

Synthesis and *in vitro* antimicrobial activity of 3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenyl-thiazol-2-yl)-2-substitutedphenyl thiazolidin-4-one

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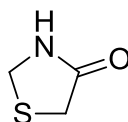
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ABSTRACT. An array of 3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenyl thiazol-2-yl)-2-substitutedphenyl thiazolidin-4-one (**7a-j**) have been synthesized by using acetophenone, thiourea, 4-mercaptocoumarin and thioglycolic acid. The structures of these compounds were confirmed by IR, ¹H NMR, ¹³C NMR and mass analysis. All the newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity (against *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes*) and antifungal activity against (*C. albicans*, *A. niger*, *A. clavatus*) using broth dilution technique. Some of the compounds showed good to moderate activity against the specific microbial strain.

1. INTRODUCTION

Thiazolidinone is a well-known saturated form of thiazole. The carbonyl group of thiazolidine-4-ones is highly un-reactive, and substitution is possible at 2nd, 3rd and 5th position. Thiazolidine-4-one are the derivatives of thiazolidine, which belongs to important groups of heterocyclic compounds containing sulfur and nitrogen in a five member ring. Thiazolidine-4-ones are ordinarily solids, often melting with decomposition but the attachment of an alkyl group to the nitrogen lowers the melting point. In the structure of thiazolidinone (**Figure 1**), carbonyl group is present on fourth carbon. A lot of research work on thiazolidinones, with a carbonyl group at position 2, 4, or 5, has been done in the recent decades [1-3]. Moreover, thiazolidinone is recognized as a magic moiety, because it shows almost all types of remarkable biological activities [1].



Thiazolidine-4- one

fig.1

Thiazolidine-4-ones and its derivatives possess some important biological activities and pharmacological properties such as anti-inflammatory [4], antitubercular [5], anticancer [6, 7], antitumor [8], anti-HIV [9], antibacterial [10], antifungal [11], antioxidant [12], antiviral [13], anticonvulsant [14], nematicidal [15], antihistaminic [16], anti YFV (yellow fever virus) [17] activity *etc.*

AVANCE instrument using TMS as internal standard (Chemical Shift in δ , ppm) and DMSO-*d*₆ as a solvent. Spectra were taken with a resonant frequency of 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR. The splitting patterns are designated as follows; **s**, singlet; **d**, doublet; **dd**, doublet of doublets; and **m**, multiplet. Elemental analysis was done on "Heraeus Rapid Analyser". The mass spectra were recorded on JOEL SX-102 (EI) model with 60 eV ionizing energy.

2.2. Synthesis of 4-phenylthiazol-2-amine

The mixture of thiourea (12.61 g, 0.166 mole) and iodine (10.41 g, 0.041 mole) were added to a stirring solution of the acetophenone (10 g, 0.083 mole) in absolute ethanol (50 mL). The mixture was heated at 80 °C for 2–3 h. Progress of the reaction was monitored by TLC using ethylacetate: hexane (2:8) as eluent. After the completion of reaction, the pH of the solution was adjusted to 7.0 by drop wise addition of NH₄OH solution. The crude generated was filtered and extracted with ether (4x10mL). It was then recrystallized from hot water to get the title compound. Yield: 85%

2.2.1. Synthesis of 5-bromo-4-phenylthiazol-2-amine

To an ice-cold solution of 4-phenylthiazol-2-amine (7.0 g, 0.040 mole) in glacial acetic acid (30 mL), a solution of bromine (5.0 mL, 0.039 mol) in acetic acid (10 mL) was added drop wise at 5-10 °C during 30 min. The mixture was further stirred at room temperature for 2 h. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (2:8) as eluent. After the completion of reaction it was dumped in to water. The precipitated solid was collected by filtration, washed with ice-cold acetic acid (5.0 mL) and water, neutralized by NH₄OH solution and recrystallized from aqueous ethanol to get a brown solid product. Yield: 80%

2.2.2. Synthesis of *N*-arylidene-5-bromo-4-phenyl thiazol-2-amine

A mixture of 5-bromo-4-phenyl thiazol-2-amine (3.5 g, 0.01 mol) and benzaldehyde (0.01 mol, 1.06 mL) in ethanol (15 mL), and acetic acid (0.5 mL) was refluxed for 6 hrs. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (1:9) as eluent. The solvent was removed and the residue was added to crushed ice. The solid precipitates obtained were collected by filtration and purified by recrystallization from ethanol to get pale yellow solid product. Yield: 78%. Other anils were synthesized by the same method as described above.

