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ULTRASOUND MEDIATED SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW THIAZOLES DERIVATIVE

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ABSTRACT

Objectives: A series of novel rhodanine derivatives **3**, **4** and **6a-l** were synthesized from 2-thioxothiazolidin-4-one and 2,4-dimethoxybenzaldehyde by Knoevenagel condensation an ultrasound irradiation and conventional technique. The compounds were synthesized with screening with various solvent, bases and characterized by spectral analysis. **Method:** The antibacterial activity was evaluated against two Gram-positive bacteria namely, *Bacillus subtilis* (NCIM-2063) and *Staphylococcus aureus* (NCIM-2901) and one Gram-negative bacterium *Escherichia coli* (NCIM-2256). The antibacterial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/mL) as previously mentioned by broth dilution method using Ciprofloxacin and Ampicillin as standard drugs. The antifungal activity was evaluated against three fungal strains; *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196). **Result:** The synthetic protocols employed for the synthesis of rhodanine derivatives **3** and **4** presented in Scheme 1 and the compounds **6a-l** are presented in Scheme 3. The compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-thioxothiazolidin-4-one **3** was prepared via a Knoevenagel

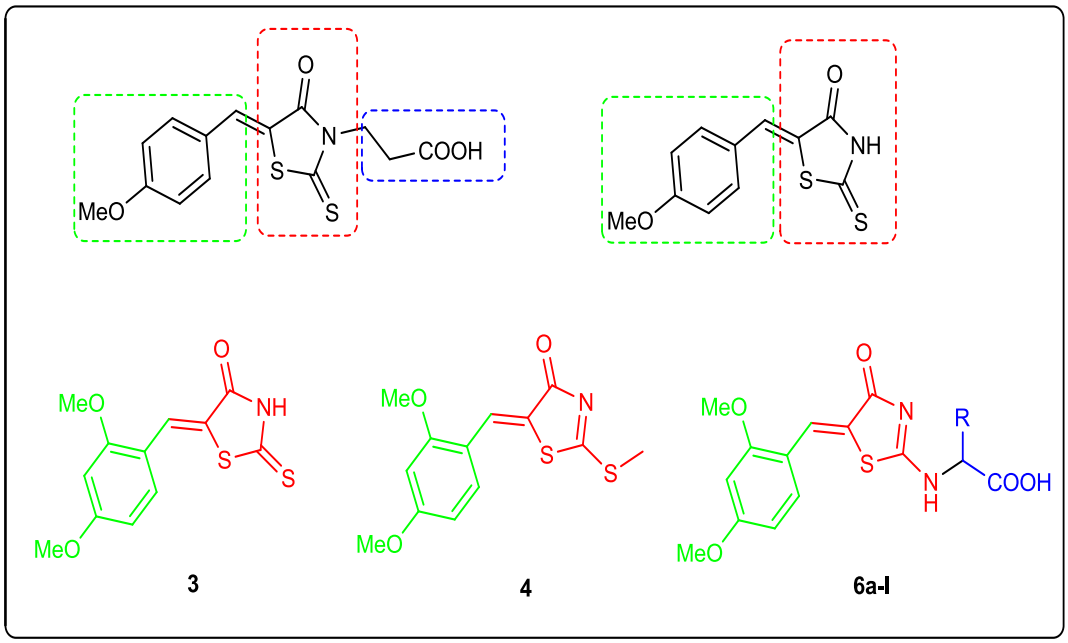
condensation. **Conclusion:** In comparison with conventional methods, our protocol is convenient and offers several advantages, such as shorter reaction time, higher yields, milder conditions and environmental friendliness. Amongst these synthesized compounds **6a, 6h**, **6j**, **6h** were shows most antibacterial and antifungal activities.

KEYWORDS: 2-thioxothiazolidin-4-one; knoevenagel condensation; ultrasonic irradiation; potassium carbonate.

INTRODUCTION

The Nitrogen-containing five and six-membered heterocyclic compounds and their derivatives, which can be easily synthesized in laboratories are particularly important and often found in natural sources. The 2-thioxothiazolidin-4-one (Rhodanine) based molecules and thiazole have been reported to exhibit a broad spectrum of biological activities, such as anti-inflammatory [1,2], antipyretic,[3,4] antidiabetic,[5] anticancer,[6] antitubercular,[7,8] anti-HIV,[9-11] antiparasitic [12], hypnotic[13] and antiproliferative agents.[14,15] 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.[16-21] These reports suggested that a chain containing free carboxyl group at rhodanine nuclei was important to the observed levels of biologycal activity[22] and synthesized structures of rhodanine containing moiety is shown (Figure 1).

