gave 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid (**1a-d**). Purity of the synthesized compounds was confirmed by TLC and structures were confirmed by infrared and nuclear magnetic spectroscopic techniques.

Scheme-1: General method for the synthesis of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid**Spectral data for 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid (1a)**

Melting point 235°C; IR (KBr, cm^{-1}): 2926 (Ar-H), 1312 (C-N), 1690 (thiazolidinone C=O), 1421 (C-O-H), 1251(C=O), 691 (C-S); $^1\text{H-NMR}$ (DMSO- d_6) : 10.24 (1H, s, Ar-COOH), 5.98 (1H, s, S-CH-N), 3.50 (2H, s, $\text{CH}_2\text{-S}$), 7.05-8.15 (9H, m, Ar-H); MS m/z (M⁺): 300.06 (Molecular weight: 299.34).

Thiazolidinone derivatives of 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid were prepared by converting 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid (**1a-d**) into 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoyl chloride (**2a-d**) which upon reaction with aniline/ substituted aniline in presence of ammonium thiocyanate yielded thiourea derivative of (**3a-h**) and thiourea derivative treated with monochloroacetic acid in presence of fused sodium acetate to yield thiazolidinone derivatives (**4a-h**).

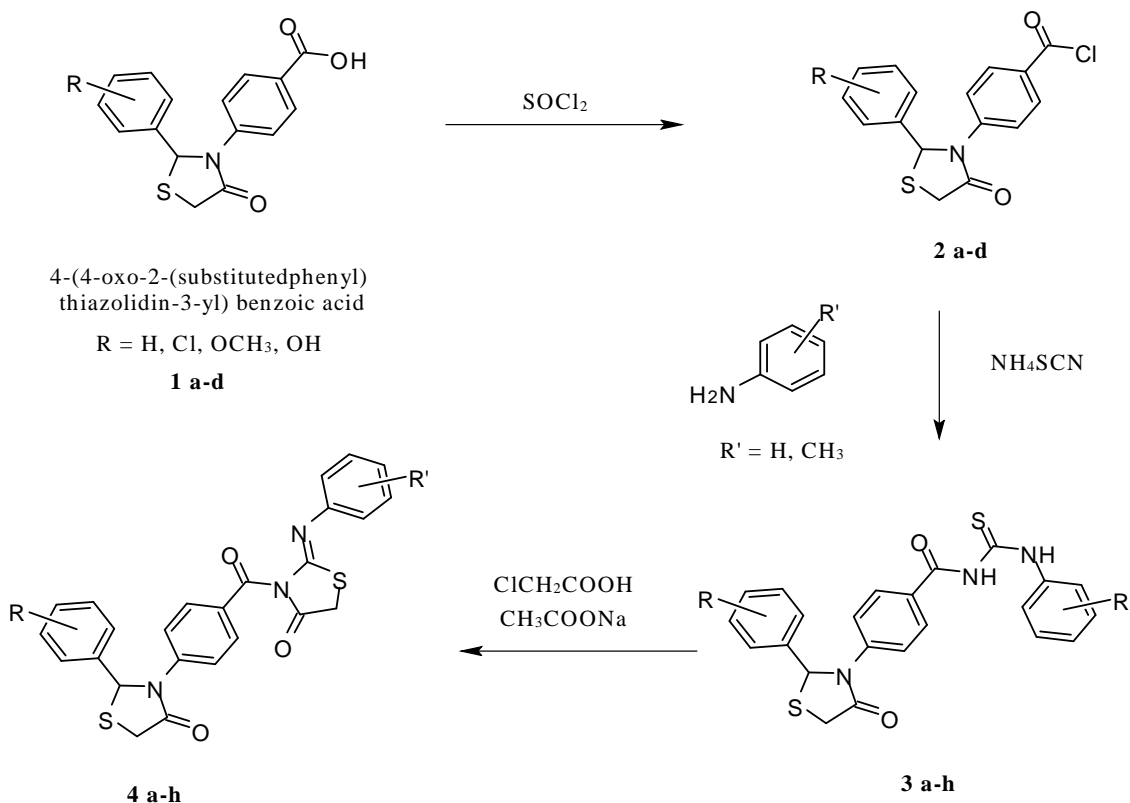
Spectral data for 4-(4-oxo-2-phenylthiazolidin-3-yl)-N-(phenylcarbamothioyl) benzamide (3a)

IR (KBr, cm^{-1}): 2990 (Ar-H), 1611 (C=N), 1577 (Ar-C=C), 1050 (C-O-C). 1710 (thiazolidinone C=O), 1250(C=O), 685 (C-S); $^1\text{H-NMR}$ (DMSO- d_6 , ppm): 7.06-8.00 (m, 8H, Ar-H); 6.40-7.07 (m, 6H, Ar-H), 5.90 (s, 1H,N=CH), 3.55 (2H, s, $\text{CH}_2\text{-S}$); MS m/z (M⁺): 434.09 (Molecular weight: 433.54).