2.2.3. Synthesis of 4-((2-(arylideneamino)-4-phenyl thiazol-5-yl) thio)-2*H*-chromen-2-one

Alcoholic solution of 4-mercapto-2*H*-chromen-2-one (3.4 g, 0.019 mol) was added to the solution of *N*-arylidene-5-bromo-4-phenyl thiazol-2-amine (5 g, 0.019 mol) in alcohol. The mixture was then refluxed on a steam bath for 5 hrs. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (1:9) as eluent. After the completion of reaction, the residue was poured onto crushed ice to give a solid. The separated solid was filtered off and recrystallized from methanol to get the title compound. Yield: 75%

2.2.4. General procedure for the synthesis of compounds 7a-j

A mixture of 4-((2-(arylidene amino)-4-phenyl thiazol-5-yl)thio)-2*H*-chromen-2-one (0.0045 mol) and thioglycolic acid (0.63 mL, 0.0090 mol) in DMF (*N,N*-dimethylformamide) was refluxed for 12 hrs. Water formed azeotropically, was removed by Dean-stark apparatus, Progress of the reaction was monitored by TLC using ethylacetate: hexane (1:9) as eluent. After the completion of reaction it was poured into cold water, and treated with 10% NaHCO₃ to remove unreacted acid. The solid obtained was filtered, dried, and recrystallized from alcohol to get the title compound. Similarly, other thiazolidinones were prepared by the same method and their analytical data are given in **Table-1**.

3-(5-((2-Oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-phenylthiazolidin-4-one (7a)

IR (vmax cm⁻¹): 2966 (alkyl C-H), 1725 (-C=O), 1100 (-C-O stretching), 890 (C-S stretching), ¹H NMR (400 MHz, DMSO) δ 7.73-7.58 (m, 3H), 7.48-7.38 (m, 3H), 7.37-7.17 (m, 8H), 6.65 (s, 1H), 6.36 (s, 1H), 3.45 (d, 2H); ¹³C NMR (100 MHz, DMSO) δ 174.57, 165.80, 162.74, 158.44, 150.17, 149.36, 142.18, 137.43, 135.25, 131.76, 130.15, 129.65, 128.14, 127.84, 127.43, 126.47, 126.07, 125.74, 125.42, 124.87, 120.22, 67.18, 36.18. ESIMS (m/z): 515.10 (M+).

2-(2-Chlorophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin -4-one (7b)

IR (vmax cm⁻¹): 2985 (alkyl C-H), 1736 (-C=O), 1118 (-C-O stretching), 881 (C-S stretching), 658 (C-Cl); ¹H NMR (400 MHz, DMSO) δ 7.87-7.62 (m, 3H), 7.59-7.37 (m, 3H), 7.35-7.02 (m, 7H), 6.69 (s, 1H), 6.50 (s, 1H), 3.63 (d, 2H); ¹³C NMR (100 MHz, DMSO) δ 175.62, 167.28, 163.57, 159.38, 152.32, 151.29, 145.34, 143.30, 138.65, 135.64, 131.33, 130.07, 129.22, 128.74, 127.30, 126.20, 125.94, 125.46, 125.09, 124.95, 122.34, 66.56, 35.29. ESIMS (m/z): 549.05 (M+).