The most common protocol for the synthesis of thioxothiazolidinone involves active methylene group followed by intermolecular condensation with aromatic substituted aldehyde. However, these reactions required long reactions times, high temperatures, produce by-products, expensive reagents and, in general, have difficult purifications.[23-25] The ultrasound irradiation, an efficient and innocuous technique for reagent activation in the synthesis of organic compounds, and in particular heterocyclic compounds, has been applied with success, and generates products in good to excellent yields.[26-28] Compared with conventional synthetic methods, the ultrasound- assisted method is reported as a fast, simple, convenient, time saving, economical, and environmentally benign method for the synthesis of novel materials.[29-31] It was known that the ultrasound agitation generate notable effects of chemical and physical effects due to the acoustic cavitation.[32,33] The ultrasonic irradiation has been acknowledged as an innocuous, green technique and its application today has been a boon in serving a new pathway for several chemical processes like reagent activation in the synthesis of organic and inorganic compounds.[34]



Figuer 1. Previously reported antimicrobial agents and synthesized compounds.

In view of the above considerations and in continuation of our previous work on triazoles, pyrimidine, thiazoles and thiazolidinones of pharmaceutical interest,[35,36] we report here on the synthesis and characterization of novel rhodanine derivatives **3**, **4** and **6a-l** were synthesized by ultrasound irradiation and conventional technique.

EXPERIMENTAL

Instruments

Rhodanine, 2,4-dimethoxybenzaldehyde, anhydrous sodium acetate, triethylamine, dichloromethane, iodomethane and various solvents were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. The reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. The 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. The Ultrasonic Bath, sonicator of PCI Analytics having ultrasound cleaner with a frequency of 35 kHz and constant frequency 100 W maintained at 25ºC by circulating water. ^{1}H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

General procedure for the synthesis of compounds (3)

Method A: Ultrasound irradiation:

A 50 mL flask was charged with 2,4-dimethoxybenzaldehyde **1** (1 mmol), 2-thioxothiazolidin-4-one **2** (1 mmol), anhydrous sodium acetate (1 mmol), acetic acid (1 mL). The mixture was sonicated (35 kHz, constant frequency) at 25 ºC for 20 min. The progress of the 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 off and washed with water (3×10 mL), dried and purified by recrystallized in ethanol as solvent to give 90 % yield.

Method B: Conventional method

A 50 mL round bottom flask, an equimolar amount of 2,4-dimethoxybenzaldehyde **1** (1 mmol), 2-thioxothiazolidin-4-one **2** (1 mmol), anhydrous sodium acetate (1 mmol) and acetic acid (1 mL) were added. The mixture was stirred under reflux condition for 3 h. The progress of the 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 off and washed with water (3×10 mL), dried and purified by recrystallized in ethanol as solvent to give 80 % yield.

*(Z)-5-(2,4-dimethoxybenzylidene)-2-thioxothiazolidin-4-one (**3**)*

Orange solid, ES-MS m/z: 281.25. IR νmax/cm^{-1}: 3208 (NH), 1688 (C=O), 1610 (C=C), 1555 (C=N), 1212 (C=S), 1194(C–N). ^{1}H NMR: □ppm = 3.90 (s, 6H, OCH_3), 6.60–6.70 (d, 2H, Ar–CH), 7.40 (s, 1H, Ar–CH), 7.80 (s, 1H, =CH), 13.60 (s, 1H, NH). ^{13}C NMR: δppm = 55.8, 56.2, 98.5, 106.5, 107.2, 116.0, 130.7, 142.9, 143.4, 160.5, 168.4, 193.7.

General procedure for the synthesis of compounds (4)

Method A: Ultrasound irradiation:

A 50 mL flask was charged with, the compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-thioxothiazolidin-4-one **3** (1 mmol), triethylamine (1.2 mmol), iodomethane (1.2 mmol) and ethanol (1 mL). The mixture was sonicated (35 kHz, constant frequency) at 25 ºC for 5 min. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the 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 90%.

Method B: Conventional method

In a 50 ml round bottom flask, the compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-thioxothiazolidin-4-one **3** (1 mmol), triethylamine (1.2 mmol), iodomethane (1.2 mmol), ethanol (1 mL) stirred at room temperature up to 2 h. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the 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 85 %.

(Z)-5-(2,4-dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (4)

Orange solid, ES-MS m/z: 295.13. IR νmax/cm^{-1}: 3026 (CH–Ar), 1694 (C=O), 1579 (C=C), 1474 (C=N),1160 (C-S), 825 (C–N). ^{1}H NMR: □ppm = 2.81 (s, 3H, S-CH_3), 3.86 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.70–6.75 (d, 2H, Ar–CH), 7.43–7.46 (d, 1H, Ar–CH), 8.00 (s, 1H, =CH). ^{13}C NMR: δppm = 14.4, 55.8, 56.2, 98.4, 106.3, 107.5, 130.5, 132.6, 143.5, 152.3, 160.3, 162.7, 167.2.

