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Synthesis and characterization of novel 2-[(5*Z*)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide based analogues

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ABSTRACT

In the present communication several 2-[(5Z)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-N-(2-methylphenyl)acetamide based small analogues have been synthesized by an efficient synthetic protocol. Variation in the functional group at 5-benzylidine ring of rhodanine led to set of 15 compounds bearing substituted N-phenyl acetamide accommodated 2-thioxo-4-thiazolidinone moiety. The chemical structures of the final synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, ESI Mass spectrometry and elemental analysis.

Keywords: 2-thioxo-4-thiazolidinone, 5-benzylidino rhodanines

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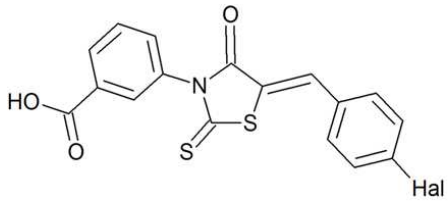
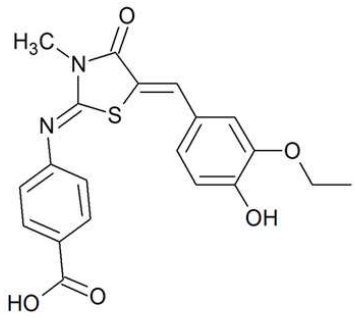
INTRODUCTION

Thiazolidines have been considered as privileged structural fragments in modern medicinal chemistry because of their broad pharmacological spectrum and affinity towards various bio targets. Among thiazolidine, various 4-thiazolidinones have been reported as novel inhibitors of the bacterial enzyme Mur B which is precursor acting during the biosynthesis of peptidoglycan [1], where peptidoglycan is an essential component of the cell wall of both gram-positive and gram-negative bacteria. Some of thiazolidine derivatives, especially 4-thiazolidinones are PPAR-receptor agonists showing hypoglycaemic, antineoplastic and anti-inflammatory activities [2] such as complex COX-2/5-LOX inhibitors [3,4] possessing anti-inflammatory action, and UDP-MurNAc/L-Alaligase inhibitors for antimicrobial effects [5]. Moreover thiazolidinones are having good affinity towards bio targets, such as JNK-stimulating phosphatase-1 (JSP-1) [6], tumour necrosis factor TNF-α [7], etc. Recently 2-thioxo-4-thiazolidinone (rhodanine) based compounds have been reported possessing broad spectrum of biological activities like antibacterial [8], antifungal [9], antidiabetic [10], antitubercular [11, 12], and anti-HIV [13].

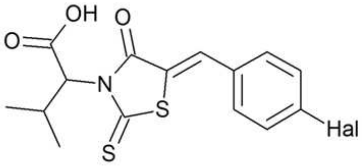
As a part of our ongoing research in synthesis of biologically active molecules [14], we have synthesized various 2-thioxo-4-thiazolidinone based N-(2-methylphenyl) acetamides. In this work, the structural variations were selected by introducing different benzylidine substituent at the fifth position of the 2-thioxo-4-thiazolidinone moiety. Literature studies revealed a conclusion that 5-arylidine or 5-benzylidine substituents at the 5th position of 4-thiazolidinones, enhances the biological activities and hence proved as a biologically active arm of the heterocyclic scaffolds [15-17] (Fig. 1).



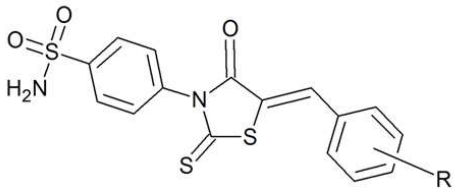
JSP- 1 inhibitors



Integrin $\alpha_{v}\beta_{3}$ antagonist



Inhibitors of apoptic proteins interaction Bcl-Xl and BH_3



Antimicrobial agents

Figure- 1: Structures of bioactive rhodanines with substitution at active N_3 and C_5 position

MATERIALS AND METHODS

3.0. Experimental procedure

3.1. Materials and Instrumentation

All reagents were of analytical reagent type and were used without further purification. Solvents used were of analytical grade and used without further purification. 2-thioxo-4-thiazolidinone was purchased from Sigma Aldrich Chemicals Pvt Ltd., Mumbai, India. 2-chloro benzaldehyde, 3-Chloro benzaldehyde, 4-Chloro benzaldehyde, 2,4-dichloro benzaldehyde, 4- methyl benzaldehyde and 3-methyl benzaldehyde were gifted by Benzo Chem industries Pvt Ltd., Jalgaon.

