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Synthesis and Antimicrobial Activity of new (Z)-2-((5-(4-Hydroxybenzylidene)-4-Oxo-4,5-Dihydrothiazol-2-Yl)Amino) Acid and its Derivatives

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ABSTRACT

A series of (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) acid and its derivatives were synthesized from appropriate 2-thioxothiazolidin-4-one using nucleophilic substitution and Knoevenagel condensation. All compounds have been synthesized, characterized and screened for their antimicrobial activity against gram positive bacteria and gram negative bacteria along with Ampicillin and Ciprofloxacin as standard drug. According to results obtained all compound shows good to moderate activity against all strain tested, compatible to Ampicillin but lower than Ciprofloxacin. Amongst these compounds (6c) shows very good and moderate activity as compare to standards drugs against Gram positive bacteria *B. subtilis* and *S. aureus*. Some of the most potent compounds, namely (6b, 6h and 6j) possessed selectively antimicrobial activity.

INTRODUCTION

Now a day the treatment of bacterial and fungal infections still remains a very challenging therapeutic problem because of emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Despite the many antibiotics and chemotherapeutics available, the emergence of old and newer antibiotic-resistant bacterial strains in the last two decades constitutes a substantial very needful for new classes of antimicrobial agents^[1,2,3]. Compounds containing the 2-thioxothiazolidin-4-one (Rhodanine) and its derivatives have also been reported to exhibit a broad spectrum of biological activities, such as antibacterial^[4,5], antidiabetic^[6], antifungal^[7,8], anticancer^[9], antitubercular^[10,11], anti-HIV^[12-14], antiparasitic^[15], hypnotic^[16] and antiproliferative agents^[17,18]. The rhodanine has been known for over 50 years, so there have been several attempts to design antimicrobial agents based on this heterocycle. There are various reports available on rhodanine derivatives as antimicrobial agents^[19,20,21]. These reports suggested that a chain containing free carboxyl group at rhodanine nucleus was important to the observed levels of antimicrobial activity^[22,23]. With this in mind, we initiated a program to synthesized rhodanine derivatives having amino acids chain as antimicrobial agent by preparing hybrid molecules having the similar features of reported potent antimicrobial agents (Figure 1).

In continuation of our work^[24-26], on the synthesis of bioactive compounds, we have synthesized some rodanine analogues. In view of the facts mentioned above, rhodanine derivatives were synthesized (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)amino acid (6a-l). The compounds (3, 4, 6a-l) were characterized by different spectral analytical techniques and screened for their in vitro antimicrobial activities against pathogenic strains such as *B. subtilis*, *S. aureus*, *E. coli*, *C. albicans*, *A. flavus*, *A. niger* species. The synthesized compounds were characterizeTAA on the basis of IR, ¹H NMR and Mass spectral data^[4-7].