General procedure for the synthesis of (Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)substituted acid (6a-l)

Method A: Ultrasound irradiation

A 50 mL flask was charged with, the compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** (1 mmol), amino acids **5a-l** (1.2 mmol), potassium carbonate (1 mmol) and ethanol (1 mL). The mixture was sonicated (35 kHz, constant frequency) at 25 ºC for 2-5 min. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The compounds (*Z*)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid **6a-l** were recrystallized from ethanol and isolated as yellowish solids.

Method B: Conventional method

In a 50 ml round bottom flask, the compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** (1 mmol), amino acids **5a-l** (1.2 mmol), potassium carbonate (1 mmol) and ethanol (5 mL) were added to the reaction mixter and stirred for 30-50 min at room temperature. The progress of the reaction was monitored by TLC (10% methanol: chloroform). After completion of the reaction, the reaction mixture was concentrated in-vacuo. The residue was washed with water (3×15 mL) to afford the crude product. The

compounds (*Z*)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid **6a-l** were recrystallized from ethanol and isolated as yellowish solids.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (6a)

Yellow solid, ES-MS m/z: 336.40. IR νmax /cm^{-1}: 3446 (OH), 3216 (NH), 2822 (CH–Ar), 1726 (HO–C=O), 1633 (C=O), 1583 (C=C), 1454 (C=N), 1016 (C-S), 836 (C–N). ^{1}H NMR: ppm = 1.20–1.30 (d, 3H, CH_3), 3.40–3.50 (q, 1H, CH), 3.90 (s, 6H, OCH_3), 6.40–6.60 (d, 2H, Ar–CH), 7.30–7.40 (d, 1H, Ar–CH), 7.30 (s, 1H, =CH), 8.30 (s, 1H, NH), 10.05 (s, 1H, COOH). ^{13}C NMR: δppm = 16.8, 53.5, 55.5, 56.2, 98.5, 106.5, 107.2, 130.4, 132.5, 143.4, 152.3, 158.6, 160.7, 167.7, 174.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methyl butanoic acid (6b)

Yellow solid, ES-MS m/z: 364.42. IR νmax /cm^{-1}: 3310 (OH), 3216 (NH), 2945 (Ar-CH), 1735 (HO–C=O), 1686 (C=O), 1526 (C=C), 1514 (C=N), 1244 (C-S), 1023 (C–N). ^{1}H NMR: ppm = 0.90–1.05 (d, 6H, CH_3), 1.40–1.50 (m, 1H, CH), 3.20–3.30 (d, 1H, CH), 3.80 (s, 6H, OCH_3), 6.40–6.60 (d, 2H, Ar–CH), 7.40–7.50 (d, 1H, Ar–CH), 7.40 (s, 1H, =CH), 8.40 (s, 1H, NH), 11.15 (s, 1H, COOH). ^{13}C NMR: δppm = 15.2, 16.2, 53.3, 55.6, 56.3, 98.1, 106.2, 107.3, 130.6, 132.7, 142.4, 153.3, 157.6, 161.7, 168.7, 174.4.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methyl pentanoic acid (6c)

Yellow solid, ES-MS m/z: 379.00. IR νmax/cm^{-1}: 3300 (OH), 3206 (NH), 2845 (Ar-CH), 1725 (HO–C=O), 1646 (C=O), 1586 (C=C), 1504 (C=N), 1294 (C-S), 1013 (C–N). ^{1}H NMR: ppm = 1.10–1.25 (m, 8H, CH_2CH_3), 1.30–1.40 (m, 1H, CH), 3.20–3.30 (d, 1H, CH), 3.70 (s, 6H, OCH_3), 7.40–7.50 (d, 2H, Ar–CH), 7.90 (s, 1H, Ar–CH), 8.20 (s, 1H, =CH), 8.80 (s, 1H, NH), 10.25 (s, 1H, COOH). ^{13}C NMR: δppm = 11.2, 15.2, 25.2, 37.5, 55.3, 55.6, 56.2, 55.8, 98.4, 106.4, 107.5, 130.6, 132.7, 143.4, 152.3, 161.7, 167.7, 174.6.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-phenyl propanoic acid (6d)

Yellow solid, ES-MS m/z: 412.46. IR νmax /cm^{-1}: 3390 (OH), 3215 (NH), 2970 (CH–Ar), 1730 (HO–C=O), 1698 (C=O), 1561 (C=C), 1541 (C=N), 1012 (C-S), 1068 (C–N). ^{1}H NMR: ppm = 2.50–2.62 (d, 2H, CH_2), 3.80 (d, 6H, OCH_3), 4.40–4.78 (q, 1H, CH), 7.20–

