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# Microwave assisted synthesis of 3-α-carboxy ethylrhodanine derivatives and their *in vitro* antibacterial activity

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**ABSTRACT**

A series of 5-benzylidene-3-α-carboxy ethylrhodanine derivatives (**3a-m**) were synthesized using 3-α-carboxy ethylrhodanine with various substituted aromatic aldehydes in anhydrous sodium acetate in glacial acetic acid by the knoevenagal condensation under microwave irradiation. The compounds synthesized within short time 10-15 min and in good yields. All the compounds characterized by IR, UV, $^{1}$H & $^{13}$C-NMR and MS spectral data and studied *in vitro* antibacterial activity.

## INTRODUCTION

In the last six decades, rhodanine and its derivatives has been serving in pharmacological activities such as JNK-stimulating 133phosphate-1 (JSP-1) (Cutshall et al., 2005), tumor necrosis factor (Carter et al., 2001), antiapoptotic biocomplex $BCLX_L$ $BH_3$ (Degterev et al., 2001), hepatitis C virus NS5B polymerase (Talele et al., 2010), capthesin D (Whitesitt et al., 1996). Additionally, these compounds have been reported antibacterial (Song et al. 2012, and Hardej et al., 2010), antidiabetic (Murugan et al., 2009), antifungal (Liaras et al., 2011), antiviral (Foye and Tovivich, 1977) and anti-inflammatory (Won et al., 2005). Apart from rhodanine derivatives possess good anticancer (Moorthy et al., 2010 and Ravi et al., 2010).

Earlier have reported many rhodanine derivatives synthesized using N-substituted rhodanine with aldehydes in presence of different catalyst and solvents under refluxing in high temperature for long period time. But in the microwave irradiation method the product obtained greatly within short time. Here we reported a series of 5-benzylidene-3-α- carboxy ethylrhodanine derivatives using various aromatic aldehydes with 3-α-carboxy ethylrhodanine in anhydrous sodium acetate in glacial acetic acid under microwave irradiation.

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## MATERIALS AND METHODS

### Instruments

Melting points were determined in a XT-5 digital melting point instrument and are uncorrected. IR spectra were recorded (in KBr) on a Shimadzu 360 FT-IR spectrometer. $^{1}$H NMR and $^{13}$C-NMR spectra were measured at 400 MHz on a Bruker-400 spectrometer using TMS as internal standard and DMSO-$d_6$ as solvent.

MS spectra were obtained on a Shimadzu MS instrument. Elemental analyses for C, H, N and S were ±0.04% of the theoretical values and determined using a PerkinElmer 240C Elemental Analyzer. The reactions carried out under microwave irradiation were performed in a Sanle WP650D 650W microwave reactor.

### General procedure for the preparation of compounds 3a-m

To a solution of compound **1** (0.001 mol) and the respective aldehydes (**2a-m**) in glacial acetic acid were added anhydrous sodium acetate (0.001 mol).

The reaction mixture was under microwave irradiation for 10-15 min at 150 °C. After completion of the reaction the reaction mixture was poured into ice-cold water. The precipitate was filtered, washed with water and dried.

**2-(5-benzylidine-4-oxo-2-thioxothiozolidene-3-yl) propanoic acid (3a)**

Yellow powder, UV λmax (nm): 375.50, 272.50; IR (KBr)$cm^{-1}$ : 2500-3400 (br. Band, COOH), 1724 (C=O), and 1589 (C=C); $^1$H NMR (DMSO-$d_6$) δ: 1.56 (d, *J* = 7.2 $H_Z$, 3H, H-1'), 5.62 (q, *J* = 7.2 $H_Z$, 1H, H-2'), 7.55 (m, 3H, H-3", 4", 5"), 7.65 (dd, *J* = 7.0 $H_Z$, 2.0 $H_Z$, 2H, H-1", 6"), 7.84 (s, 1H, H-6); $^{13}$C NMR (DMSO-$d_6$): δ 13.38 (C-1'), 52.81 (C-2'), 121.46 (C-5), 129.52 (C-2", 6"), 130.67 (C-3", 5"), 131.14 (C-4"), 132.84 (C-1"), 133.65 (C-6), 166.18 (C-3'), 169.48 (C-4) and 192.98 (C-2). Anal. Calcd. for $C_{13}H_{11}NO_3S_2$: C, 53.22; H, 3.78; N, 4.77; Found: C, 53.23; H, 3.75; N, 4.81. The spectral data of the compounds (**3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l** and **3m**) are similar to the above data.

**Antibacterial assay**

This assay consists in the determination of chemical agent spectrum of action, according to resistance of studied microorganisms. It was developed the determination of minimum inhibitory concentration (MIC) by serial dilution method (Chen et al., 2010) for every chemical agent, through the classic method of successive dilution. The serial dilutions of each stock solutions containing 10 mg/ml concentration. Further dilutions, were carryout TSB media containing 20µg, 40µg, 80µg, 160µg and 320µg dilutions per ml concentration. The total cells concentration was add to the TSB medium for $10^7$ CFU/ml for each dilution. Control for Amikacin 10 mg/ml concentration.