2-(3-Chlorophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin -4-one (7c)

IR (vmax cm⁻¹): 2992 (alkyl C-H), 1729 (-C=O), 1129 (-C-O stretching), 870 (C-S stretching), 712 (C-Cl); ¹H NMR (400 MHz, DMSO) δ 7.79-7.68 (m, 3H), 7.67-7.29 (m, 3H), 7.27-7.03 (m, 7H), 6.79 (s, 1H), 6.62 (s, 1H), 3.68 (s, 2H); ¹³C NMR (100 MHz, DMSO) δ 176.59, 169.35, 165.66, 161.25, 153.05, 152.21, 146.07, 145.30, 140.11, 138.01, 133.94, 131.77, 130.87, 129.39, 128.75, 127.56, 126.03, 125.55, 125.10, 124.61, 123.59, 68.29, 37.22. ESIMS (m/z): 549.13 (M+).

2-(4-Chlorophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin -4-one (7d)

IR (vmax cm⁻¹): 3014 (alkyl C-H), 1739 (-C=O), 1195 (-C-O stretching), 888 (C-S stretching), 802 (C-Cl); ¹H NMR (400 MHz, DMSO) δ 7.83-7.71 (m, 3H), 7.69-7.34 (m, 3H), 7.33-7.13 (m, 7H), 6.68 (s, 1H), 6.46 (s, 1H), 3.76 (s, 2H); ¹³C NMR (100 MHz, DMSO) δ 179.62, 170.26, 166.36, 163.22, 151.41, 150.33, 145.77, 145.08, 138.69, 137.14, 132.79, 130.65, 129.88, 129.14, 127.71, 127.22, 126.89, 125.37, 125.01, 124.82, 123.64, 65.33, 34.88. ESIMS (m/z): 549.46 (M+).

3-(5-((2-Oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-(*o*-tolyl) thiazolidin-4-one (7e)

IR (vmax cm⁻¹): 2954 (alkyl C-H), 1728 (-C=O), 1096 (-C-O stretching), 749 (C-S stretching); ¹H NMR (400 MHz, DMSO) δ 7.92-7.77 (m, 3H), 7.76-7.51 (m, 3H), 7.50-7.14 (m, 7H), 6.79 (s, 1H), 6.60 (s, 1H), 3.81 (s, 2H), 2.24 (s, 3H); ¹³C NMR (100 MHz, DMSO) δ 175.32, 169.55, 164.59, 162.63, 150.79, 149.21, 144.29, 143.79, 137.55, 133.49, 131.04, 130.13, 128.53, 127.33, 126.09, 125.62, 124.36, 123.29, 123.02, 122.92, 122.77, 64.46, 35.92, 20.36. ESIMS (m/z): 529.26 (M+).

3-(5-((2-Oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-(*m*-tolyl)thiazolidin-4-one (7f)

IR (vmax cm⁻¹): 2969 (alkyl C-H), 1736 (-C=O), 1123 (-C-O stretching), 779 (C-S stretching); ¹H NMR (400 MHz, DMSO) δ 7.82-7.71 (m, 3H), 7.70-7.58 (m, 3H), 7.57-7.04 (m, 7H), 6.83 (s, 1H), 6.72 (s, 1H), 3.74 (s, 2H), 2.43 (s, 3H); ¹³C NMR (100 MHz, DMSO) δ 176.56, 170.49, 165.33, 163.53, 151.74, 150.20, 145.60, 144.43, 138.01, 134.76, 132.55, 131.44, 129.75, 128.61, 127.40, 126.33, 125.70, 124.39, 124.13, 123.30, 122.45, 65.88, 36.63, 21.71. ESIMS (m/z): 529.55 (M+).

3-(5-((2-Oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-(*p*-tolyl) thiazolidin-4-one (7g)

IR (vmax cm⁻¹): 2988 (alkyl C-H), 1732 (-C=O), 1129 (-C-O stretching), 830 (C-S stretching); ¹H NMR (400 MHz, DMSO) δ 7.97-7.82 (m, 3H), 7.81-7.68 (m, 3H), 7.67-7.19 (m, 7H), 6.91 (s, 1H), 6.88 (s, 1H), 3.34 (s, 2H), 2.37 (s, 3H); ¹³C NMR (100 MHz, DMSO) δ 175.77, 171.63, 164.53, 162.09, 152.43, 151.40, 146.22, 145.39, 139.79, 138.59, 137.54, 135.50, 133.49, 130.28, 129.63, 128.61, 127.79, 126.33, 125.43, 124.72, 123.33, 64.56, 34.22, 20.44. ESIMS (m/z): 529.13 (M+).