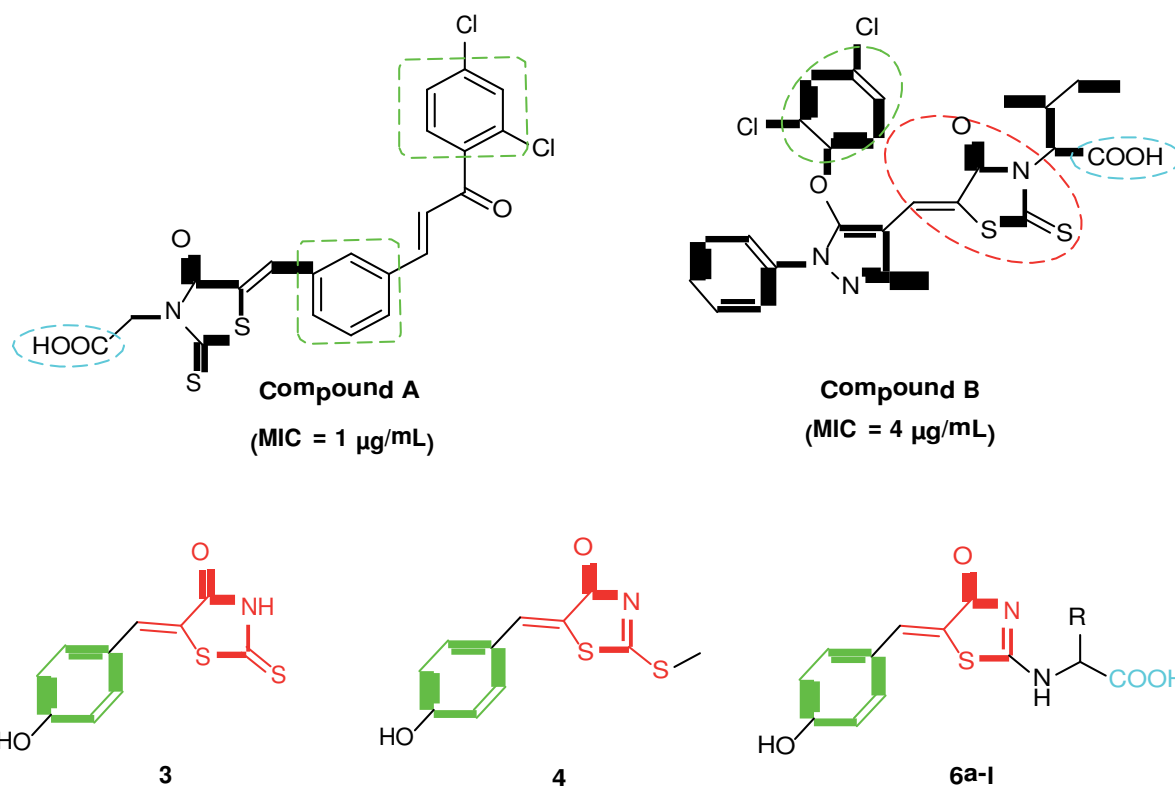


Figure 1: Previously reported antibacterial agents and synthesized compounds.

EXPERIMENTAL

Rhodanine (2-thioxothiazolidin-4-one), 4-hydroxybenzaldehyde, anhydrous sodium acetate, triethylamine, dichloromethane, iodomethane and various solvents were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. ^1H NMR spectra (δ , ppm) were recorded in DMSO- d_6 solutions on a Varian-Mercury 400 MHz spectrometer using tetramethylsilane as the internal reference. Chemical shifts are reported as δ ppm units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). ^{13}C NMR spectra were recorded in DMSO- d_6 solutions on a Bruker Avance II 400 spectrometer at 400 MHz using tetramethylsilane as the internal reference. Mass spectra were taken with Micromass-QUATTRO-II or WATER mass spectrometer.

Synthesis of (Z)-5-(4-hydroxybenzylidene)-2-thioxothiazolidin-4-one (3)

In a 100 ml round bottom flask, equimolar amount of rhodanine (1 mmol), anhydrous sodium acetate (1 mmol) was added in glacial acetic acid (5 mL) and 4-hydroxybenzaldehyde was added to the reaction mixture. The mixture was stirred under reflux condition for 6 h. The progress of reaction was monitored by TLC (20% ethyl acetate: n-hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered, washed with water (3×10 mL), dried, and purified by recrystallization in ethanol as solvent to give 80% yield.

Synthesis of (Z)-5-(4-hydroxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (4)

In a 100 ml round bottom flask, the compound (3) (1 mmol), triethylamine (1.5 mmol) was added in dichloromethane (5 mL) at room temperature. To the stirred reaction mixture with iodomethane (1.5 mmol) was added after 4 min and stirred for 2 h. at room temperature. The progress of reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 82%.

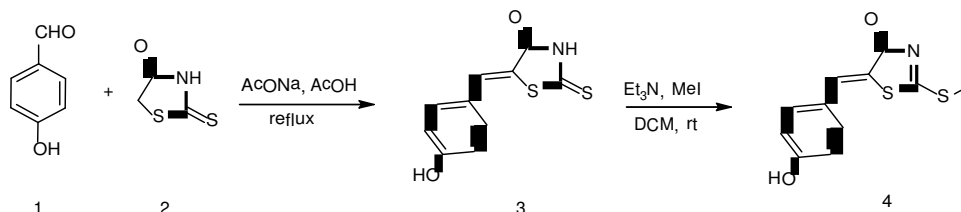
Synthesis of (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) amino acid (6a-l)

In a 50 ml round bottom flask, the compound (4) (1 mmol), amino acids (5a-l) (1.5 mmol) with a catalytic amounts of potassium carbonate (K_2CO_3) (1.5 mmol) were added in ethanol and water (1:1 v/v) and stirred for 30-55 min at room temperature. The progress of reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The compounds (6a-l) were recrystallized from ethanol and isolated as yellow solid.