The melting points were determined in open capillaries on a Veego (Model: VMP-D, Veego Instrument Corporation, Mumbai, India) electronic apparatus and are uncorrected. To monitor the reactions as well as to establish the identity and purity of the reactants and products, thin layer chromatography was performed on E. Merck Silica gel 0.50 mm plate and spots were visualized under UV radiation. FT-IR spectra (4000-400 cm^{-1}) were recorded on Shimadzu spectrophotometer (Model: 8400-S, Shimadzu India Pvt Ltd., Mumbai, India) using KBr disk. ^{1}H NMR and ^{13}C NMR were performed at CSMCRI, Bhavnagar, on 500 MHz instrument using $CDCl_3$ as a solvent and TMS as an internal reference (Chemical shifts are in δppm). Mass analysis was performed at Oxygen Healthcare Research Pvt Ltd., Ahmedabad using ESI technique.

3.2. General procedure for synthesis

Potassium salt of 2-thioxo-4-thiazolidinone was synthesized by following the procedure reported earlier [17].

3.2.1. Synthesis of *N*-(2-methylphenyl)-2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide (intermediate-5)

N-Potassium salt of 2-thioxo-4-thiazolidinone (10 mmol, 1.713 g) was taken in a mixed solvent system EtOH: DMF (ratio, 1:1) along with 2-Chloro-N-(2-methylPhenyl)acetamide (11 mmol, 1.869 g). Additionally, catalytic amount of potassium iodide and carbonate was added to the reaction mass and refluxed for about 6 h. Status of the reaction was monitored by using eluent system toluene: acetone (9:1). After complete conversion, both of the solvents DMF

and ethanol were removed using rotary evaporator under vacuum. The residual mass obtained was triturated with n-hexane and then poured to crushed ice. Product was extracted from reaction mass by using dichloro methane, followed by separation of the organic layer. Obtained organic layer was treated with sodium sulphate to remove trapped moisture and followed by filtration. Obtained filtrate was evaporated up to dryness under vacuum to obtain compound *N*-(2-methylphenyl)-2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide in a pure form which was recrystallized with the mixture of EtOH: DMF or glacial acetic acid.

^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.63 (1H, s, -NH, exchangeable with D_2O), 7.03- 7.56 (5H, m, Ar-H), 3.37 (2H, s, -CH_2), 2.26 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.05 (C=O), 129.14- 120.04 (Ar-C), 36.75 (-CH_2), 22.47 (-CH_3); IR (KBr, cm^{-1}): 3293.45 (-NH), 1694.99, 1682.99 (C=O str.), 1143.12 (C-N str.)

3.2.2. General procedure for synthesis of final compounds

Final analogues were synthesized by treating intermediate compound *N*-(2-methylphenyl)-2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide with various benzaldehyde derivatives. First of all benzaldehyde were dissolved in ethanol along with equimolar amount of piperidine as a catalyst, followed by addition of equimolar amount of intermediate-5. Resulted reaction mass was refluxed for about 5-9 h. Status of the reaction was monitored by TLC using eluent system 5 % MeOH in $CHCl_3$. After the complete conversion, reaction mass was treated with crushed ice, followed by filtration, drying and recrystallization with ethanol to get the final compound.

Same knoevenagel condensation was also carried out in acidic medium, by dissolving intermediate-5 in glacial acetic acid along with 2.1 equivalent amount of anhydrous sodium acetate and equimolar amount of benzaldehyde. Reaction mass was refluxed for about 10-15 h and treated with crushed ice to separate the product. Product was filtered, washed, dried and recrystallized by using glacial acetic acid.

3.2.1.1. 2-[(5*Z*)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methyl phenyl)acetamide (7a)

^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.58 (1H, s, -NH, exchangeable with D_2O), 7.90 (1H, s, =CH exocyclic), 7.08-7.52 (10H, m, Ar-H), 3.44 (2H, s, -CH_2), 2.25 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.12 (C=O), 137.28 (exocyclic =CH), 129.10- 120.01 (Ar-C), 36.91 (-CH_2), 22.85 (-CH_3); IR (KBr, cm^{-1}): 3295.60 (-NH), 1689.04, 1693.08 (C=O str.), 1153.14 (C-N str.); ESI-MS (m/z): 387 (M+$H_2$0, 12 %), 329 (100 %).