7.72 (m, 8H, Ar–CH), 7.90 (s, 1H, =CH), 9.14 (s, 1H, NH), 11.02 (s, 1H, COOH). ^{13}C NMR: δppm = 55.4, 56.2, 36.4, 58.4, 98.5, 106.2, 107.2, 125.9, 127.7, 128.6, 128.9, 135.3, 136.9, 143.4, 152.2, 158.5, 167.1, 175.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-(methy lthio)butanoic acid (6e)

Yellow solid, ES-MS m/z: 396.40. IR νmax /cm^{-1}: 3495 (OH), 3217 (NH), 2924 (CH–Ar), 1714 (HO–C=O), 1585 (C=C), 1456 (C=N), 1212 (C-S), 1019 (C–N). ^{1}H NMR: δppm = 1.10–1.20 (q, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.60–2.70 (t, 2H, CH_2), 3.30–3.40 (q, 1H, CH), 3.90 (s, 6H, OCH_3), 7.10–7.20 (d, 2H, Ar–CH), 7.50–7.60 (t, 1H, Ar–CH), 7.90 (s, 1H, =CH), 8.00 (s, 1H, NH), 8.20 (s, 1H, COOH). ^{13}C NMR: δppm = 15.2, 29.2, 30.5, 55.4, 55.7, 56.6, 56.8, 98.4, 106.7, 107.6, 130.4, 132.3, 143.5, 152.3, 161.7, 167.7, 174.6.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-methyl pentanoic acid (6f)

Yellow solid, ES-MS m/z: 378.44. IR νmax /cm^{-1}: 3392 (OH), 3222 (NH), 3010 (CH–Ar), 1731 (HO–C=O), 1695 (C=O), 1535 (C=C), 1573 (C=N), 1023 (C-S), 1051 (C–N). ^{1}H NMR: δppm = 0.92–0.99 (d, 6H, CH–$(CH_3)_2$), 1.40–1.50 (m, 1H, CH), 1.70–1.88 (t, 2H, CH_2), 3.85 (s, 6H, OCH_3), 4.44–4.79 (q, 1H, CH), 6.70–7.10 (m, 3H, Ar–CH), 7.80 (s, 1H, =CH), 9.10 (s, 1H, NH), 10.84 (s, 1H, COOH). ^{13}C NMR: δppm = 22.8, 24.6, 40.3, 55.0, 55.5, 56.2, 106.8, 107.8, 127.8, 128.9, 129.2, 132.1, 135.4, 152.2, 159.1, 167.1, 174.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-hydroxy propanoic acid (6g)

Yellow solid, ES-MS m/z: 352.36. IR νmax /cm^{-1}: 3450 (OH), 3214 (NH), 3007 (CH–Ar), 1738 (HO–C=O), 1688 (C=O), 1553 (C=C), 1511 (C=N), 1019 (C-S), 1097 (C–N). ^{1}H NMR: δppm = 3.60 (s, 1H, CH), 3.85 (s, 6H, OCH_3), 4.01–4.19 (q, 1H, CH), 4.23–4.48 (d, 2H, CH_2), 7.10–7.20 (d, 2H, Ar–CH), 7.30 (s, 1H, Ar–CH), 7.78 (s, 1H, =CH), 9.12 (s, 1H, NH), 10.86 (s, 1H, COOH). ^{13}C NMR: δppm = 55.5, 56.2, 59.2, 62.3, 98.4, 106.8, 107.8, 127.1, 128.5, 132.9, 135.1, 151.9, 158.1, 167.9, 171.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-mercapto propanoic acid (6h)

Yellow solid, ES-MS m/z: 368.43. IR νmax /cm^{-1}: 3455 (OH), 3201 (NH), 3017 (CH–Ar), 2500 (SH), 1739 (HO–C=O), 1698 (C=O), 1559 (C=C), 1501 (C=N), 1011 (C-S), 1099 (C–

N). ^{1}H NMR: □ppm = 1.50 (s, 1H, CH), 3.11–3.29 (d, 2H, CH_2), 3.85 (s, 6H, OCH_3), 4.15–4.38 (t, 1H, CH), 7.02–7.20 (d, 2H, Ar–CH), 7.30 (s, 1H, Ar–CH), 7.68 (s, 1H, =CH), 9.18 (s, 1H, NH), 11.84 (s, 1H, COOH). ^{13}C NMR: δppm = 26.9, 55.2, 56.2, 60.5, 98.5, 106.5, 107.7, 128.8, 130.1, 132.5, 143.6, 152.9, 158.3, 167.2, 178.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)succinic acid (6i)