2-(2-Nitrophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin-4-one (4h)

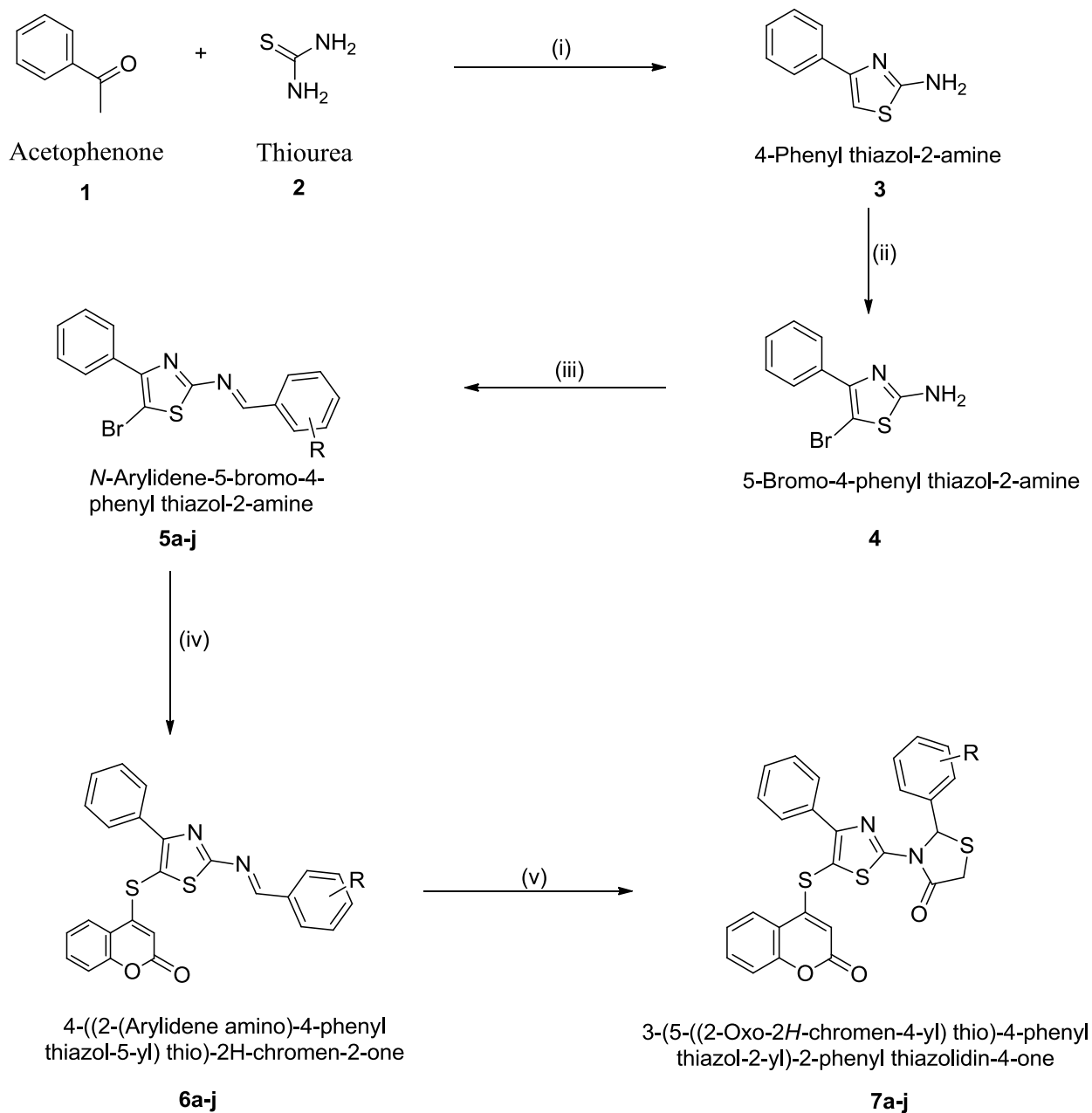
IR (ν_{\max} cm^{-1}): 3017 (alkyl C-H), 1729 (-C=O), 1327 (N-O stretch), 1153 (-C-O stretching), 823 (C-S stretching); ^1H NMR (400 MHz, DMSO) δ 8.18-7.95 (m, 3H), 7.94-7.81 (m, 3H), 7.80-7.53 (m, 7H), 6.97 (s, 1H), 6.91 (s, 1H), 3.89 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 178.59, 175.29, 166.38, 164.25, 154.56, 152.43, 150.59, 148.36, 147.74, 140.89, 139.60, 138.62, 137.20, 136.47, 135.52, 134.28, 132.59, 131.55, 130.79, 129.98, 129.49, 128.89, 66.58, 36.76. ESIMS (m/z): 560.39 (M+).