3.2.1.2.2-[(5*Z*)-5-(4-chlorobenzylidene)-4-oxo-2-thioxotetrahydrothiophen-3-yl]-*N*-(2-methylphenyl)acetamide (7b)

^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.76 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 7.03-7.55 (9H, m, Ar-H), 3.50 (2H, s, -CH_2), 2.28 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 166.21 (C=O), 137.35 (exocyclic =CH), 129.07- 120.15 (Ar-C), 36.97 (-CH_2) 22.20 (-CH_3); IR (KBr, cm^{-1}): 3295.56 (-NH), 1699.03, 1696.10 (C=O str.), 1157.99 (C-N str.), 694.04 (C-Cl str.); ESI-MS (m/z): 421 (M+$H_2$0, 10 %).

3.2.1.3.2-[(5*Z*)-5-(3-chlorobenzylidene)-4-oxo-2-thioxotetrahydrothiophen-3-yl]-*N*-(2-methylphenyl)acetamide (7c)

^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.75 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 7.17-7.53 (9H, m, Ar-H), 3.52 (2H, s, -CH_2), 2.29 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 166.23 (C=O), 137.27 (exocyclic =CH), 129.45- 121.36 (Ar-C), 37.15 (-CH_2) 23.67 (-CH_3); IR (KBr, cm^{-1}): 3309.99 (-NH str.), 1690.78- 1695.22 (C=O str.), 1145.35 (C-N str.), 695.23 (C-Cl str.); ESI-MS (m/z): 421 (M+$H_2$0, 10 %).

3.2.1.4.2-[(5*Z*)-5-(2-chlorobenzylidene)-4-oxo-2-thioxotetrahydrothiophen-3-yl]-*N*-(2-methylphenyl)acetamide (7d)

^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.77 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 7.12-7.57 (9H, m, Ar-H), 3.46 (2H, s, -CH_2), 2.23 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 166.35 (C=O), 136.93 (exocyclic =CH), 128.84- 119.93 (Ar-C), 36.92 (-CH_2) 24.55 (-CH_3); IR (KBr, cm^{-1}): 3294.50 (-NH), 1695.15-1692.80 (C=O str.), 1159.34 (C-N str.), 694.56 (C-Cl str.); ESI-MS (m/z): 420 (M+$H_2$0, 10 %).

3.2.1.5. 2-[(5*Z*)-5-(2,4-dichlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7e)

^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.75 (1H, s, -NH, exchangeable with D_2O), 7.98(1H, s, =CH exocyclic), 7.08-7.60 (8H, m, Ar-H), 3.48 (2H, s, -CH_2), 2.27 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 165.95 (C=O), 136.93 (exocyclic =CH), 129.16- 120.50 (Ar-C), 37.04 (-CH_2) 22.38 (-CH_3); IR (KBr, cm^{-1}): 3310.50 (-NH), 1695.12, 1697.79 (C=O str.), 1165.70 (C-N str.), 693.99 (C-Cl str.); ESI-MS (m/z): 456 (M+$H_2$0, 8 %).

3.2.1.6. 2-[(5*Z*)-5-(3-fluorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7f)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.78 (1H, s, -NH, exchangeable with D_2O), 7.93 (1H, s, =CH exocyclic), 7.10-7.60 (9H, m, Ar-H), 3.45 (2H, s, -CH_2), 2.30 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 166.15 (C=O), 137.25 (exocyclic =CH), 128.58- 121.18 (Ar-C), 36.95 (-CH_2) 22.67 (-CH_3); IR (KBr, cm^{-1}): 3285.52 (-NH), 1684.49-1695.37 (C=O str.), 1289.19 (C-F str.), 1155.15 (C-N str.); ESI-MS (m/z): 404 (M+$H_2$0, 9 %).

3.2.1.7.2-[(5*Z*)-5-(4-bromobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7g)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.83 (1H, s, -NH, exchangeable with D_2O), 7.90 (1H, s, =CH exocyclic), 7.15-7.77 (9H, m, Ar-H), 3.52 (2H, s, -CH_2) , 2.34 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.20 (C=O), 138.85 (exocyclic =CH), 129.62- 120.35 (Ar-C), 36.75 (-CH_2) 24.37 (-CH_3); IR (KBr, cm^{-1}): 3310.99 (-NH), 1679.67, 1689.78 (C=O str.), 1165.78 (C-N str.); ESI-MS (m/z): 464 (M+$H_2$0, 9%).

3.2.1.8.2-[(5*Z*)-5-(4-methylbenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide(7h)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.65 (1H, s, -NH, exchangeable with D_2O), 7.95 (1H, s, =CH exocyclic), 7.03-7.75 (9H, m, Ar-H), 3.43 (2H, s, -CH_2), 2.46 (3H, s, -CH_3), 2.33 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 166.57 (C=O), 136.66 (exocyclic =CH), 129.05- 120.21 (Ar-C), 36.05 (-CH_2), 21.24 (-CH_3) 22.61 (-CH_3); IR (KBr, cm^{-1}): 3290.02 (-NH), 1685.45, 1695.10 (C=O str.), 1162.43 (C-N str.); ESI-MS (m/z): 401 (M+$H_2$0, 10%).