RESULTS AND DISCUSSION

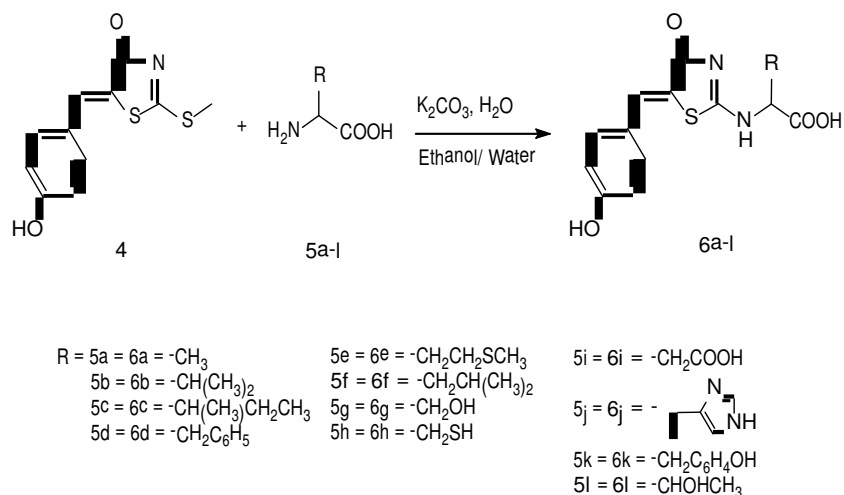
Chemistry

The compound (3) was then subjected to a Knoevenagel condensation with the appropriate rhodanine, which had themselves been synthesized using the reported procedure [27,28], to provide new series of target compounds (6a-l). The structures of the desired compounds were confirmed by IR, ¹H NMR, ¹³C NMR, mass spectral analysis. The (Z)-5-(4-hydroxybenzylidene)-2-thioxothiazolidin-4-one (3) was prepared in prominent good yields via a Knoevenagel condensation between the corresponding heterocyclic cores of rhodanine and 4-hydroxybenzaldehyde (Scheme 1).



Scheme 1: Synthesis of (Z)-5-(4-hydroxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (4).

2-thioxothiazolidin-4-one based compounds were synthesized by reflux with sodium acetate which acts as a base and glacial acetic acid as catalysts. In theory of E and Z geometrical isomers around the exocyclic double bond (CH=C) are possible for 5-benzylidene derivatives (3). The IR spectrum of (Z)-5-(4-hydroxybenzylidene)-2-thioxothiazolidin-4-one (3), showed a strong absorption band at 1672 cm⁻¹ that is due to a carbonyl group. The mass spectrum revealed a molecular ion peak at *m/z* = 237 (M+H) corresponding to a molecular formula C₁₀H₇N₂O₂S₂. ¹H NMR spectra of compounds (3) show only one signal for the methyne proton in the range δ 7.70 ppm, at lower field values than those expected for the E-isomers, which was strongly indicates that the compounds have the Z-configuration. The isolation of single crystals for some compounds permitted us to corroborate the postulated structures including their Z-configuration by single crystal X-ray diffraction analysis [29,30]. Compound (4) was synthesized (Scheme 1) from Compound (3) and the structures of the desired compounds were confirmed by spectral analysis. The IR spectrum of (Z)-5-(4-hydroxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (4), showed a strong absorption band at 1694 cm⁻¹ that is due to a carbonyl group. The mass spectrum revealed a molecular ion peak at *m/z* = 252 (M+H) corresponding to a molecular formula C₁₁H₉N₂O₂S₂. ¹H NMR spectra of compounds (4) show only one signal for the methyne proton in the range δ 7.70 ppm, sulfur attached methyl proton shows the singlet in the range δ 2.71 ppm. We synthesized series of novel (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl) amino) acid (6a-l) (Scheme 2) from compound (4), was displacement of a methyl sulfinyl group by amino acids from the C2 position of the thiazolone ring. The structures of the desired compounds (6a-l) were confirmed by IR, ¹H NMR, ¹³C NMR, mass spectral analysis. The IR spectrum of (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) propanoic acid (6a), showed a strong absorption band at 1732 cm⁻¹ that is due to a carbonyl of carboxylic group and 3386 cm⁻¹ due to hydroxyl of carboxylic group. The mass spectrum revealed a molecular ion peak at *m/z* = 293.05 (M+H) corresponding to a molecular formula C₁₃H₁₂N₂O₄S. Their ¹H NMR spectra revealed the signals of (6a) as a representative example, show one signal for the methyne proton in the range δ 7.70 ppm, phenyl ring proton shows the multiplet in the range δ 7.30–7.66 ppm, one of the methyl group proton shows doublet in the range of δ 1.25–1.42 ppm and adjacent to carboxylic acid proton shows quartet in the range of δ 4.51–4.85 ppm, carboxylic acid proton shows singlet in the range of δ 14.13 ppm (Table 1).



