Introduction

Chalcones, considered to be the precursor of flavonoids and isoflavonoids, are abundant in edible plants. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system. Studies revealed that compounds with a chalcone-based structure have anti-inflammatory,\(^1\) anti-bacterial,\(^2\) anti-fungal,\(^3,^5\) and anti-tumor activities.\(^6^-^9\) These activities are largely attributed due to the α, β-unsaturated ketone moiety. Introduction of various substituents into the two aryl rings is also a subject of interest because it leads to useful structure-activity relationship (SAR).

Chemistry and biological activity of chalcones

Renate et al.\(^10\) have reported synthesis of a acetylenic chalcones. The new acetylenic chalcones were evaluated for antimalarial and antitubercular activity. The antimalarial data for this series suggests that growth inhibition of the W2 strain of *Plasmodium falciparum* can be imparted by the introduction of a methoxy group ortho to the acetylenic group. Most of the compounds were active against *Mycobacterium tuberculosis* H37Rv.

Babasaheb et al.\(^11\) have reported synthesis and biological evaluation of β-chloro vinyl chalcones. All synthesized compounds were evaluated for their anti-inflammatory activity
and antimicrobial activity. Most of the compounds showed very good antibacterial and antifungal activity.

\[
\text{O} \quad \text{C} \quad \text{OH} \quad \text{O} \quad \text{OH} \quad + \quad \text{R}_2 \quad \text{R}_1 \quad \text{Cl} \quad \text{CHO} \quad \xrightarrow{\text{NaOH}} \quad \text{O} \quad \text{O} \quad \text{Cl} \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4
\]

R1, R2, R3, R4 \equiv Cl, Br and F

Anindra et al.\textsuperscript{12} have reported synthesis of (2E)-1,1-(3-hydroxy-5-methylbiphenyl-2,6-diyl)-bis(3-phenylprop-2-ene-1-ones. The new chalcones were prepared by the reaction of 1,3-diacyetyl biphenyls with different aldehydes in presence of catalytic amount of solid potassium hydroxide in ethanol in excellent yields. The synthesized compounds were evaluated for anticancer activity against human breast cancer MCF-7 (estrogen responsive proliferative breast cancer model) and MDA-MB-231 (estrogen independent aggressive breast cancer model) cell lines, HeLa (cervical cancer) cell line, and human embryonic kidney (HEK-293) cells. Most of the compounds preferentially inhibited the growth of the aggressive human breast cancer cell lines.

\[
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4 \quad \text{O} \quad \text{C} \quad \text{H}_3 \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{H}
\]

R = H, Cl, Br, F, OCH\textsubscript{3}

Zohreh et al.\textsuperscript{13} have reported synthesis of novel chalconoids containing a 6-chloro-2H-chromen-3-yl group. The target compounds were evaluated against the promastigote form of \textit{Leishmania major} using MTT assay. All of the evaluated compounds have shown high \textit{in vitro} antileishmanial activity at concentrations less than 3.0 \textmu M. The results of cytotoxicity
assessment against mouse peritoneal macrophage cells showed that these compounds display antileishmanial activity at non-cytotoxic concentrations.

\[
\text{R}_1 = \text{H, Cl, F, OCH}_3, \text{3,4,5-tri-OCH}_3
\]

Jen-Hao et al.\textsuperscript{14} have reported synthesis of 2,5-dialkoxychalcones. The new chalcones were prepared by Claisen–Schmidt condensation of appropriate acetophenones with suitable aromatic aldehyde. The novel 2,5-dialkoxychalcones were evaluated for their cytotoxic, anti-inflammatory, and anti-oxidant activities.

Julio et al.\textsuperscript{15} have reported solution-phase parallel synthesis of substituted chalcones and their antiparasitary activity against *Giardia lamblia*. A library of 25-membered chalcones was prepared by parallel synthesis. Substituted acetophenones and benzaldehydes were
condensed using the Claisen–Schmidt base-catalyzed aldol condensation. Several chalcones showed *in vitro* antiparasitic activity against *Giardia lamblia*.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{OH} + \text{O} \begin{array}{c}
\text{CH}_3 \\
\text{KOH}
\end{array} \begin{array}{c}
\text{O} \\
\text{C}_2\text{H}_5\text{OH}
\end{array} & \rightarrow \begin{array}{c}
\text{O} \\
\text{R}_1
\end{array} \\
\text{R}_1 & = \text{H, Cl, F, OH, OCH}_3 \\
\text{R}_2 & = \text{H}
\end{align*}
\]

Anastasia *et al.*\(^{16}\) have reported synthesis, characterization and evaluation of the antioxidant and soybean lipoxygenase inhibitory activity of synthetic 2-hydroxy-chalcones and aurones. An extensive structure-relationship study was performed and revealed that several chalcones and aurones possess an appealing pharmacological profile combining high antioxidant and lipid peroxidation activity with potent soybean LOX inhibition.

\[
\begin{align*}
\text{OH} & \begin{array}{c}
\text{O} \\
\text{C}_2\text{H}_5\text{OH}
\end{array} \begin{array}{c}
\text{CHO} \\
\text{KOH}
\end{array} & \rightarrow \begin{array}{c}
\text{OH} \\
\text{R}_1
\end{array} \\
\text{R}_1 & = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H, R}_5 = \text{OCH}_3 \\
\text{R}_1 & = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H, R}_5 = \text{CH}_3 \\
\text{R}_1 & = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H, R}_5 = \text{Cl}
\end{align*}
\]

Yerra *et al.*\(^{17}\) have reported synthesis and biological evaluation of 3,4,5-trimethoxychalcones. The novel 3,4,5-trimethoxychalcones were evaluated for their nitric oxide production and tumor cell proliferation activities.
Tanvir et al.\textsuperscript{18} have reported synthesis and biological activity of new 3-[4-(1H-imidazol-1-yl) phenyl]prop-2-en-1-ones. All the synthesized compounds were subjected to evaluation for their anti-leishmanial, anti-oxidant and anti-fungal activities. Few of the synthesized compounds showed significant anti-fungal activity.

