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

Himanshu R. Prajapati, Harshad P. Lakum, Kishor H. Chikhalia*
Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad- 380009, Gujarat, India
*E-mail address: chikhalia_kh@yahoo.com.

Keywords: 4-Thiazolidinone; thioether; coumarin-thiazole; antibacterial activity; antifungal activity

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 2\textsuperscript{nd}, 3\textsuperscript{rd} and 5\textsuperscript{th} 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].

![Figure 1](https://example.com/image.png)

Thiazolidine-4- one

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.
In this study, design and synthesis of new thiazolidine-4-one compounds, through the combination of different pharmacophores such as coumarin and thiazol in one structure may lead to compounds with increased biological activity. Consequently, coumarin [18] and thiazole containing thiazolidine-4-one moiety are expected to have enhanced biological activities. Thus, these observations encouraged us to synthesize new thiazolidine-4-one derivatives which were attached with thiazole as well as coumarin ring joined through sulphur bridge (Scheme 1).

![Scheme 1](image)

3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-substituted phenyl thiazolidin-4-one

fig.3

These compounds showed good activity against particular bacterial including *E. coli*, *P. aeruginosa*, *S. aureus*, & *S. pyogenes* respectively, as well as antifungal activity against *C. albicans*, *A. niger*, and *A. clavatus*. The structure of all newly synthesized derivatives were confirmed by IR, \(^1\)H-NMR, \(^13\)C NMR, mass spectra as well as elemental analysis.

2. EXPERIMENTAL

2.1. Material and methods

All the chemicals and solvents used for the synthesis work acquired from commercial sources, were of analytical grade, and used without further purification. Melting points were determined by using open capillary tubes and are uncorrected. TLC was checked on E-Merck pre-coated 60 F254 plates and the spots were rendered visible by exposing to UV light or iodine. IR spectra were recorded on SHIMADZU HYPER IR. NMR spectra were recorded on 400 MHz BRUKER...
AVANCE instrument using TMS as internal standard (Chemical Shift in δ, ppm) and DMSO-d6 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 “Haraeus 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 solid precipitates 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)-2H-chromen-2-one

Alcoholic solution of 4-mercapto-2H-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-(arylidine amino)-4-phenyl thiazol-5-yl)thio)-2H-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 ethyl acetate: 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): 3014 (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, 123.64, 65.33, 34.88. ESIMS (m/z): 549.13 (M+).
2-(2-Nitrophenyl)-3-(5-((2-oxo-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl) thiazolidin-4-one (4h)

IR (νmax cm⁻¹): 3017 (alkyl C-H), 1729 (-C=O), 1327 (N-O stretch), 1153 (-C-O stretching), 823 (C-S stretching); \(^1^H\) 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); \(^1^3^C\) 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 (νmax cm⁻¹): 2997 (alkyl C-H), 1739 (-C=O), 1345 (N-O stretch), 1149 (-C-O stretching), 759 (C-S stretching); \(^1^H\) 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); \(^1^3^C\) 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 (νmax cm⁻¹): 2980 (alkyl C-H), 1721 (-C=O), 1314 (N-O stretch), 1098 (-C-O stretching), 771 (C-S stretching); \(^1^H\) NMR (400 MHz, DMSO) δ 8.13-7.91 (m, 3H), 7.98-7.89 (m, 3H), 7.88-7.48 (m, 7H), 6.90 (s, 1H), 6.82 (s, 1H), 3.59 (s, 2H); \(^1^3^C\) 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⁺).
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 |
|----------|----|-------------------|---------|---------|-------------------|
| 7a       | -H | C_{27}H_{18}N_{2}O_{3}S_{3} | 147     | 80      | R: 63.01 % C 3.53, H 5.44 |
| 7b       | 2-Cl | C_{27}H_{17}ClN_{2}O_{3}S_{3} | 299     | 72      | F: 63.05 % C 3.58, H 5.48 |
| 7c       | 3-Cl | C_{27}H_{17}ClN_{2}O_{3}S_{3} | 289     | 70      | R: 59.06 % C 3.12, H 5.10 |
| 7d       | 4-Cl | C_{27}H_{17}ClN_{2}O_{3}S_{3} | 296     | 69      | F: 59.11 % C 3.16, H 5.15 |
| 7e       | 2-CH_{3} | C_{28}H_{20}N_{2}O_{3}S_{3} | 295     | 73      | R: 59.06 % C 3.12, H 5.10 |
| 7f       | 3-CH_{3} | C_{28}H_{20}N_{2}O_{3}S_{3} | 292     | 78      | F: 59.03 % C 3.09, H 5.07 |
| 7g       | 4-CH_{3} | C_{28}H_{20}N_{2}O_{3}S_{3} | 276     | 70      | R: 59.09 % C 3.15, H 5.13 |
| 7h       | 2-NO_{2} | C_{27}H_{19}N_{3}O_{3}S_{3} | 277     | 73      | F: 63.61 % C 3.81, H 5.30 |
| 7i       | 3-NO_{2} | C_{27}H_{19}N_{3}O_{3}S_{3} | 290     | 75      | R: 63.66 % C 3.86, H 5.35 |
| 7j       | 4-NO_{2} | C_{27}H_{19}N_{3}O_{3}S_{3} | 288     | 75      | F: 63.57 % C 3.78, H 5.26 |