Scheme 2: Synthesis of (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl) amino) acid (6a-l).

Table 1: Physical and analytical data of thiazolone derivatives (6a-l)^a.

Compounds	Substituent (R)	Time (min)	Mol. formula	Yield ^b (%)	M. P. (°C)
6a	-CH ₃	35	C ₁₃ H ₁₂ N ₂ O ₄ S	90	230-232
6b	-CH(CH ₃) ₂	35	C ₁₅ H ₁₆ N ₂ O ₄ S	90	178-180
6c	-CH(CH ₃)CH ₂ CH ₃	40	C ₁₆ H ₁₈ N ₂ O ₄ S	88	130-132
6d	-CH ₂ C ₆ H ₅	30	C ₁₉ H ₁₆ N ₂ O ₄ S	86	170-172
6e	-CH ₂ CH ₂ SCH ₃	45	C ₁₅ H ₁₆ N ₂ O ₄ S ₂	90	156-158
6f	-CH ₂ CH(CH ₃) ₂	55	C ₁₆ H ₁₈ N ₂ O ₄ S	92	229-231
6g	-CH ₂ OH	50	C ₁₃ H ₁₂ N ₂ O ₅ S	92	185-187
6h	-CH ₂ SH	55	C ₁₃ H ₁₂ N ₂ O ₄ S ₂	90	169-171
6i	-CH ₂ COOH	50	C ₁₄ H ₁₂ N ₂ O ₆ S	85	155-157
6j	N NH	30	C ₁₆ H ₁₄ N ₄ O ₄ S	88	152-154
6k	-CH ₂ C ₆ H ₄ OH	45	C ₁₉ H ₁₆ N ₂ O ₅ S	86	182-184
6l	-CHOHCH ₃	35	C ₁₄ H ₁₄ N ₂ O ₅ S	90	219-221

a -Reaction condition (6a-l): Compound (4) (1 mmol), amino acids (5a-l) (1.5 mmol), K₂CO₃ (1.5 mmol), 4 ml ethanol and 4 ml water at room temperature

b -Isolated yields

Table 2: Antimicrobial minimal inhibitory concentrations (MIC, µg/mL) of synthesized compounds (3,4, 6a-l).

Compounds	MIC Values (µg/mL) ^a					
	B. subtilis	S. aureus	E. coli	C. albicans	A. flavus	A. niger
3	70	90	90	95	100	100
4	100	100	100	95	95	80
6a	85	90	90	60	100	80
6b	10	90	90	3.5	8.5	7.5
6c	09	100	100	4.0	7.5	6.5
6d	30	95	95	75	70	30
6e	80	100	100	90	80	70
6f	40	75	75	40	70	85
6g	20	90	90	70	75	100
6h	6.0	100	100	65	60	80
6i	80	95	95	90	100	90
6j	5.5	85	85	75	80	75
6k	60	100	100	95	90	100
6l	90	100	100	90	85	100
Ciprofloxacin	6.25	4.0	4.0	-	-	-
Ampicillin	12.5	12.5	12.5	-	-	-
Fluconazole	-	-	-	10	6.25	6.25
Miconazole	-	-	-	3.25	3.25	3.25

^aValues are the average of three readings

Antimicrobial activity

All the synthesized compounds (3,4 and 6a-l) were screened for their in-vitro antimicrobial activity against two gram positive bacteria; Bacillus subtilis (NCIM-2063) and Staphylococcus aureus (NCIM-2901), one gram negative bacteria; Escherichia coli (NCIM-2256) and three fungal strains; Candida albicans (NCIM-3471), Aspergillus flavus (NCIM-539) and Aspergillus niger (NCIM-1196). The antibacterial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/mL) as previously mentioned [31,32,33] by broth dilution method with Ciprofloxacin and Ampicillin as control drugs. While the antifungal study was carried by standard agar dilution method were Fluconazole and Miconazole used as control drugs. Methanol was used as solvent control for both antibacterial and antifungal testing (Table 2).