3.2.1.9.2-[(5*Z*)-5-(3-methylbenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7i)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.69 (1H, s, -NH, exchangeable with D_2O), 7.95 (1H, s, =CH exocyclic), 7.12-7.70 (9H, m, Ar-H), 3.45 (2H, s, -CH_2), 2.47 (3H, s, -CH_3), 2.44 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.84 (C=O), 136.85 (exocyclic =CH), 129.15- 121.50 (Ar-C), 36.32 (-CH_2), 21.50 (-CH_3) 22.93 (-CH_3); IR (KBr, cm^{-1}): 3296.75 (-NH), 1675.99, 1698.58 (C=O str.), 1167.78 (C-N str.); ESI-MS (m/z): 400 (M+$H_2$0, 9 %).

3.2.1.10.2-[(5*Z*)-5-(4-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7j)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.72 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 7.11-7.85 (9H, m, Ar-H), 3.56 (3H, s, -OCH_3), 3.35 (2H, s, -CH_2), 2.41 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.11 (C=O), 154.37 (ArC-OCH_3), 137.25 (exocyclic =CH), 129.15- 120.02 (Ar-C), 56.80 (-OCH_3), 36.85 (-CH_2), 23.99 (-CH_3); IR (KBr, cm^{-1}): 3298.01 (-NH), 1690.95, 1694.58 (C=O str.), 1159.01 (C-N str.); ESI-MS (m/z): 411 (M+$H_2$0, 14 %).

3.2.1.11. 2-[(5*Z*)-5-(3-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7k)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.75 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 7.04-7.74 (9H, m, Ar-H), 3.43 (3H, s, -OCH_3), 3.27 (2H, s, -CH_2), 2.30 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.23 (C=O), 151.35 (ArC-OCH_3), 137.22 (exocyclic =CH), 128.22- 120.07 (Ar-C), 55.37 (-OCH_3), 36.53 (-CH_2), 25.46 (-CH_3); IR (KBr, cm^{-1}): 3307.48 (-NH), 1689.52, 1701.30 (C=O str.), 1157.85 (C-N str.); ESI-MS (m/z): 410 (M+$H_2$0, 9 %).

3.2.1.12.2-[(5*Z*)-5-(3,4-dimethoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl) acetamide (7l)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.72 (1H, s, -NH, exchangeable with D_2O), 7.95 (1H, s, =CH exocyclic), 7.30-7.57 (8H, m, Ar-H), 3.63 (6H, s, -OCH_3), 3.27 (2H, s, -CH_2), 2.55 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 168.95 (C=O), 149.20 (ArC-OCH3), 135.11 (exocyclic =CH), 129.30- 120.61 (Ar-C), 54.83 (-OCH3), 36.51 (-CH_2), 23.12 (-CH_3); IR (KBr, cm^{-1}): 3312.85 (-NH), 1679.01, 1701.85 (C=O str.), 1162.78 (C-N str.); ESI-MS (m/z): 447 (M+$H_2$0, 13%).

3.2.1.13.2-[(5*Z*)-5-(4-nitrobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide(7m)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 9.12 (1H, s, Ar-H, adjacent to –NO_2 group), 9.07 (1H, d, Ar-H, adjacent to –NO_2 group), 8.65 (1H, s, -NH, exchangeable with D_2O), 7.92 (1H, s, =CH exocyclic), 7.02- 7.63 (7H, m, Ar-H), 3.42 (2H, s, -CH_2), 2.20 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 167.53 (C=O), 136.33 (exocyclic =CH), 129.11- 120.65 (Ar-C), 37.04 (-CH_2) 22.56 (-CH_3); IR (KBr, cm^{-1}): 3300.85 (-NH), 1661.01, 1694.87 (C=O str.), 1154.76 (C-N str.); ESI-MS (m/z): 431 (M+$H_2$0, 10 %).