Yellow solid, ES-MS m/z: 380.37. IR νmax /cm^{-1}: 3466 (OH), 3214 (NH), 3010 (CH–Ar), 1730 (HO–C=O), 1699 (C=O), 1539 (C=C), 1513 (C=N), 1034 (C-S), 1080 (C–N). ^{1}H NMR: □ppm = 2.61–2.88 (d, 2H, CH_2), 3.71–3.85 (t, 1H, CH), 3.90 (s, 6H, OCH_3), 7.12–7.25 (d, 2H, Ar–CH), 7.30 (s, 1H, Ar–CH), 7.78 (s, 1H, =CH), 9.30 (s, 1H, NH), 11.74 (s, 2H, COOH). ^{13}C NMR: δppm = 35.9, 53.2, 55.3, 56.4, 98.3, 106.5, 107.7, 127.5, 128.8, 132.5, 135.6, 152.9, 158.3, 167.2, 172.2, 178.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(1H-imidazol-4-yl)propanoic acid (6j)

Yellow solid, ES-MS m/z: 402.40. IR νmax /cm^{-1}: 3442 (OH), 3296 (NH), 2921 (CH–Ar), 1693 (C=O), 1500 (C=C), 1455 (C=N), 1015 (C-S), 824 (C–N). ^{1}H NMR: □ppm = 3.10 (s, 2H, CH_2), 3.70 (s, 1H, CH), 3.85 (s, 6H, OCH_3), 6.15 (s, 2H, Ar–CH), 7.64 (s, 1H, =CH), 7.30–7.50 (m, 3H, Ar–CH), 7.70 (s, 2H, NH), 9.90 (s, 1H, COOH). ^{13}C NMR: δppm = 28.9, 58.3, 117.9, 55.2, 56.6, 98.5, 106.5, 107.5, 124.7, 127.9, 128.6, 129.2, 132.1, 135.2, 152.3, 158.2, 167.5, 176.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(4-hydroxyphenyl) propanoic acid (6k)

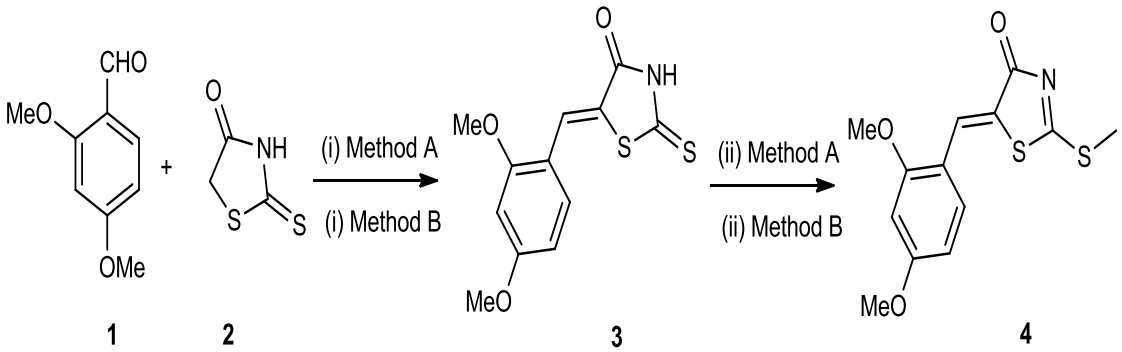
Yellow solid, ES-MS m/z: 428.46. IR νmax /cm^{-1}: 3455 (O=C-OH), 3392 (OH), 3218 (NH), 2984 (CH–Ar), 1733 (HO–C=O), 1698 (C=O), 1553 (C=C), 1591 (C=N), 1011 (C-S), 1082 (C–N). ^{1}H NMR: □ppm = 2.80–2.99 (d, 2H, CH_2), 3.80 (s, 6H, OCH_3), 4.43–4.70 (t, 1H, CH), 5.30 (s, 1H, OH),7.10–7.20 (d, 2H, Ar–CH), 7.30 (s, 1H, Ar–CH), 7.31–7.72 (m, 4H, Ar–CH), 7.72 (s, 1H, =CH), 9.32 (s, 1H, NH), 10.16 (s, 1H, COOH). ^{13}C NMR: δppm = 36.4, 55.6, 56.6, 58.6, 105.9, 106.9, 115.9, 127.7, 128.6, 128.9, 129.2, 130.2, 135.3, 136.9, 152.2, 155.7, 158.5, 167.7, 174.2.

(Z)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-hydroxy butanoic acid (6l)

Yellow solid, ES-MS m/z: 366.39. IR νmax /cm^{-1}: 3464 (OH), 3202 (NH), 3013 (CH–Ar), 1736 (HO–C=O), 1681 (C=O), 1555 (C=C), 1597 (C=N), 1046 (C-S), 1112 (C–N). ^{1}H NMR: □ppm = 1.15–1.25 (d, 3H, CH_3), 3.50–3.58 (d, 1H, CH), 3.64 (s, 1H, OH), 3.80 (s, 6H, OCH_3), 3.93–4.18 (m, 1H, CH), 6.80–6.98 (d, 2H, Ar–CH), 7.10 (s, 1H, Ar–CH), 7.74 (s, 1H, =CH), 9.68 (s, 1H, NH), 11.24 (s, 1H, COOH). ^{13}C NMR: δppm = 19.7, 55.6, 56.6, 64.4, 66.6, 105.2, 106.3, 127.8, 128.7, 128.9, 132.4, 135.1, 152.9, 158.2, 167.8, 175.2.