Xuelin et al.\textsuperscript{19} have reported a series of dihydroartemisinin derivatives containing a substituted chalcone linked by either ether or ester. The novel chalcones were investigated for their cytotoxicity in human leukemia HL-60 and mouse lymphoma P388 cells. These derivatives have greater cytotoxic effects in both cell lines than dihydroartemisinin.
Amit et al.\textsuperscript{20} have reported synthesis of series of chalcone derivatives. The new chalcone combination with artemisinin was evaluated \textit{in vitro} antimalarial activity against \textit{Plasmodium falciparum}.

Susanne et al.\textsuperscript{21} have reported synthesis of series of prenylated chalcones. The novel chalcones were evaluated for their cytotoxic and anti-oxidative activities.

Louise et al.\textsuperscript{22} have reported synthesis of series of chalcone derivatives. The chalcones derived from 2,4,6-trimethoxyacetophenone. The chalcone derivatives were evaluated their inhibitory action of nitric oxide (NO) production in murine macrophages.
Lorena et al.\textsuperscript{23} have reported synthesis of a series of novel new 1-phenyl-3-\{4-[(2E)-3-phenylprop-2-enoyl]phenyl\}-thiourea and urea derivatives. The synthesized compounds were evaluated against writhing test in mice. The results of the preliminary bioassays indicate that most of the compounds promising anti-nociceptive activity in acetic acid, formalin, and glutamate-induced pain in mice.

![Chemical structure](image1)

Marek et al.\textsuperscript{24} have reported the acid-catalyzed synthesis of oxathiolone fused chalcones. The new chalcone derivatives evaluated for their anticancer activity toward various human cancer cells line. Most of the compounds displayed greater potencies towards HeLa cell lines.

![Chemical structure](image2)

Xiaoling et al.\textsuperscript{25} have reported a library of chalcones with different basic groups. The novel chalcone derivatives were evaluated for antiproliferative activities against the human breast cancer (MCF 7) and colon cancer (HCT 116) cell lines. Structure-activity relationship was analyzed by projection methods and multiple linear regressions. Polar volume, hydrogen
bonding features, HOMO energies, and charge on the β-carbon were found to be important factors.

Nishida et al.\textsuperscript{26} have reported synthesis of series of 2,4,6-trihydroxychalcone derivatives. The 2,4,6-trihydroxychalcone derivatives were evaluated for new class of tyrosinase inhibitors. Most of the compounds showed good tyrosinase inhibitor activity.

Aneta et al.\textsuperscript{27} have reported series of novel chalcones and bis-chalcones containing boronic acid moieties. The chalcone derivatives evaluated for antitumor activity against the human breast cancer MDA-MB-231 and MCF7 cell lines and against two normal breast epithelial cell lines, MCF-10A and MCF-12A. These molecules inhibited the growth of the human breast cancer cell lines at low micro molar to nanomolar concentrations.
Shen-Jeu et al.\textsuperscript{28} have reported synthetic chalcones as potential anti-inflammatory and cancer chemopreventive agents. Chalcones were prepared by Claisen-Schmidt condensation of appropriate acetophenones with suitable aromatic aldehyde or prepared with appropriate dihydrochalcone reacted with appropriate alkyl bromide or prepared in one-pot procedure involving acetophenone and convenient aromatic aldehyde using ultrasonic agitation on basic alumina.

\[
\begin{align*}
\text{Cl} & \quad \text{H} & \quad \text{H}_2\text{C} & \quad \text{O} & \quad \text{O} & \quad \text{Ba(OH)}_2 & \quad \text{CH}_3\text{OH} \\
\text{Cl} & \quad \text{Cl} & \quad \text{O} & \quad \text{O} & \quad & \quad & \\
\text{Cl} & \quad \text{Cl} & \quad \text{OH} & \quad & \quad & \quad & \\
\end{align*}
\]

Jaime et al.\textsuperscript{29} have reported synthesis of \textit{E}-2-quinolinyl-benzocycloalcanones. The novel quinolinyl-benzocycloalcanones were evaluated for their antimalarial activity.

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{N} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{R} \\
\text{H}_3\text{CO} & \quad \text{H} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{F} \\
\end{align*}
\]

Hasse et al.\textsuperscript{30} have reported synthesis of licochalcone. The synthesized licochalcones were evaluated for antimicrobial activity. Most of the compounds showed good antimicrobial activity.
Nguyen-Hai et al.\textsuperscript{31} have reported synthesis of series of 2,5-dihydroxychalcones. The synthesized dihydroxychalcones were evaluated for cytotoxicity against tumor cell lines and human umbilical venous endothelial cells.