3.2.1.14. 2-[(5*Z*)-5-(3-nitrobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methylphenyl)acetamide (7n)
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 8.92 (1H, s, Ar-H, adjacent to –NO_2 group), 8.90 (1H, d, Ar-H, adjacent to –NO_2 group), 8.72 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 6.07- 7.81 (7H, m, Ar-H), 3.44 (2H, s, -CH_2), 2.37 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 168.51 (C=O), 135.30 (exocyclic =CH),

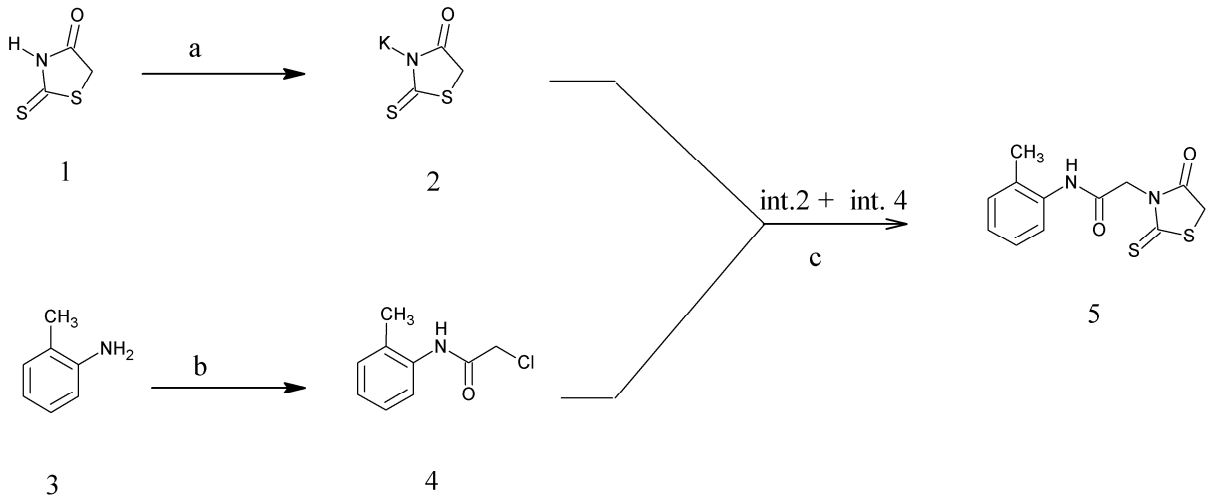
128.75- 120.35 (Ar-C), 37.22 (-CH_2) 23.11 (-CH_3); IR (KBr, cm^{-1}): 3315.98(-NH), 1660.95, 1694.54 (C=O str.), 1158.15 (C-N str.); ESI-MS (m/z): 430 ($M+H_20$, 9 %).

3.2.1.15.2-{(5*Z*)-4-oxo-2-thioxo-5-[4-(trifluoromethyl)benzylidene]-1,3-thiazolidin-3-yl}-*N*-(2-methylphenyl) acetamide (7o)

^1H NMR (500 MHz, $CDCl_3$, δppm): 8.55 (1H, s, -NH, exchangeable with D_2O), 7.94 (1H, s, =CH exocyclic), 7.14-7.73 (9H, m, Ar-H), 3.52 (2H, s, -CH_2), 2.33 (2H, s, -CH_3); ^{13}C NMR (500 MHz, $CDCl_3$, δppm): 168.65 (C=O), 139.35 (exocyclic =CH), 130.45 (Ar-C-CF_3), 128.37- 121.13 (Ar-C), 119.60 (-CF_3), 35.49 (-CH_2), 22.76 (-CH_3); IR (KBr, cm^{-1}): 3341.01 (-NH), 1679.79, 1698.76 (C=O str.), 1164.79 (C-N str.); ESI-MS (m/z): 454 ($M+H_20$, 9%).

RESULTS AND DISCUSSION

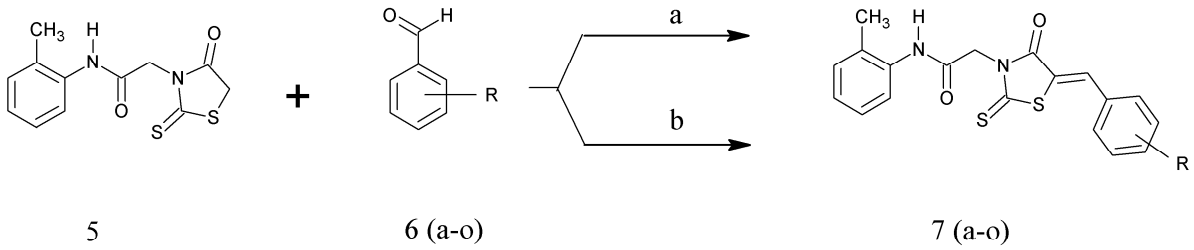
Presently 2-[(5*Z*)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-*N*-(2-methyl-phenyl)acetamide derivatives were synthesized by using known synthetic approaches [18] in several stages as presented in scheme-1,2 (figure-2,3), which included reactions like condensation, and alkylation. The starting material, 2-thioxo-4-thiazolidinone were converted into potassium salt by reaction with potassium hydroxide in ethanolic medium [19].