RESULTS AND DISCUSSION

The synthetic protocols employed for the synthesis of rhodanine derivatives **3** and **4** presented in Scheme 1 and the compounds **6a-l** are presented in Scheme 3. The compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-thioxothiazolidin-4-one **3** was prepared via a Knoevenagel condensation between and 2,4-dimethoxybenzaldehyde (**1**) rhodanine (**2**). The compound (*Z*)-5-(2,4-dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one **4** was obtained via reaction of the compound (**3**) with iodomethane in ethanol using triethylamine as catalyst.



[a]Reaction condition: **(i) Method A:** Ultrasound irradiation: Sodium acetate, Acetic acid, 25 ºC, 20 min. **(i) Method B:** Conventional method: Sodium acetate, Acetic acid, reflux, 3 h. **(ii) Method A:** Ultrasound irradiation: Triethylamine, Iodomethane, Ethanol, rt, 5 min. **(ii) Method B:** Conventional method: Triethylamine, Iodomethane, Ethanol, rt, 2 h.

Scheme 1. Synthesis of (*Z*)-5-(2,4-dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (**4**)[a].

Table 1: Ultrasound irradiation: Screening of catalyst, solvents, reaction time and yield for the synthesis (6a)[a].

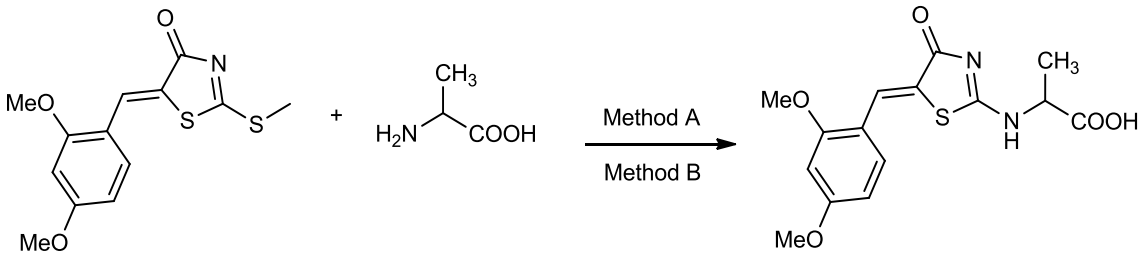
Entry	Base	Solvent	Time (min)	Yield[b] (%)
1	Diethylamine	Ethanol	16	60
2	Diethylamine	Methanol	18	32
3	Diethylamine	Acetic acid	15	37
4	Diethylamine	DCM	18	42
5	Diethylamine	Toluene	16	30
6	Triethylamine	Ethanol	10	72
7	Triethylamine	Methanol	15	40
8	Triethylamine	Acetic acid	16	30
9	Triethylamine	DCM	18	45
10	Triethylamine	Toluene	20	35
11	Potassium carbonate	Ethanol	2	99
12	Potassium carbonate	Methanol	12	72
13	Potassium carbonate	Acetic acid	11	72
14	Potassium carbonate	DCM	11	72
15	Potassium carbonate	Toluene	12	66

[a] All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent
[b] Isolated yield.

Effect of catalyst and solvents

A variety of catalysts were screened under ultrasound irradiation in order to validate the right choice and the results are shown in Table 1. To justify the influence of the catalyst, the reaction was carried out in the presence of catalyst potassium carbonate wherein a maximum yield of 99% could be obtained (Table 1, Entry 11). It was further observed that the yield of the **4** (1 mmol) and the compound **5a** (1 mmol), various catalyst and various solvents were selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvents and catalyst on the condensation reaction, potassium carbonate was found to be the better catalyst and ethanol was found to be the best solvent for the reaction (Table 1, entry 11); other solvents, including methanol, acetic acid, dichloromethane (DCM) and toluene were less efficient (Table 1, entries 2–5, 7–10 and 12–15). Nevertheless, all of these yields were generally low before condensation reaction, the effects of different catalyst were investigated (Table 1, entries 1–15). The potassium carbonate exhibited the best performance with used solvents and gave better yield, (Table 1, entries 11–15). The sodium acetate and triethylamine gave lower yields with other solvents, but gave better yield in ethanol as a solvent (Table 1, entries 1 and 6). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent,

namely 1 mL of ethanol turned out to be the best choice with yields of 60%, 72% and 99% (Table 1, entries 1, 6 and 11).