Javier et al.\textsuperscript{32} have reported synthesis of dimethylamino-chalcone. The novel dimethylamino-chalcone was evaluated as potential inhibitors of nitric oxide (NO) and PGE2 production in the RAW 264.7 macrophage cell line.
Thiazolidine-2, 4-diones, chalcones and 4-thioxo-thiazolidine-2-ones are known to be effective anti-bacterial compounds. We initiated a program to synergize the biological activity of chalcones and thiazolidines by preparing hybrid molecules having the features of both moieties to discover new potent lead. In the light of above facts, we have designed and synthesized a novel series of thiazolidine-2,4-diones coupled with chalcones. The newly synthesized (5Z)-5-(4-((E)-3-oxo-3-arylprop-1-enyl) benzylidene) thiazolidine-2,4-dione and (5Z)-5-(4-((E)-3-oxo-3-arylprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-ones are evaluated for their antibacterial, antifungal and cytotoxic activities.
Present work:

The synthetic work carried out during present investigation has been described in the following schemes.

\[
\text{thiazolidine-2,4-dione} \xrightarrow{(a)} \text{4-thioxothiazolidin-2-one}
\]

\[
\text{(2 a-g)} \quad \text{RCH}_3 + \text{KOH} \rightarrow \text{CH}_2^+ \xrightarrow{(b)} \text{R}^+ \quad \text{(3 a-g)}
\]

\[
\text{(3 a-g)} + \text{thiazolidine-2,4-dione} \rightarrow \text{A 43-49}
\]

\[
\text{(3 a-g)} + \text{4-thioxothiazolidin-2-one} \rightarrow \text{A 50-56}
\]

**Scheme 4.** Reagents: (a) Lawesson’s Reagent, Dioxane; (b) Ethanol; (c) Piperidine, acetic acid, toluene; (d) Piperidine, acetic acid, toluene.
Results and discussion

Chemistry

The reaction sequences employed for synthesis of the target thiazolidine-2,4-dione and 4-thioxo-thiazolidine-2-one derivatives are illustrated in scheme 4. The key chalcone 4-((E)-3-oxo-3-phenylprop-1-enyl)benzaldehydes (3a-g) were synthesized by a base-catalyzed Claisen Schmidt reaction between equimolar amount of substituted acetophenone and terephthalaldehyde. Mechanistically, the reaction involves formation of a carbanion from the acetophenone in the presence of base, followed by nucleophilic attack by the carbanion on the carbonyl carbon of the aldehyde and subsequent loss of water to give the chalcone.

Thus obtained 4-((E)-3-oxo-3-phenylprop-1-enyl)benzaldehydes (3a-g) were subjected to Knoevenagel condensation with 2,4-thiazolidinedione and 4-thioxo-thiazolidine-2-one in the presence of catalytic amount of piperidine and acetic acid to afford 5-substituted thiazolidine-2,4-diones (A43-49) and 4-thioxo-thiazolidine-2-ones (A49-56) respectively.

Antimicrobial activity

The synthesized compounds were tested for their in vitro antibacterial activity against the Gram-positive Staphylococcus aureus (ATCC25923), Enterococcus faecalis (ATCC35550), Gram-negative Escherichia coli (ATCC35218), Pseudomonas aeruginosa (ATCC25619) bacteria and antifungal activity against Candida albicans (ATCC2091), Aspergillus flavus (NCIM No. 524), Aspergillus niger (ATCC6275), and Cryptococcus neoformans (Clinical isolate). The MIC values were determined by using the twofold serial dilution technique in Mueller-Hinton broth and Sabouraud dextrose agar for the antibacterial and antifungal assays, respectively. Ciprofloxacin was used as the reference antibacterial agents; Ketoconazole was used as the reference antifungal agents.
The results of \textit{in vitro} antibacterial activities of compounds (A43-49) and (A49-56) against various bacterial and fungal strains are summarized in Table 4a. It has been observed that some of the compounds exhibited interesting antibacterial and antifungal activities. Compounds A47, A54, and A55 showed effective activity against Gram-negative \textit{Escherichia coli}, \textit{Pseudomonas aeruginosa} bacteria, and compounds A43, A44, A45, A46, A48, A49, A50, A51, A52, A53, and A56 showed slightly active against Gram-negative, whereas these compounds showed moderate activity against Gram-positive. Compounds A47, A53, A54, and A55 were displayed a good activity against \textit{Staphylococcus aureus}, \textit{Enterococcus faecalis}. The investigation of antibacterial activity revealed that most of the compounds were showed significant level of activity at MIC concentration 4-16 µg/ml. Compounds A46, A47, A52 and A55 showed good activity against all tested fungal strains. From these studies of antibacterial and antifungal activity, it was observed that compounds A47, A54 and A55 were exhibited broad spectrum activity against all tested bacterial and fungal strains, and compounds like A46, A52 showed good activity against all tested fungal strains.

\textbf{Cytotoxic activity}

The MTT [3-(4,5-dimethylthiazolo-2-yl)-2,5-diphenyl-tetrazolium bromide] cell proliferation assay was used to evaluate cytotoxic activity of the synthesized compounds against four human cancer cell lines including HeLa (cervical carcinoma), HT29 (colorectal cancer), A549 (lung cancer), MCF-7 (breast adenocarcinoma) cell lines. The inhibition of the cell proliferation was determined 24 h after cells were exposed to the tested compounds. The IC$_{50}$ (the concentration that causes 50\% growth inhibition) values were determined and summarized in Table 4b.

The investigation of cytotoxic activity revealed that most of the compounds showed weak activity towards all cancer cell lines. Among the fourteen compounds A46 and A50...
exhibited the moderate inhibitory activity against HeLa, HT29, A549 and MCF-7 cell lines, with the inhibitory concentration (IC$_{50}$) value 40-56 µM range.