Scheme- 1: Synthesis of *N*-(2-methylphenyl)-2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide; a- KOH, EtOH, R.T., 1 hr; b-Chloro acetyl chloride, acetone/ benzene, K_2CO_3, 5 hr reflux; c- KI, K_2CO_3, DMF+EtOH (1:1), reflux 4 hr.

Resulted potassium salt was used in situ thereafter into the alkylation reaction with 2-chloro-*N*-(2-methylphenyl)acetamide to form *N*-(2-methylphenyl)-2-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide (Intermediate-5). This reaction was performed in a mixed solvent system i.e., ethanol and DMF along with potassium iodide and carbonate. The described method is relatively simple, convenient and does not require any additional reagent, as in a case of 4-azolidinone-3-acetic acid carboxylic group functionalization [19]. Formation of the intermediate-5 was confirmed by ^1H NMR by considering a singlet observed of a –NH lactam at 8.63 δppm. Moreover ^{13}C NMR spectra of intermediate-5 showed two peaks for carbon of a carbonyl group at167.05 and 165.84 δppm leading to the favourable conclusion for successful formation of intermediate-5.

Intermediate-5 on knoevenagel condensation reaction with various benzaldehyde derivatives, in the presence of piperidine in ethanolic medium, gives final analogues. Final compounds can also be synthesized in acidic condition by using sodium acetate along with glacial acetic acid. Reaction of benzaldehyde with intermediate-5, in both medium suggested that reaction in basic condition are more preferable than acidic one considering yield and reaction time. Thus, for the reactions of intermediate-5 with the rest of the substituted benzaldehydes, only basic conditions were preferred.



5 6 (a-o) 7 (a-o)

Scheme- 2: Synthesis of final compounds 7 (a-o): a- EtOH, piperidine, reflux, 5-7 hrs; b- gla CH_3COOH, anhy. CH_3COONa (2 eq.), reflux, 8-12 hrs; **7 (a-o): R =** 7a: H, 7b: 4-Cl, 7c: 3-Cl, 7d: 2-Cl, 7e: 2,4-Cl, 7f: 3-F, 7g: 4-Br, 7h: 4-Me, 7i: 3-Me, 7j: 4-OCH_3, 7k: 3-OCH_3, 7l- 3,4-OCH_3, 7m: 4-NO_2, 7n: 3-NO_2, 7o: 4-CF_3.

The structures of the synthesized final compounds were elucidated by spectral analysis. ^{1}H NMR spectra of compound 7a showed a singlet in the downfield region at 8.58 δppm accounting for a –NH lactam proton of amide. $–CH_2$ alkyl fragment at the position of N_3 of the final synthesized compound 7a, revealed a sharp singlet at 3.44 δppm. The chemical shift of methylidene group of 5-benzylidine derivatives was observed in the weak magnetic field at 7.90 δppm, and clearly indicated the formation of *Z* isomer in the knoevenagel condensation [20] (Fig. 4).

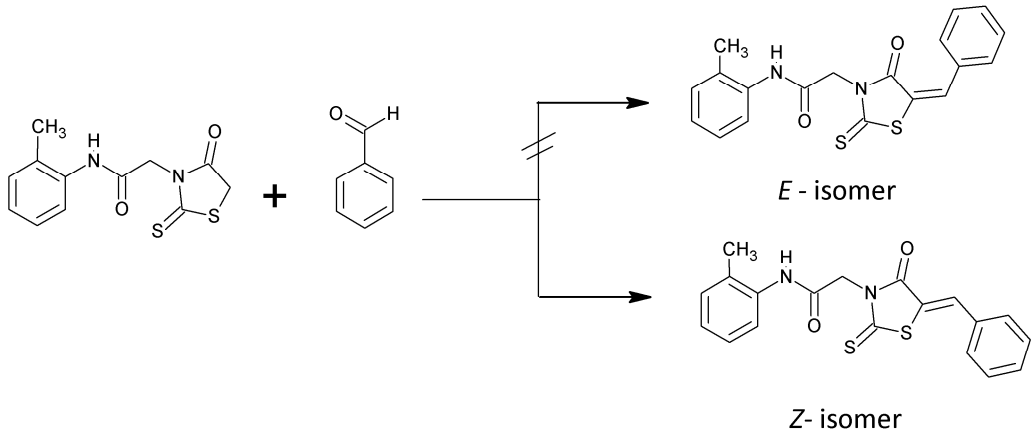
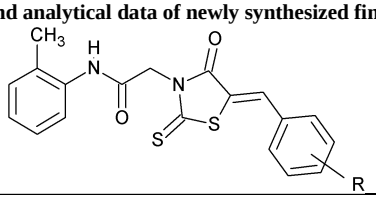