4 **5a** **6a-l**

[a]Reaction condition: **Method A:** Ultrasound irradiation: Compound **4** (1 mmol), L-Alanine (**5a**) (1 mmol), catalyst (1 mmol), solvent 1 mL, rt. 2-20 min. **Method B:** Conventional method: Compound **4** (1 mmol), L-Alanine (**5a**) (1 mmol), catalyst (1 mmol), solvent 1 mL, rt. 30-150 min.

Scheme 2. Screening of model reaction (*Z*)-2-((5-(2,4-dimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (**6a**)[a].

We also synthesized and screening of model reaction under conventional method and the results of these findings are presented in Table 2. The reaction in which the compound **4** (1 mmol) and the compound **5a** (1.2 mmol), various catalyst and various solvents were selected as a model reaction to optimize the reaction conditions.

In terms of the effect of solvents and catalyst on the condensation reaction, potassium carbonate was found to be the better catalyst and ethanol was found to be the best solvent for the reaction (Table 2, entry 11); other solvents, including methanol, acetic acid, DCM and toluene were less efficient (Table 2, entries 2–5, 7–10 and 12–15). Nevertheless, all of these yields were generally low before further optimizations. Ethanol gave the corresponding product in 52–85% yield, which was the best among these solvents

Table 2 Conventional method: Screening of catalyst, solvents, reaction time and yield for the synthesis (6a)[a]

Entry	Base	Solvent	Time (min)	Yield[b] (%)
1	Diethylamine	Ethanol	110	52
2	Diethylamine	Methanol	130	30
3	Diethylamine	Acetic acid	150	35
4	Diethylamine	DCM	110	40
5	Diethylamine	Toluene	140	30
6	Triethylamine	Ethanol	100	65
7	Triethylamine	Methanol	110	40
8	Triethylamine	Acetic acid	130	30
9	Triethylamine	DCM	120	45
10	Triethylamine	Toluene	125	35
11	Potassium carbonate	Ethanol	30	85
12	Potassium carbonate	Methanol	50	70
13	Potassium carbonate	Acetic acid	60	70
14	Potassium carbonate	DCM	50	70
15	Potassium carbonate	Toluene	60	65

[a] All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent
[b] Isolated yield.

(Table 2, entries 1, 6 and 11). To increase the efficiency of the condensation reaction, the effects of different catalyst were investigated (Table 2, entries 1–15). Potassium carbonate exhibited the best performance with used solvents and gave better yield, (Table 2, entries 11–15). Sodium acetate and triethylamine gave lower yields with other solvents, but gave better yield in ethanol as a solvent (Table 2, entries 1 and 6). All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of ethanol turned out to be the best choice with yields of 52%, 65% and 85% (Table 2, entries 1, 6 and 11).

We would like to mention here that ethanol as a solvent with potassium carbonate as catalyst was the best choice with a yield of 99% and less time required for the completion of the reaction (Table 1, entry 11). Thus we decided to carry out the further reactions in ethanol as a solvent with potassium carbonateas a catalyst. As a result the reaction time was shortened; thermal decomposition was also minimized, at room temperature stirring, resulting in higher isolated yields. But in this synthesis, we compared to the reaction between ultrasound irradiation and conventional method, the ultrasound irradiation is the best method. Because the studies indicated that the use of ultrasound irradiation made the reactions very fast, very less time required to complete the reaction, and recorded high product yields 60%, 72% and

99% (Table 1, entries 1, 6 and 11) and surprisingly, in the conventional method, the reactions very sluggish and recorded low yields 52%, 65% and 85% (Table 2, entries 1, 6 and 11).

The physical data of the synthesized compounds are presented in Table 3. All the reactions proceeded well in 2-5 min to give products in very good yields (96–98%) by ultrasound irradiation and in conventional method, the reactions proceeded in 30-50 min to give products in yields (72–85%). The purity of the synthesized compounds was checked by TLC on silica gel precoated F254 Merck plates and melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis.

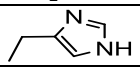
Mechanistic role under ultrasonic irradiation

The chemistry in liquid medium via pressure waves is sonochemistry. When sonic waves are propagate through a liquid medium, vibrational motions are induced via an alternating compression and rarefaction cycles. When rarefaction cycle surpasses the attractive intermolecular van der Waals forces of attraction between the molecules of the liquid medium, it breaks and leads to cavitation. The micro bubbles stretch, oscillate around their mean position and expand. Since these bubbles are unstable they implode releasing super high temperature and pressure in short duration which can never be achieved by traditional methods. This in turn sets the platform for the molecular fragmentation and generation of highly reactive species (chemical effects of ultrasound) which are responsible to trigger and enable the reaction in homogeneous solutions. The transmission of ultrasonic energy is higher in the case of water and also the occurrence of cavitation in water is faster in comparison to other solvents.