2-(3-Nitrophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin-4-one (4i)

IR (ν_{\max} cm^{-1}): 2997 (alkyl C-H), 1739 (-C=O), 1345 (N-O stretch), 1149 (-C-O stretching), 759 (C-S stretching); ^1H NMR (400 MHz, DMSO) δ 8.27-7.99 (m, 3H), 7.98-7.89 (m, 3H), 7.88-7.48 (m, 7H), 6.94 (s, 1H), 6.88 (s, 1H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 182.29, 176.72, 168.41, 166.53, 155.49, 151.50, 151.09, 149.71, 148.44, 147.49, 146.63, 139.77, 138.45, 137.50, 136.28, 135.18, 134.27, 133.23, 132.43, 130.48, 129.86, 129.15, 67.43, 37.50. ESIMS (m/z): 560.61 (M+).

2-(4-Nitrophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin-4-one (4j)

IR (ν_{\max} cm^{-1}): 2980 (alkyl C-H), 1721 (-C=O), 1314 (N-O stretch), 1098 (-C-O stretching), 771 (C-S stretching); ^1H NMR (400 MHz, DMSO) δ 8.13-7.91 (m, 3H), 7.89-7.71 (m, 3H), 7.70-7.31 (m, 7H), 6.90 (s, 1H), 6.82 (s, 1H), 3.59 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 179.38, 177.45, 170.63, 167.40, 156.63, 152.36, 151.43, 150.73, 149.29, 148.63, 147.48, 140.43, 139.52, 138.55, 137.45, 136.22, 135.59, 134.47, 133.89, 131.33, 130.78, 129.33, 66.46, 36.29. ESIMS (m/z): 560.49 (M+).



Where R = -H, 2-Cl, 3-Cl, 4-Cl, 2-CH₃, 3-CH₃, 4-CH₃,
2-NO₂, 3-NO₂, 4-NO₂

Reagents and conditions: (i) Iodine, thiourea, ethanol, 2-3 h; (ii) Bromine/acetic acid reflux, 2h; (iii) Aromatic aldehyde, acetic acid, ethanol, reflux, 6 h; (iv) 4-Mercapto coumarin, ethanol, reflux, 5 h; (v) Thioglycolic acid, ZnCl₂, DMF reflux, 12 h.

Scheme 1. Synthetic pathway for compounds 7a-j.

Table 1. Characterization of compounds **7a-j**.