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. \textit{In vitro} antibacterial activity of compounds 7a-j.

| Compound | R    | \textit{E. coli} MTCC 442 | \textit{P. aeruginosa} MTCC 441 | \textit{S. aureus} MTCC 96 | \textit{S. pyogenes} 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-CH₃| 100                       | 125                          | 62.5                   | 100                         |
| 7f       | 3-CH₃| 125                       | 100                          | 200                    | 200                         |
| 7g       | 4-CH₃| 200                       | 250                          | 250                    | 250                         |
| 7h       | 2-NO₂| 50                        | 25                           | 50                     | 50                          |
| 7i       | 3-NO₂| 25                        | 100                          | 100                    | 100                         |
| 7j       | 4-NO₂| 100                       | 100                          | 50                     | 50                          |
| Ciprofloxacain | - | 25                        | 25                           | 50                     | 50                          |
| Chloramphenicol | - | 50                        | 50                           | 50                     | 50                          |

\textit{S. aureus Staphylococcus aureus, E. coli Escherichia coli, P. aeruginosa Pseudomonas aeruginosa, S.pyogenes Streptococcus pyogenes}

Table 3. \textit{In vitro} anti-fungal activity of newly synthesized compounds 7a-j

| Compound | R    | \textit{C. albicans} MTCC 227 | \textit{A. niger} MTCC 282 | \textit{A. clavatus} 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-CH₃| 500                           | 500                       | 1000                        |
| 7f       | 3-CH₃| 1000                          | >1000                     | 1000                        |
| 7g       | 4-CH₃| 1000                          | >1000                     | 1000                        |
| 7h       | 2-NO₂| 500                           | 500                       | 1000                        |
| 7i       | 3-NO₂| 500                           | 250                       | 100                         |
| 7j       | 4-NO₂| 100                           | 250                       | 250                         |
| Nystatin | --   | 100                           | 100                       | 100                         |
| Greseofulvin | - | 500                           | 100                       | 100                         |

\textit{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-2H-chromen-4-yl)thio)-4-phenylthiazol-2-yl)-2-substitutedphenylthiazolidin-4-one in good yield. Synthesized derivatives were characterized by IR, mass, $^{1}$H NMR, $^{13}$C NMR as well as elemental analysis and tested for their antibacterial activity against various bacteria such as \textit{E. coli, P. aeruginosa, S. aureus} and \textit{S. pyogenes} and their antifungal activity against various fungal strains such as \textit{C. albicans, A. niger} and \textit{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.
Acknowledgements

Authors are very thankful to department of chemistry, School of Sciences, Gujarat University, Ahmedabad, India for providing research facility. The authors wish to offer their deep gratitude to oxygen health care, Ahmedabad, India for carrying out spectral analysis.

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. Karali, A. Gürsoy, F. Kandemirli, N. Shvets, F. B. Kaynak, S. Özbey, V. Kovalishyn, A. Dimoglo, *Bioorganic & Medicinal Chemistry* 15 (2007) 5888.

[6] D. Kaminskyy, 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, I. Küçükgüzel, E. De Clercq, F. Şahin, M. Guelluunce, *Arkidoc 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. Yogeeswari, 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. Brahmbhatt, *International Letters of Chemistry, Physics and Astronomy* 1 (2015).