Figure-4 : E- Z isomerism of synthesized compounds

Table- 1: Physical and analytical data of newly synthesized final compounds 7a-o



Entry	R=	Mol. Formula	% Yield	M.W	M.P. (^{0}C)	Elemental Analysis Found (%)			Calculated (%)		
						C	H	N	C	H	N
7a	H	$C_{19}H_{16}N_2O_2S_2$	75.09	368.47	252-253	61.97	4.46	7.62	61.93	4.38	7.60
7b	4-Cl	$C_{20}H_{16}ClN_2O_2S_2$	69.56	401.92	280-282	56.66	3.87	6.98	56.64	3.75	6.95
7c	3-Cl	$C_{20}H_{16}ClN_2O_2S_2$	66.76	401.92	251-252	56.67	3.88	6.98	56.64	3.75	6.95
7d	2-Cl	$C_{20}H_{16}ClN_2O_2S_2$	71.44	401.92	252-253	56.66	3.85	6.97	56.64	3.75	6.95
7e	2,4-Cl	$C_{19}H_{14}Cl_2N_2O_2S_2$	73.96	437.36	269-270	52.23	3.34	6.44	52.18	3.23	6.41
7f	3-F	$C_{19}H_{15}FN_2O_2S_2$	68.39	386.46	257-258	59.12	4.05	7.27	59.05	3.91	7.25
7g	4-Br	$C_{19}H_{15}BrN_2O_2S_2$	61.08	447.36	>280	51.09	3.51	6.27	51.01	3.38	6.26
7h	4-Me	$C_{20}H_{18}N_2O_2S_2$	75.28	382.49	243-244	62.83	4.86	7.35	62.80	4.74	7.32
7i	3-Me	$C_{20}H_{18}N_2O_2S_2$	77.91	382.49	239-240	62.84	4.89	7.34	62.80	4.74	7.32
7j	4-OCH_3	$C_{20}H_{18}N_2O_3S_2$	78.25	398.49	277-278	60.31	4.68	7.07	60.28	4.55	7.03
7k	3-OCH_3	$C_{20}H_{18}N_2O_3S_2$	73.66	398.49	>280	60.31	4.67	7.06	60.28	4.55	7.03
7l	3,4-OCH_3	$C_{21}H_{20}N_2O_4S_2$	76.03	428.2	260-261	58.85	4.83	6.55	58.86	4.70	6.54
7m	4-NO_2	$C_{19}H_{15}N_3O_4S_2$	71.01	413.47	>280	55.20	3.75	10.15	55.19	3.66	10.16
7n	3-NO_2	$C_{19}H_{15}N_3O_4S_2$	76.46	413.47	279-280	55.21	3.74	10.16	55.19	3.66	10.16
7o	4-CF_3	$C_{20}H_{15}F_3N_2O_2S_2$	65.09	436.47	>280	55.08	3.61	6.44	55.04	3.46	6.42

^{13}C NMR spectra of compound 7a revealed signals of two carbonyl carbon in the downfield region at 167.12 δppm. Moreover exocyclic carbon (=CH) at the 5th position of the rhodanine, was observed at 137.28 δppm that also confirms the successful completion of knoevenagel condensation in the final step. Rest aromatic carbons of the final analogues were observed in the range of 129.09-120.01 δppm and aliphatic carbon of amide linkage at N_3 position was observed at 36.91 δppm. Mass spectra of compound 7a showed most stable fragment at 329 m/z with intensity of 100 %. Moreover compound 7a revealed M+H_2O peak at 387 m/z, leading to the conclusion that final analogue 7a contains water molecule in its crystalline structure. The physical and analytical data of the synthesized final compounds have been presented in Table-1.

CONCLUSION

- 15 analogues by accommodating N-(2-methylphenyl) acetamide with various 5-benzylidino rhodanines have been synthesized by an easy and efficient synthetic protocol.
- From the ^{1}H NMR results it was confirmed that synthesized final analogues showed *Z* isomerism instead of *E* isomer.
- Synthesized analogues can be screened and explored for various biological activities like anti- inflammatory, antimicrobial and anti tuberculosis activity.