**Drug Likeliness**

In order to predict the drug likeliness of the synthesized compounds on the guidelines of Lipinski rule of 5 (Molecular weight ≤500, Log P ≤5, HBD≤5 and HBA≤10) study was carried out using Pallas software the result are given in Table 4c. The relevance of the synthesized molecules with respect to Lipinski rule of five is as follows. Molecular weight of the compound is important in drug action, if the molecular weight is increases beyond a limit, the bulkiness of the compounds also increases, which will affect the drug action (affect the drug receptor/DNA interactions). Molecular weight of compounds lie between 335 and 430 show that it follows Lipinski rule of 5. So the bulkiness of the compounds is in optimum limit for the action.

Pharmacokinetic property optimization is a rather complex undertaking that is likely to require changes in those molecular determinants that are responsible for binding affinity and specificity like hydrogen bonds. Hydrogen bond acceptor (HBA) and Hydrogen bond donor (HBD) groups in the compound optimize the drug receptor interaction. Number of hydrogen bond acceptors (≤10) and hydrogen bond donors (≤5) in the proposed compounds obeys the Lipinski rule of 5, so it may have good absorption or permeability properties through the biological membrane. Dissolution is highly interdependent influences of aqueous solubility, ionizability (pKa) and lipophilicity (log P). Furthermore, log P is a crucial factor governing passive membrane partitioning, influencing permeability opposite to its effect on solubility. The log P values of the synthesized compounds lie in between 3.79 and 4.49.
Conclusion

A series of novel (5Z)-5-(4-((E)-3-oxo-3-arylprop-1-enyl) benzylidene) thiazolidine-2,4-diones and (5Z)-5-(4-((E)-3-oxo-3-arylprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-ones were prepared and studied for their antimicrobial, antifungal and cytotoxic activities. Of the synthesized molecules, compounds A47, A54 and A55 were found to be most active against both bacterial and fungal strains, whereas compounds A46 and A52 were found to be most active against only fungal strains. It is also demonstrated that the bioisosteric replacement of thiocarbonyl instead of carbonyl in thiazolidine ring has resulted in an enhancement of antimicrobial activity.

Experimental

Synthesis of 4-thioxo-thiazolidine-2-one (1)

A mixture of 2,4-thiazolidinedione (10 mmol) and Lawesson’s reagent (3 mmol) in anhydrous dioxane was refluxed for 24 h. The reaction was monitored by TLC for completion. After cooling to room temperature, precipitate was filtered and crude solid was washed with n-hexane and recrystallized from ethanol, Yield: 80%; m.p.: 205-208 °C; IR (KBr) cm⁻¹: 3310, 1680, 1672; ¹H NMR (400 MHz, δ, ppm, DMSO-d₆): 13.49 (s, 1H, NH), 4.58 (s, 2H, -CH₂-); ¹³C NMR (100 MHz, δ, ppm, DMSO-d₆): 206.63, 175.90, 45.85; Anal. Calcd for C₃H₃NOS₂ (133): C, 27.05; H, 2.27; N, 10.52. Found: C, 27.06; H, 2.26; N, 10.53.

General procedure for the synthesis of 4-((-3-oxo-3-arylprop-1-enyl) benzaldehyde (3a-g)

A stirred solution of substituted acetophenones (6.0 mmol) in ethanol (30 ml) were added to KOH (1.2 mmol), and the mixture was stirred at 0-5 °C temperature for 1 h. The
terephthalaldehyde (6.0 mmol) was added to the mixture, and resulting mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure, and the residue was treated with water (35 mL). The aqueous mixture was neutralized by the additions of aqueous 10% HCl solution and extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with aqueous saturated NH₄Cl solution (30 mL) and brine (30 mL). The organic layer was separated and dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give the crude products, which were recrystallized from ethanol.

4-((E)-3-oxo-3-phenylprop-1-enyl) benzaldehyde (3a) Yield 91%; m.p.: 202°C; ¹H-NMR (DMSO-d₆) δ in ppm: 10.08 (s, 1H, CHO), 8.21-8.17 (m, 5H, Ar-H), 8.01 (d, 1H, R-CH=C-), 7.91 (d, 2H, Ar-H), 7.69 (d, 1H, R-CH=C-), 7.42 (d, 2H, Ar-H).

4-((E)-3-oxo-3-p-tolylprop-1-enyl) benzaldehyde (3b) Yield 90%; m.p.: 160°C; ¹H-NMR (DMSO-d₆) δ in ppm: 10.04 (s, 1H, CHO), 8.10-8.07 (m, 4H, Ar-H), 8.02 (d, 1H, R-CH=C-), 7.97 (d, 2H, Ar-H), 7.75 (d, 1H, R-CH=C-), 7.38 (d, 2H, Ar-H), 2.07 (s, 3H, CH₃); ¹³C NMR (100 MHz, δ, ppm, DMSO-d₆): 192.67, 188.59, 143.94, 142.71, 140.36, 136.98, 134.78, 129.86, 129.26, 128.80, 124.99, 123.07, 30.66.
4-((E)-3-(4-methoxyphenyl)-3-oxoprop-1-enyl) benzaldehyde (3c) Yield 90%; m.p.: 143°C; 

\[ ^1H\text{-NMR (DMSO-}d_6\text{) } \delta \text{ in ppm: 10.04 (s, 1H, CHO), 8.10-8.07 (m, 4H, Ar-H), 8.02 (d, 1H, R-CH=CH-), 7.97 (d, 2H, Ar-H), 7.75 (d, 1H, R-CH=C-), 7.38 (d, 2H, Ar-H), 2.07 (s, 3H, CH}_3\).}