## RESULTS AND DISCUSSION

**Chemistry**

The compounds **3a-m** was synthesized (**Table. 1**) according to **scheme 1**. 3-α-carboxy ethylrhodanine **1** was synthesized using dl-alanine, carbon disulfide, sodium hydroxide, chloroacetic acid under stirring followed by ring closure Conc. Hydrochloric acid. Knoevenagal condensation (Lee and Sim, 2000) of **1** with various substituted aromatic aldehydes **2a-m** in anhydrous sodium acetate in glacial acetic acid under microwave irradiation 10-15 min at 150 ˚C afforded the **3a-m**. All the compounds are characterized by IR, UV, $^1$H & $^{13}$C-NMR and MS spectral data. In the IR spectral data, the targeted compounds showed broad band in the region 3000-3400 $cm^{-1}$ due to hydroxyl group and strong band at 1690-1730 $cm^{-1}$ due to C=O group. In the $^1$H NMR spectral data of the compound **3a** methyl proton appeared in the up field region at δ 1.55 (d, 3H, H-1′, *J* = 7.2 Hz) and the H-2' methine proton appeared at δ 5.60 (q, 1H, *J* = 7.2 Hz). The aromatic protons appeared in the region at δ 6.00 – 8.00 as multiplets. In addition $^{13}$C NMR spectra the peak at δ 13.00 and δ 52.00 are due to methyl (C-1′) and methine (C-2′) carbon atoms. A cluster of signals appeared δ 100-160 are due to aromatic carbons. The carboxy carbonyl group (C-3′) appeared at δ 165.99 and the ring carbonyl (C-4) at δ 169.46. Further the signal at δ 192.08 was assigned to the thio carbonyl group (C-2). In the compound **3m**, N, N-dimethyl proton appeared at δ 3.04 (s, 6H).

**Table. 1:** Synthesis of **3a-m** by microwave irradiation.

| Compounds | R | Time (min) | Yield (%) |
|---|---|---|---|
| **3a** | H | 10 | 90 |
| **3b** | 4-$CH_3$ | 10 | 85 |
| **3c** | 4-$OCH_3$ | 12 | 82 |
| **3d** | 2-$NO_2$ | 15 | 79 |
| **3e** | 3-$NO_2$ | 15 | 88 |
| **3f** | 4-$NO_2$ | 15 | 90 |
| **3g** | 2-Cl | 10 | 89 |
| **3h** | 3-Cl | 13 | 82 |
| **3i** | 4-Cl | 10 | 92 |
| **3j** | 3-Br | 15 | 85 |
| **3k** | 4-Br | 12 | 94 |
| **3l** | 4-CHO | 10 | 90 |
| **3m** | 4-N($CH_3$)$_2$ | 15 | 91 |

**Antibacterial activity**

The synthesized compounds **3a-m** were evaluated for their *in vitro* antibacterial activity (**Table. 2**) against different strains such as *staphylococcus aureus*, *Escherichia coli* and *Bacillus sereus* by minimum inhibitory concentration (MIC) method. Amikacin was used as a positive control. The results suggested that most of the compounds showed moderate activity against all the strains. The compound **3c** and **3m** only active against *S. aureus* and *E. coli* and *B. cereus* (MIC = 80 µg/ml). The compounds **3c** and **3i** showed activity 80 µg/ml against *S. aureus* and *E. coli*. The compound **3h** displayed activity against *B. cereus* with an MIC 80 µg/ml. The compound **3h** showed possess only against *B. sereus* in 80 µg/ml concentration. This suggests that the compounds **3c** and **3m** which contains $e^-$ donating groups showed higher activity than the compounds with $e^-$ withdrawing groups. The hetero atoms present in the p- position of the aromatic ring may increase the tendency of the compounds to form the H-bonding with the bacteria studied.

**Table. 2:** Anti-bacterial activity of compound **3a-m** by MIC method against *Staphylococcus aureus* (Gram positive), *Escherichia coli* (Gram negative) and *Bacillus cereus* (Gram positive).

| Compounds | Minimum inhibition concentration (MIC) µg/ml | | |
|---|---|---|---|
| | ***S. aureus*** **Gram positive** | ***E. coli*** **Gram negative** | ***B. cereus*** **Gram positive** |
| **3a** | >320 | >320 | >320 |
| **3b** | 160 | >160 | 320 |
| **3c** | 80 | 80 | >80 |
| **3d** | 160 | >320 | >320 |
| **3e** | 320 | 320 | >320 |
| **3f** | >160 | >320 | >320 |
| **3g** | >160 | >320 | 320 |
| **3h** | 160 | 160 | 80 |
| **3i** | 80 | 80 | 160 |
| **3j** | NIL | 160 | 320 |
| **3k** | 320 | NIL | 160 |
| **3l** | 160 | >320 | >320 |
| **3m** | 80 | 80 | 80 |
| **Amikacin** | 10 | 10 | 10 |

## CONCLUSION

We synthesized a quick and high yielding eco friendly procedure for synthesis of 5-benzylidene-3-α-carboxy

ethylrhodanines **3a-m** under microwave irradiation. The *In vitro* antibacterial activity the compound **3c** and **3m** showed better activity compared other compounds. This may serve as a template for further studies in the development of the antibacterial agents.

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