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REFERENCES

[1] C. J. Andres, J. J. Bronson, S. D. Andrea, M. S. Deshpande, P. J. Falk, K. A. Grant- Young, W. E. Harte, H. T. Ho, P. F. Misco, J. G. Robertson, D. Stock, Y. Sun, A. W. Walsh, *Bioorg. Med. Chem. Lett.*, **2000**, 10, 715-717.
[2] G. I. Murphy, J. C. Holder, *Trends Pharmacol. Sci.*, **2000**, 21, 469–474.
[3] C. Charlier, C. Mishaux, *Eur. J. Med. Chem.*, **2003**, 38, 645–659.
[4] K. Seno, T. Okuno, K. Nishi, Y. Murakami, F. Watanabe, T. Matsuura, M. Wada, Y. Fujii, M. Yamada, T. Ogawa, T. Okada, H. Hashizume, M. Kii, S. Hara, S. Hagishita, S. Nakamoto, K. Yamada, Y. Chikazawa, M. Ueno, I. Teshirogi, T. Ono and M. Ohtani, *J. Med. Chem.*, **2000,** 43**,** 1041–1044.
[5] M. M. Sim, S. B. Ng, A. D. Buss, S. C. Crasta, K. L. Goh S. K. Lee, *Bioorg. Med. Chem. Lett.*, **2002,** 12, 679–699.
[6] N. S. Cutshall, C. O'Day, M. Prerzhdo, *Bioorg. Med. Chem. Lett.*, **2005**, 15, 3374–3379.
[7] P. H. Carter, P. A. Scherle, J. A. Muckelbauer, M. E. Voss, R. Q. Liu, L. A. Thompson, A. J. Tebben, K. A. Solomon, Y. C. Lo, Z. Li, P. Strzemienski, G. Yang, N. Falahatpisheh, M. Xu, Z. Wu, N. A. Farrow, K. Ramnarayan, J. Wang, D. Rideout, V. Yalamoori, P. Domaille, D. J. Underwood, J. M. Trzaskos, S. M. Friedman, R. C. Newton, C. P. Decicco, *Proc. Natl. Acad. Sci.*, U.S.A., **2001**, 98 (21), 11879–11884**.**
[8] M. Gualtieri, L. Bastide, P. V. Latouche, J. P. Leonette, *J. Antimicrob. Chemother.*, **2006**, 58, 778–783.
[9] M. Sortino, P. Delgado, S. Juarez, J. Quiroqa, R. Abonia, B. Insuasty, M. Noqueras, L. Rodero, F. M. Garibatto, R. D. Enriz, S. A. Zacchino, *Bioorg. Med. Chem.*, **2007** 15, 484–494.
[10] R. Nurugan, S. Anbazhagan, S. Sriman Narayanan, *Eur. J. Med. Chem.*, **2009**, 44, 3272–3279.
[11] S. Chandrappa, C. V. Kavitha, M. S. Shahabuddin, K. Vinaya, C. S. AnandaKumar, S. R. Ranganatha, S. C. Raghavan, K. S. Rangappa, *Bioorg. Med. Chem.*, **2009**, 17, 2576–2584.
[12] E. W. Brooke, S. G. Davies, A. W. Mulvaney, M. Okada, F. Pompeo, E. Sim, R. J. Vickers, I. M. Westwood, *Bioorg. Med. Chem.*, **2003**, 13, 2527–2530.
[13] S. Ozkirimli, F. Kazan, Y. J. Tunali, *Enzym. Inhib. Med. Chem.*, **2009**, 24, 447–452.
[14] A. M. Rana, K. R. Desai, S. Jauhari, *Med. Che. Res.*, **2012**, doi: 10.1007/s00044-012-0004-3.
[15] P. Vinci, F. Zani, P. Cozzini, I. Doytchinova, *Eur. J. Med. Chem.*, **2002**, 37, 553.
[16] F. Zani, P. Vinci, M. Incerti, *Eur. J. Med. Chem.*, **2004**, 39, 135.
[17] V. Gududuru, E. Hurh, J. T. Dalton, D. D. Miller, *Bioorg. Med. Chem. Lett.*, **2004**, 14, 5289–5293.
[18] R. Lesyk, B. Zimenkovsky, *Curr. Org. Chem.*, **2004**, 8, 1547–1578.
[19] H. Stilz, W. Guba, B. Jablonka, M. Just, O. Klingler, W. Konig, V. Wehner, G. Zoller, *J. Med. Chem.*, **2001**, 44, 1158–1176.
[20] G. Bruno, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana and M.G. Vigorita, *Bioorg. Med. Chem.*, **2002**, 10, 1077–1084.