4-((E)-3-(4-chlorophenyl)-3-oxoprop-1-enyl) benzaldehyde (3d) Yield 86%; m.p.: 137°C; 

\[ ^1H\text{-NMR (DMSO-}d_6\text{) } \delta \text{ in ppm: 10.05 (s, 1H, CHO), 8.21 (d, 2H, Ar-H), 8.11 (d, 2H, Ar-H), 8.08 (d, 1H, R-CH=CH-), 7.98 (d, 2H, Ar-H), 7.78 (d, 1H, R-CH=C-), 7.64 (d, 2H, Ar-H); }^{13}C\text{ NMR (100 MHz, } \delta \text{, ppm, DMSO-}d_6\text{): 192.61, 188.00, 142.71, 140.13, 138.35, 137.07, 135.53, 130.53, 129.94, 129.45, 128.92, 124.60.}

4-((E)-3-(4-bromophenyl)-3-oxoprop-1-enyl) benzaldehyde (2e) Yield 86%; m.p.: 118°C; 

\[ ^1H\text{-NMR (DMSO-}d_6\text{) } \delta \text{ in ppm: 10.05 (s, 1H, CHO), 8.29 (d, 2H, Ar-H), 8.12 (d, 1H, R-CH=CH-), 8.09 (d, 2H, Ar-H), 7.98 (d, 2H, Ar-H), 7.79 (d, 1H, R-CH=C-), 7.41 (d, 2H, Ar-H); }^{13}C\text{ NMR (100 MHz, } \delta \text{, ppm, DMSO-}d_6\text{): 192.61, 187.60, 142.42, 140.20, 137.03, 131.71, 131.62, 129.81, 129.41, 124.70, 115.96, 115.74.}

4-((E)-3-(4-fluorophenyl)-3-oxoprop-1-enyl) benzaldehyde (3f) Yield 80%; m.p.: 95°C; 

\[ ^1H\text{-NMR (DMSO-}d_6\text{) } \delta \text{ in ppm: 10.05 (s, 1H, CHO), 8.13 (d, 2H, Ar-H), 8.11 (d, 2H, Ar-H), 8.09 (d, 1H, R-CH=CH-), 8.97 (d, 2H, Ar-H), 7.81 (d, 1H, R-CH=C-),} \]
7.79 (d, 2H, Ar-H); $^{13}$C NMR (100 MHz, $\delta$, ppm, DMSO-$d_6$): 192.62, 188.23, 142.74, 140.13, 137.08, 136.22, 131.88, 129.81, 129.46, 127.57, 124.58.

4-((E)-3-(4-nitrophenyl)-3-oxoprop-1-enyl) benzaldehyde (3g) Yield 83%; m.p.: 132 °C;

$^1$H-NMR (DMSO-$d_6$) $\delta$ in ppm: 10.03 (s, 1H, CHO), 8.16 (d, 2H, Ar-H), 8.09 (d, 1H, R-CH=C-), 7.97 (d, 2H, Ar-H), 7.24 (d, 2H, Ar-H), 7.80(d, 1H, R-CH=C-), 7.61(d, 2H, Ar-H); $^{13}$C NMR (100 MHz, $\delta$, ppm, DMSO-$d_6$): 192.58, 186.58, 155.27, 140.34, 137.43, 136.76, 132.07, 129.07, 128.98, 127.23, 124.76.

General procedure for the synthesis of (5Z)-5-(4-((E)-3-oxo-3-arylprop-1-enyl) benzylidene) thiazolidine-2,4-dione(A42-49)

A mixture of the 4-(3-oxo-3-arylprop-1-enyl) benzaldehyde (10 mmol), 2,4-thiazolidinedione (10 mmol), piperidine (1 mmol) and acetic acid (1 mmol) in toluene (50 ml) was heated under reflux with azeotropically removal of water for 15 h. The mixture was cooled to 5 °C; filtration gave crude (5Z)-5-(4-((E)-3-oxo-3-arylprop-1-enyl) benzylidene) thiazolidine-2,4-dione. The crude product was washed with cold toluene and ether.

(5Z)-5-(4-((E)-3-oxo-3-phenylprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A43) Light yellow powder; Yield 80%; m.p.: >300 °C; $^1$H-NMR (DMSO-$d_6$) $\delta$ in ppm: 12.65 (s, 1H, NH), 8.21 (d, 2H, Ar-H), 8.20 (d, 1H, R-CH=C-), 8.05-7.98(m, 5H, Ar-H), 7.78 (s, 1H, R-CH=C,TZD), 7.75 (d, 1H, R-CH=C-), 7.58 (d, 2H, Ar-H); Anal. Calcd for (C$_{19}$H$_{13}$NO$_3$S) (%): C, 68.04; H, 3.91; N, 4.18. Found; C, 68.11; H, 3.90; N, 4.20; LCMS m/z: 336 (M$^+$)
(5Z)-5-(4-(E)-3-oxo-3-p-tolylprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A44) Yellow powder; Yield 82%; m.p.: 298°C; \(^1\)H-NMR (DMSO-\(d_6\)) δ in ppm: 12.60 (s, 1H, NH), 8.07 (d, 2H, Ar-H), 8.02 (d, 2H, Ar-H), 8.00 (d, 1H, R-CH=C-), 7.79 (s, 1H, R-CH=C,TZD), 7.73 (d, 1H, R-CH=C-), 7.66 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 2.40 (s, 3H Ar-CH\(_3\)); Anal. Calcd for (C\(_{20}\)H\(_{15}\)NO\(_3\)S) \((\%): \) C, 68.75; H, 4.33; N, 4.01. Found; C, 68.73; H, 4.32; N, 4.02; LCMS m/z: 350 (M\(^+\)).