Compound	-R	Molecular Formula	M.P. °C	Yield %	Elemental Analysis			
					% C	% H	% N	
7a	-H	C ₂₇ H ₁₈ N ₂ O ₃ S ₃	147	80	R	63.01	3.53	5.44
					F	63.05	3.58	5.48
7b	2-Cl	C ₂₇ H ₁₇ ClN ₂ O ₃ S ₃	299	72	R	59.06	3.12	5.10
					F	59.11	3.16	5.15
7c	3-Cl	C ₂₇ H ₁₇ ClN ₂ O ₃ S ₃	289	70	R	59.06	3.12	5.10
					F	59.03	3.09	5.07
7d	4-Cl	C ₂₇ H ₁₇ ClN ₂ O ₃ S ₃	296	69	R	59.06	3.12	5.10
					F	59.09	3.15	5.13
7e	2-CH ₃	C ₂₈ H ₂₀ N ₂ O ₃ S ₃	295	73	R	63.61	3.81	5.30
					F	63.66	3.86	5.35
7f	3-CH ₃	C ₂₈ H ₂₀ N ₂ O ₃ S ₃	292	78	R	63.61	3.81	5.30
					F	63.57	3.78	5.26
7g	4-CH ₃	C ₂₈ H ₂₀ N ₂ O ₃ S ₃	276	70	R	63.61	3.81	5.30
					F	63.66	3.84	5.33
7h	2-NO ₂	C ₂₇ H ₁₇ N ₃ O ₅ S ₃	277	73	R	57.95	3.06	7.51
					F	58.00	3.07	7.56
7i	3-NO ₂	C ₂₇ H ₁₇ N ₃ O ₅ S ₃	290	75	R	57.95	3.06	7.51
					F	57.91	3.03	7.47
7j	4-NO ₂	C ₂₇ H ₁₇ N ₃ O ₅ S ₃	288	75	R	57.95	3.06	7.51
					F	57.97	3.09	7.53

3. BIOLOGICAL EVALUATION

3.1. *In vitro* antibacterial activity

In this series, we have synthesized a series of compounds containing thiazolidinyl-thiazole fused motif with coumarin through sulphur bridge. Functionalization has been done on phenyl nucleus of thiazolidinone ring to get various compounds. It has been observed that the test compounds (**7a-j**) exhibited interesting antibacterial activity (**Table 2**), however with a degree of variation. The chloro group containing final compounds i.e. **7b** and **7d** showed very good potency against specific bacterial strain. The final derivatives containing electron withdrawing nitro group i.e. **7h** and **7j** exhibited superior inhibition profile for the selected bacterial strains. On the other hand significant deviation of activity has been observed against Gram-negative strains where the unsubstituted phenyl ring containing thiazolidinone compounds i.e. **7a** exhibited higher inhibition against the bacterial strain *P. aeruginosa*. Rest of the compounds exhibited moderate to poor activity.

3.2. *In vitro* antifungal activity

Antifungal activity data (**Table 3**) showed that the final compound **7a** exhibited virtuous inhibition against the fungal strain *A. clavatus*. Also compounds **7b**, **7c**, **7i**, and **7j** showed good inhibition against *C. albicans*, *A. niger* and *A. clavatus*. Rest of the compounds appeared with moderate to poor activity profile.

Table 2. *In vitro* antibacterial activity of compounds **7a-j**.

Compound	R	MIC ($\mu\text{g/ml}$)			
		<i>E. coli</i> MTCC 442	<i>P. aeruginosa</i> MTCC 441	<i>S. aureus</i> MTCC 96	<i>S. pyogenes</i> MTCC 443
7a	-H	50	25	100	100
7b	2-Cl	50	25	50	50
7c	3-Cl	100	50	100	100
7d	4-Cl	100	25	50	50
7e	2-CH ₃	100	125	62.5	100
7f	3-CH ₃	125	100	200	200
7g	4-CH ₃	200	250	250	250
7h	2-NO ₂	50	25	50	50
7i	3- NO ₂	25	100	100	100
7j	4-NO ₂	100	100	50	50
Ciprofloxacin	-	25	25	50	50
Chloramphenicol	-	50	50	50	50

S. aureus *Staphylococcus aureus*, *E. coli* *Escherichia coli*, *P. aeruginosa* *Pseudomonas aeruginosa*, *S.pyogenes* *Streptococcus pyogenes*

Table 3. *In vitro* anti-fungal activity of newly synthesized compounds **7a-j**

Compound	R	MIC ($\mu\text{g/ml}$)		
		<i>C. albicans</i> MTCC 227	<i>A. niger</i> MTCC 282	<i>A. clavatus</i> MTCC 1323
7a	-H	250	250	100
7b	2-Cl	250	100	500
7c	3-Cl	100	500	500
7d	4-Cl	500	250	250
7e	2-CH ₃	500	500	1000
7f	3-CH ₃	1000	>1000	1000
7g	4-CH ₃	1000	>1000	1000
7h	2-NO ₂	500	500	1000
7i	3- NO ₂	500	250	100
7j	4-NO ₂	100	250	250
Nystatin	--	100	100	100
Greseofulvin	-	500	100	100