Spectral data for 2-(phenylimino)-3-[[4-(4-oxo-2-phenylthiazolidin-3-yl) phenyl] carbonyl] thiazolidinone (4a)

Melting point 215°C; IR (KBr, cm^{-1}): 3102 (Ar-H), 1341 (C-N), 1710 (thiazolidinone C=O), 688 (C-S); $^1\text{H-NMR}$ (DMSO- d_6 , ppm): 7.04-8.06 (m, 14H, Ar-H), 5.94 (s, 1H, N-CH), 3.78 (s, 2H, S- CH_2 of 2-phenylimino thiazolidinone), 3.30-3.40 (m, 2H, S- CH_2); MS m/z (M⁺): 474.09 (Molecular weight: 473.57).

Scheme-2: Synthesis of thiazolidinone derivatives of 4-(4-oxo-2-(substituted phenyl) thiazolidin-3-yl) benzoic acid



Reaction progress of every synthetic step was monitored by TLC and purity of the synthesized compounds was also confirmed by TLC. The structure of synthesized compounds have been established on the basis of their spectral (IR, ¹H NMR and mass) data. Physical properties of compounds prepared are tabulated in table-1.

Antifungal activity study

The antifungal activity of compounds **4a-h** has been assayed in vitro at two concentrations (50

and 100 ppm) against selected fungi, *Aspergillus flavus*, *Aspergillus niger* and *Candida albicans* strains. The percentage inhibition zones of the compounds **4a-h** were determined by the using filter paper disc diffusion method. Griseofulvin used as standard showed 100% inhibition at both (50 and 100 ppm) concentrations. The percentage inhibition zones of the tested compounds are given in **Table 2**.

Table 1: Physical properties of compounds prepared

Comp Name	R	R'	Mol. formula	Mol. weight	Yield (%)	M.P. (°C)	Elemental analysis (%)		
							Calculated (Found)		
							C	H	N
4a	H	H	C ₂₅ H ₁₉ N ₃ O ₃ S ₂	473.57	60	215	63.41 (63.39)	4.04 (4.01)	8.87 (8.80)
4b	Cl	H	C ₂₅ H ₁₈ ClN ₃ O ₃ S ₂	508.01	60	206	59.11	3.57	8.27
4c	OCH ₃	H	C ₂₆ H ₂₁ N ₃ O ₄ S ₂	503.59	58	212	62.01	4.20	8.34
4d	OH	H	C ₂₅ H ₁₉ N ₃ O ₄ S ₂	489.57	62	218	61.33	3.91	8.58
4e	H	CH ₃	C ₂₆ H ₂₁ N ₃ O ₃ S ₂	487.59	64	199	64.04	4.34	8.62
4f	Cl	CH ₃	C ₂₆ H ₂₀ ClN ₃ O ₃ S ₂	522.04	62	201	59.82	3.86	8.05
4g	OCH ₃	CH ₃	C ₂₇ H ₂₃ N ₃ O ₄ S ₂	517.62	58	181	62.65	4.48	8.12
4h	OH	CH ₃	C ₂₆ H ₂₁ N ₃ O ₄ S ₂	503.59	64	198	62.01	4.20	8.34

Table 2: In vitro antifungal activity of compounds and their inhibition zone (%)

Comp Name	Mol. Formula	Mol. Weight	Zone of inhibition (%)					
			<i>Aspergillus flavus</i>		<i>Aspergillus niger</i>		<i>Candida albicans</i>	
			50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm
4a	C ₂₅ H ₁₉ N ₃ O ₃ S ₂	473.57	40	46	38	47	46	52
4b	C ₂₅ H ₁₈ ClN ₃ O ₃ S ₂	508.01	48	52	45	52	48	55
4c	C ₂₆ H ₂₁ N ₃ O ₄ S ₂	503.59	30	39	38	46	40	48
4d	C ₂₅ H ₁₉ N ₃ O ₄ S ₂	489.57	39	45	29	44	38	41
4e	C ₂₆ H ₂₁ N ₃ O ₃ S ₂	487.59	33	41	28	40	38	45
4f	C ₂₆ H ₂₀ ClN ₃ O ₃ S ₂	522.04	48	58	45	55	47	51
4g	C ₂₇ H ₂₃ N ₃ O ₄ S ₂	517.62	40	49	36	40	40	48
4h	C ₂₆ H ₂₁ N ₃ O ₄ S ₂	503.59	32	44	28	35	33	42

Conclusion

The present study reports the successful synthesis of a thiazolidinone derivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid i.e. 2-(substituted phenylimino)-3-{[4-(4-oxo-2-substituted phenylthiazolidin-3-yl) phenyl]

carbonyl}-thiazolidin-4-one **4a-h** with several structural variations. Antifungal activity study of the synthesized thiazolidinone derivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid revealed that all compounds showed moderate activities against selected microbial strains.

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