(5Z)-5-(4-(E)-3-(4-methoxyphenyl)-3-oxoprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A45) Light yellow powder; Yield 84%; m.p.: >300°C; \(^1\)H-NMR (DMSO-\(d_6\)) δ in ppm: 12.64 (s, 1H, NH), 8.19 (d, 2H, Ar-H), 8.04 (d, 2H, Ar-H), 7.98 (d, 1H, R-CH=C-), 7.82 (s, 1H, R-CH=C,TZD), 7.71 (d, 1H, R-CH=C-), 7.66 (d, 2H, Ar-H), 7.09 (d, 2H, Ar-H), 3.87 (s, 3H Ar-OCH\(_3\)); \(^{13}\)C NMR (100 MHz, δ, ppm, DMSO-\(d_6\)): 187.13, 167.66, 167.31, 163.29, 141.66, 136.47, 134.59, 130.94, 130.33, 129.40, 129.21, 124.50, 123.58, 122.89, 114.00, 55.53. Anal. Calcd for (C\(_{20}\)H\(_{15}\)NO\(_4\)S) \((\%): \) C, 65.74; H, 4.14; N, 3.83. Found; C, 65.75; H, 4.13; N, 3.82; LCMS m/z: 366 (M\(^+\)).

(5Z)-5-(4-((E)-3-(4-chlorophenyl)-3-oxoprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A46) Light yellow powder; Yield 86%; m.p.: >300°C; \(^1\)H-NMR (DMSO-\(d_6\)) δ in ppm: 12.64 (s, 1H, NH), 8.19 (d, 2H, Ar-H), 8.03 (d, 2H, Ar-H), 8.01 (d, 1H, R-CH=C-), 7.80 (s, 1H, R-CH=C,TZD), 7.76 (d, 1H, R-CH=C-), 7.66 (d, 2H, Ar-H), 7.63 (d, 2H, Ar-H); \(^{13}\)C NMR (100 MHz, δ, ppm, DMSO-\(d_6\)): 187.91, 167.88, 167.82, 143.02, 138.22, 136.09, 136.03, 135.04, 130.44, 130.37, 130.30,
129.60, 128.87, 125.19, 123.19; Anal. Calcd for (C$_{19}$H$_{12}$ClNO$_3$S) (%): C, 61.61; H, 3.27; N, 3.79. Found; C, 61.73; H, 3.25; N, 3.77; LCMS m/z: 370 (M$^+$)

(5Z)-5-(4-((E)-3-(4-bromophenyl)-3-oxoprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A47)

Light orange powder; Yield 84%; m.p.: >300 ºC; $^1$H-NMR (DMSO-$d_6$) δ in ppm: 12.65 (s, 1H, NH), 8.27 (d, 2H, Ar-H), 8.04 (d, 2H, Ar-H), 8.00 (d, 1H, R-CH=C-), 7.82 (s, 1H, R-CH=C,TZD), 7.75 (d, 1H, R-CH=C-), 7.67 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H); Anal. Calcd for (C$_{19}$H$_{12}$BrNO$_3$S) (%): C, 55.09; H, 2.92; N, 3.38. Found; C, 55.06; H, 2.90; N, 3.37; LCMS m/z: 416 (M$^{+2}$)

(5Z)-5-(4-((E)-3-(4-fluorophenyl)-3-oxoprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A48)

Light yellow powder; Yield 82%; m.p.: >300 ºC; $^1$H-NMR (DMSO-$d_6$) δ in ppm: 12.64 (s, 1H, NH), 8.10 (d, 2H, Ar-H), 8.03 (d, 2H, Ar-H), 8.00 (d, 1H, R-CH=C-), 7.80 (d, 2H, Ar-H), 7.78(s, 1H, R-CH=C,TZD), 7.75 (d, 1H, R-CH=C-), 7.66 (d, 2H, Ar-H); Anal. Calcd for (C$_{19}$H$_{12}$FNO$_3$S) (%): C, 64.58; H, 3.42; N, 3.96. Found; C, 64.59; H, 3.40; N, 3.95;

(5Z)-5-(4-((E)-3-(4-nitrophenyl)-3-oxoprop-1-enyl) benzylidene) thiazolidine-2,4-dione (A49)

Light yellowish-brown; Yield 70%; m.p.: >300 ºC; $^1$H-NMR (DMSO-$d_6$) δ in ppm: 12.63 (s, 1H, NH), 8.05 (d, 2H, Ar-H), 8.00 (d, 1H, R-CH=C-), 7.88 (d, 2H, Ar-H), 7.78 (s, 1H, R-CH=C,TZD), 7.66 (d, 2H, Ar-H), 7.65(d, 1H, R-CH=C-), 7.60 (d, 2H, Ar-H); Anal. Calcd for (C$_{19}$H$_{12}$N$_2$O$_5$S) (%):C, 60.00; H, 3.18; N, 7.36. Found; C, 60.02; H, 3.16; N, 7.37.
General procedure for the synthesis of \((5Z)-5-(4-((E)-3-\text{oxo-3-arylprop-1-enyl})\) benzylidene)-4-thioxothiazolidin-2-one (A50-56)

A mixture of the 4-(-3-\text{oxo-3-arylprop-1-enyl}) benzaldehyde (10 mmol), 4-thioxothiazolidine-2-one (10 mmol), piperidine (1 mmol) and acetic acid (1 mmol) in toluene (50 ml) was heated under reflux with azeotropic removal of water for 15 h. The mixture was cooled to 5 °C; filtration gave crude \((5Z)-5-(4-((E)-3-\text{oxo-3-arylprop-1-enyl})\) benzylidene)-4-thioxothiazolidin-2-one. The crude product was washed with cold toluene and ether.