A. niger *Aspergillus niger*, *A. clavatus* *Aspergillus clavatus*, *C. albicans* *Candida albicans*

4. CONCLUSION

The present study determined the design and development of 3-(5-((2-oxo-2*H*-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-substitutedphenylthiazolidin-4-one in good yield. Synthesized derivatives were characterized by IR, mass, ¹H NMR, ¹³C NMR as well as elemental analysis and tested for their antibacterial activity against various bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* and their antifungal activity against various fungal strains such as *C. albicans*, *A. niger* and *A. clavatus*. The unsubstituted phenyl ring containing final compound i.e. **7a** and the chloro group containing final motifs i.e. **7b**, **7c**, **7d** exhibited interesting activity against particular bacterial and fungal strain, however with a degree of variation. The nitro group containing final analogues i.e. **7h**, **7i** and **7j** showed excellent inhibition profile for the specific microbial strain.

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References

- [1] M. Abhinit, M. Ghodke, N. A. Pratima, *International Journal of Pharmacy and Pharmaceutical Sciences 1* (2009) 47.
- [2] S. P. Singh, S. S. Parmar, K. Raman, V. I. Stenberg, *Chemical reviews 81* (1981) 175.
- [3] P. Mehta, P. Dawedra, V. Goswami, H. S. Joshi, *International Letters of Chemistry, Physics and Astronomy 11* (2014) 1.
- [4] A. D. Taranalli, A. R. Bhat, S. Srinivas, E. Saravanan, *Indian Journal of Pharmaceutical Sciences 70* (2008) 159.
- [5] N. Karalı, A. Gürsoy, F. Kandemirli, N. Shvets, F. B. Kaynak, S. Özbey, V. Kovalishyn, A. Dimoglo, *Bioorganic & Medicinal Chemistry 15* (2007) 5888.
- [6] D. Kaminsky, B. Bednarczyk-Cwynar, O. Vasylenko, O. Kazakova, B. Zimenkovsky, L. Zaprutko, R. Lesyk, *Medicinal Chemistry Research 21* (2012) 3568.
- [7] S. Wang, Y. Zhao, W. Zhu, Y. Liu, K. Guo, P. Gong, *Archiv der Pharmazie 345* (2012) 73.
- [8] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, *Journal of Medicinal Chemistry 55* (2012) 8630.
- [9] J. Balzarini, B. Orzeszko-Krzesińska, J. K. Maurin, A. Orzeszko, *European journal of medicinal chemistry 44* (2009) 303.
- [10] V. S. Palekar, A. J. Damle, S. Shukla, *European journal of medicinal chemistry 44* (2009) 5112.
- [11] K. Omar, A. Geronikaki, P. Zoumpoulakis, C. Camoutsis, M. Soković, A. Ćirić, J. Glamočlija, *Bioorganic & Medicinal Chemistry 18* (2010) 426.
- [12] M.-H. Shih, F.-Y. Ke, *Bioorganic & Medicinal Chemistry 12* (2004) 4633.
- [13] E. Tatar, İ. Küçükgülzel, E. De Clercq, F. Şahin, M. Guelluece, *Arkivoc 14* (2008) 191.
- [14] F. Ragab, N. M. Eid, H. El-Tawab, *Die Pharmazie 52* (1997) 926.
- [15] A. Srinivas, A. Nagaraj, C. Sanjeeva Reddy, *Journal of Heterocyclic Chemistry 46* (2009) 497.
- [16] M. V. Diurno, O. Mazzoni, E. Piscopo, A. Calignano, F. Giordano, A. Bolognese, *Journal of Medicinal Chemistry 35* (1992) 2910.
- [17] D. Sriram, P. Yogeewari, T. Kumar, *Journal of Pharmacy & Pharmaceutical Sciences 8* (2005) 426.
- [18] V. G. Bhila, Y. L. Chovatiya, C. V. Patel, R. R. Giri, D. I. Brahmhatt, *International Letters of Chemistry, Physics and Astronomy 1* (2015).