Synthesized compounds of present series shows variety of antimicrobial activity, ranging from broad spectrum molecule active against the majority of bacterial and fungal strains tested to the narrow spectrum compounds, active only against only one strains. Amongst the series compounds (6b, 6g, 6h and 6j) are found to be most active molecules and they are specific towards

the gram positive bacterial, *S. aureus* and *B. subtilis*. Compound (6j) is more active (MIC of 5.5 and 6.0 µg/mL against *B. subtilis* and *S. aureus* respectively) than both standards used in the experiment, while compound (6g and 6h) (MIC of 7.2 and 10 µg/mL against *S. aureus* and MIC of 6.0 and 10 µg/mL against *B. subtilis*) have better activity, but little lower than Ciprofloxacin and comparative level of activity as Ampicillin. The compounds (6b and 6c) have somewhat better activity compare to both the standard drugs, more important is that, they are broad spectrum in nature and shows the activity against majority of bacterial and fungal strains tested which is not shown by any other molecule of the series; both are active against bacteria *S. aureus* and *B. subtilis*, and fungus *C. albicans*, *A. flavus* and *A. niger*. On the other hand compounds (6d, 6e and 6f) are found to be narrow spectrum molecules, Remaining compounds of the series (3, 4, 6a, 6i, 6k, and 6l) have very high MIC values and therefore they are inactive as antimicrobial agents. It interesting to find out that bacterium *E. coli* is resistance to all compounds, suggest that molecules of the series may be inactive against gram negative bacteria.

Structure activity relationship (SAR)

The results of the antimicrobial screening demonstrated some definite and interesting facts about the structural-activity relationship (SAR) of synthesized thiazolone moiety. In majority of cases, dependence of activity profile on structural modifications of the molecule is clear and fascinating. Due to different types of amino acid and variation in activity profile of molecules are also directly attributed with the structural variations. The important highlights of structure-activity relationship are as follows

Effect of alkane chain: In the present study it is clear that the activity profile of molecule is strongly affected by the branching pattern and chain length of alkane chain. Attachment of methyl group at C2 position on the thiazolone moiety (6a) makes molecule inactive against bacterial and fungal strains may be due to its small size and electron donating effects.

Effect of alkane chain with hydroxyl group: Compounds (6g and 6l) containing alkane chain with hydroxyl groups with deferent position. Substitution by hydroxymethyl (6g) at C2 position on the thiazolone moiety make the molecule selective active against gram positive bacteria, *S. aureus*, while substitution by 1-hydroxyethyl (6l), however, make the molecule inactive.

Effect of heterocyclic ring: Substitution by phenylmethyl (6d) at thiazolone moiety gives the inactive molecule towards *S. aureus*, *B. subtilis*, *A. niger* and *C. albicans*, not good as standard drugs. While 4-hydroxyphenyl (6k) substitution make the molecule inactive. This observation clearly shows that only phenyl ring gives inactive molecule and addition of hydroxyl group at position 4 causes lose in this activity.

Effect of heterocyclic ring: The compounds (6j) containing methyl-imidazole ring at thiazolone moiety makes the molecule specifically active towards Gram positive bacteria *B. subtilis* and *S. aureus*.

Effect of sulfur containing group: The compound (6e) with terminal methylthio group is inactive to all strain, but compound (6h) with terminal mercapto group shows specificity active towards Gram positive bacteria *B. subtilis*.

CONCLUSION

In conclusion, the objective of the our present study was to synthesize and investigated the potent antimicrobial activities of some new (Z)-2-((5-(4-hydroxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) acid with the hope of discovering new structures that could be used as potent antimicrobial agents. Our aim has been verified by the synthesis of thiazolone moiety, different types of amino acids attached at C2 position on thiazolone moiety, which are very effective for the enhanced antimicrobial activities. Our results clearly revealed that the substituted thiazolone exhibited good antimicrobial activity.

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