\((5Z)-5-(4-((E)-3-\text{oxo-3-phenylprop-1-enyl})\) benzylidene)-4-thioxothiazolidin-2-one (A50)

Light orange powder; Yield 78%; m.p.: >300 °C; \(^1\text{H-}

\text{NMR (DMSO-d}_6\) \(\delta\) in ppm: 13.12 (s, 1H, NH), 8.17 (d, 2H, Ar-H), 8.03 (d, 1H, R-CH=C), 7.98 (s, 1H, R-CH=C,TZD), 7.77 (d, 1H, R-CH=C-), 7.67 (d, 2H, Ar-H); 7.60-7.56(m, 5H, Ar-H), Anal. Calcd for \((\text{C}_{10}\text{H}_{13}\text{NO}_{2}\text{S}_2)\) (%): C, 64.93; H, 3.73; N, 3.99. Found; C, 64.90; H, 3.71; N, 3.98.

\((5Z)-5-(4-((E)-3-\text{oxo-3-p-tolylprop-1-enyl})\) benzylidene)-4-thioxothiazolidin-2-one (A51)

Light yellow powder; Yield 80%; m.p.: >300 °C; \(^1\text{H-}

\text{NMR (DMSO-d}_6\) \(\delta\) in ppm: 13.870 (s, 1H, NH), 8.07 (d, 2H, Ar-H), 8.05 (d, 2H, Ar-H), 8.01 (d, 1H, R-CH=C), 7.73 (d, 1H, R-CH=C), 7.67 (s, 1H, R-CH=C,TZD), 7.66 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 2.40 (s, 3H Ar-CH); Anal. Calcd for \((\text{C}_{20}\text{H}_{15}\text{NO}_{2}\text{S}_2)\) (%): C, 65.73; H, 4.14; N, 3.83. Found; C, 65.74; H, 4.13; N, 3.82.
(5Z)-5-((E)-3-(4-methoxyphenyl)-3-oxoprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-one (A52) Yellow powder; Yield 86%; m.p.: >300 °C; ¹H-NMR (DMSO-δ6) δ in ppm: 13.88 (s, 1H, NH), 8.18 (d, 2H, Ar-H), 8.05 (d, 2H, Ar-H), 8.01 (d, 1H, R-CH=C-), 7.96 (s, 1H, R-CH=C,TZD), 7.74 (d, 1H, R-CH=C-), 7.66 (d, 2H, Ar-H), 7.09 (d, 2H, Ar-H), 3.87 (s, 3H Ar-CH3); Anal. Calcd for (C20H15NO3S2) (%): C, 62.97; H, 3.96; N, 3.67. Found; C, 62.95; H, 3.96; N, 3.66;

(5Z)-5-((E)-3-(4-chlorophenyl)-3-oxoprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-one (A53) Light orange powder; Yield 84%; m.p.: >300 °C; IR (KBr) cm⁻¹: 3215, 3042, 2853, 1715, 1669, 1610, 1505, 1456, 1334, 1210; ¹H-NMR (DMSO-δ6) δ in ppm: 13.86 (s, 1H, NH), 8.18 (d, 2H, Ar-H), 8.04 (d, 2H, Ar-H), 8.01 (d, 1H, R-CH=C-), 8.00 (s, 1H, R-CH=C,TZD), 7.76 (d, 1H, R-CH=C-), 7.66 (d, 2H, Ar-H), 7.64 (d, 2H, Ar-H); Anal. Calcd for (C19H12ClNO2S2) (%): C, 59.14; H, 3.13; N, 3.63. Found; C, 59.12; H, 3.12; N, 3.60.

(5Z)-5-((E)-3-(4-bromophenyl)-3-oxoprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-one (A54) Light yellow solid; Yield 85%; m.p.: >300 °C; ¹H-NMR (DMSO-δ6) δ in ppm: 13.88 (s, 1H, NH), 8.27 (d, 2H, Ar-H), 8.06 (d, 2H, Ar-H), 8.04 (d, 1H, R-CH=C-), 7.99 (s, 1H, R-CH=C,TZD), 7.76 (d, 1H, R-CH=C-), 7.67 (d, 2H, Ar-H), 7.41 (d, 2H, Ar-H); Anal. Calcd for (C19H12BrNO2S2) (%): C, 53.03; H, 2.81; N, 3.25. Found; C, 53.04; H, 2.80; N, 3.23.
(5Z)-5-(4-((E)-3-(4-fluorophenyl)-3-oxoprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-one (A55) Yellow powder; Yield 82%; m.p.: >300 °C; $^1$H-NMR (DMSO-$d_6$) δ in ppm: 13.84 (s, 1H, NH), 8.07 (d, 2H, Ar-H), 8.01 (d, 2H, Ar-H), 7.95 (d, 1H, R-CH=C-), 7.77 (d, 2H, Ar-H), 7.75 (d, 1H, R-CH=C-), 7.71 (s, 1H, R-CH=C,TZD), 7.63(d, 2H, Ar-H); Anal. Calcd for (C$_{19}$H$_{12}$FNO$_2$S$_2$) (%): C, 61.77; H, 3.27; N, 3.79. Found; C, 61.78; H, 3.26; N, 3.78;

(5Z)-5-(4-((E)-3-(4-nitrophenyl)-3-oxoprop-1-enyl) benzylidene)-4-thioxothiazolidin-2-one (A56) Light yellow powder; Yield 66%; m.p.: >300 °C; $^1$H-NMR (DMSO-$d_6$) δ in ppm: 13.73 (s, 1H, NH), 8.21 (d, 2H, Ar-H), 8.12 (d, 1H, R-CH=C-), 7.78 (d, 2H, Ar-H), 7.75(s, 1H, R-CH=C,TZD), 7.42 (d, 2H, Ar-H), 7.40(d, 1H, R-CH=C-), 7.35 (d, 2H, Ar-H); Anal. Calcd for (C$_{19}$H$_{12}$N$_2$O$_4$S$_2$) (%):C, 57.56; H, 3.05; N, 7.07. Found; C, 57.55; H, 3.03; N, 7.08;
Table 4a. *In vitro* Antimicrobial activity of A43-56 expressed as Minimum inhibitory concentration (MIC) in μg/ml

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Table 4b. *In vitro* cytotoxicity profile of A43-56 against selected human cancer cell lines

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Cell lines include cervical carcinoma (HeLa); colorectal cancer (HT29); lung cancer (A549); breast adenocarcinoma (MCF-7).
Table 4c. Drug Likeliness of A 43-56

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MW: molecular weight; LogP: calculated using software; HBD: hydrogen bond donors; HBA: hydrogen bond acceptor; Lipinski rule of 5: (Molecular weight ≤500, Log P ≤5, HBD ≤5 and HBA ≤10) study was carried out using Pallas and molinspiration software.
Spectrum No.1: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of **4-thioxo-thiazolidine-2-one** in DMSO-$d_6$.

Spectrum No.2: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of **4-thioxo-thiazolidine-2-one** in DMSO-$d_6$. 
Spectrum No.3: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound 3a in DMSO-$d_6$

Spectrum No.4: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound 3a
Spectrum No. 5: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound 3b in DMSO-$d_6$

Spectrum No. 6: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound 3b in DMSO-$d_6$
Spectrum No. 7: IR (KBr, \( \nu \), cm\(^{-1} \)) spectrum of compound 3b

Spectrum No. 8: \(^1\)H NMR (400 MHz, \( \delta \), ppm) Spectrum of compound 3c in DMSO-\(d_6\)
Spectrum No.9: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound 3c

Spectrum No.10: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound 3d in DMSO-$d_6$
Spectrum No.11: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound 3d in DMSO-$d_6$

Spectrum No.12: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound 3d
Spectrum No. 13: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound 3e in DMSO-$d_6$

Spectrum No. 14: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound 3e in DMSO-$d_6$
Spectrum No.15: IR (KBr, ν, cm⁻¹) spectrum of compound 3e

Spectrum No.16: ¹H NMR (400 MHz, δ, ppm) Spectrum of compound 3f in DMSO-d₆
Spectrum No.17: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound 3f in DMSO-$d_6$

Spectrum No.18: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A43 in DMSO-$d_6$
Spectrum No. 19: Mass spectrum of Compound A43

Spectrum No. 20: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A44 in DMSO-$d_6$
Spectrum No.21: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound A44

Spectrum No.22: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A45 in DMSO-$d_6$
Spectrum No. 23: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound A45 in DMSO-$d_6$

Spectrum No. 24: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound A45
Spectrum No.25: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A46 in DMSO-$d_6$

Spectrum No.26: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound A46 in DMSO-$d_6$
Spectrum No. 27: IR (KBr, v, cm⁻¹) spectrum of compound A46

Spectrum No. 28: Mass spectrum of Compound A46
Spectrum No.29: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A47 in DMSO-$d_6$

Spectrum No.30: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound A47
Spectrum No.31: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A48 in DMSO-$_d$6

Spectrum No.32: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound A48
Spectrum No.33: Mass spectrum of Compound A48

Spectrum No.34: $^1$H NMR (400 MHz, δ, ppm) Spectrum of compound A49 in DMSO-$d_6$
Spectrum No.35: Mass spectrum of Compound A49

Spectrum No.36: $^1$H NMR (400 MHz, δ, ppm) Spectrum of compound A50 in DMSO-$d_6$
Spectrum No.37: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound A50 in DMSO-$d_6$

Spectrum No.38: IR (KBr, $\nu$, cm$^{-1}$) spectrum of compound A50
Spectrum No.39: Mass spectrum of Compound A50

Spectrum No.40: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A51 in DMSO-$d_6$
Spectrum No.41: IR (KBr, ν, cm$^{-1}$) spectrum of compound A51

Spectrum No.42: $^1$H NMR (400 MHz, δ, ppm) Spectrum of compound A52 in DMSO-$d_6$
Spectrum No.43: IR (KBr, \( \nu, \text{cm}^{-1} \)) spectrum of compound A52

Spectrum No.44: Mass spectrum of Compound A52
Spectrum No.45: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A53 in DMSO-$d_6$

Spectrum No.46: $^1$H NMR (400 MHz, $\delta$, ppm) Spectrum of compound A54 in DMSO-$d_6$
Spectrum No.47: IR (KBr, ν, cm⁻¹) spectrum of compound A54

Spectrum No.48: $^1$H NMR (400 MHz, δ, ppm) Spectrum of compound A55 in DMSO-d$_6$
Spectrum No.49: $^{13}$C NMR (100 MHz, $\delta$, ppm) Spectrum of compound A55 in DMSO-$d_6$
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