Antimicrobial activity

The antibacterial activity was evaluated against two Gram-positive bacteria namely, *Bacillus subtilis* (NCIM-2063) and *Staphylococcus aureus* (NCIM-2901) and one Gram-negative bacterium *Escherichia coli* (NCIM-2256). The antibacterial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/mL) as previously mentioned [37] by broth dilution method using Ciprofloxacin and Ampicillin as standard drugs. The antifungal activity was evaluated against three fungal strains; *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196) using Fluconazole and Miconazole as standard drugs. Minimum inhibitory concentration (MIC, µg/mL) values for

Table 3 Physical data for synthesized rhodanine derivatives 6(a-l)[a]

Sr. No.	Substituent (R)	Time (min)		Yield[b] (%)		Melting point (°C)
		Ultrasound irradiation	Conventional method	Ultrasound irradiation	Conventional method	
6a	$-CH_3$	2	30	98	85	230-232
6b	$-CH(CH_3)_2$	2	40	98	80	202-204
6c	$-CH(CH_3)CH_2CH_3$	3	35	98	82	140-142
6d	$-CH_2C_6H_5$	3	45	96	80	170-172
6e	$-CH_2CH_2SCH_3$	2	45	96	82	156-158
6f	$-CH_2CH(CH_3)_2$	4	35	98	84	233-235
6g	$-CH_2OH$	3	30	98	82	201-203
6h	$-CH_2SH$	5	35	96	84	206-208
6i	$-CH_2COOH$	5	50	98	80	182-184
6j		5	50	96	76	192-194
6k	$-CH_2C_6H_4OH$	2	45	96	72	150-152
6l	$-CHOHCH_3$	2	35	96	78	170-172

[a]Reaction condition (**6a-l**). Compound (**4**) (1 mmol), amino acids (**5a-l**) (1.2 mmol), **Method A:** Ultrasound irradiation: potassium carbonate, ethanol, rt, 2-5 min. **Method B:** Conventional method: potassium carbonate, ethanol, rt, 30-50 min.
[b]Isolated yields

Table 4 Antibacterial and antifungal activity of the synthesized compounds 3, 4, 6a-l (MIC/MBC Values (µg/mL))

Entry	Antibacterial activity (MIC values in µg/mL)			Antifungal activity (MIC values in µg/mL)		
	B. subtilis	***S. aureus***	***E. coli***	***C. albicans***	***A. flavus***	***A. niger***
3	90	45	90	100	98	100
4	100	100	100	12	100	100
6a	75	65	75	90	80	20
6b	65	57	90	85	59	80
6c	55	30	75	60	83	85
6d	20	15	70	90	65	70
6e	35	60	75	70	90	65
6f	45	40	75	60	90	65
6g	70	100	90	95	65	60
6h	85	15	100	95	10	90
6i	75	12.5	60	95	75	65
6j	20	50	70	65	90	60
6k	90	80	70	95	85	100
6l	6.0	5.0	90	70	85	70
Ciprofloxacin	7.25	7.25	5.0	-	-	-
Ampicillin	15.5	15.5	15.5	-	-	-
Fluconazole	-	-	-	4.25	4.25	4.25
Miconazole	-	-	-	12	7.25	7.25

10% of the mean; (-) denotes not tested.
The data represents the mean values of three replicates; Standard errors were all within

specific towards the Gram-positive bacteria, *S. aureus*, *B. subtilis* and *A. nigar*. The compound 6d (MIC= 15 µg/mL) against *S. aureus*, **6h** (MIC= 15 µg/mL) against *S. aureus* were more active than both standards; Ampicillin (MIC= 15.5 µg/ antifungal were determined using standard agar dilution method.[38-40] Methanol was used as solvent control for both antibacterial and antifungal testing. MIC values of the tested compounds are presented in Table 4. From the antibacterial activity data (Table 4), the synthesized compounds of present series showed moderate to good antibacterial activity. Amongst the synthesized series, compounds **6a** (MIC= 20 µg/mL), **6d** (MIC= 20 µg/mL and 15 µg/mL) and **6h** (MIC= 15 µg/mL) and **6j** (MIC= 20 µg/mL and 12.50 µg/mL), were found to be most active molecules and they are found to mL). The compounds **3, 4, 6b, 6c, 6f, 6g, 6k** and **6l** inactive against *B. subtilis, S. aureus* and *E. coli* showed lower activity than Ciprofloxacin and comparative level of activity as Ampicillin. 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.

The results of in vitro antifungal activities (Table 4) showed that synthesized compounds have moderate activity. Most of the synthesized compounds were inactive against fungal strains. The compound **6a** (MIC= 20 µg/mL) had shown significant activity against *A. nigar* when compared with Miconazole (MIC= 7.25 µg/mL). The compound **6h** (MIC= 10 µg/mL) showed moderate activity against *A. flavus* when compared with Miconazole (MIC= 7.25 µg/mL). Compounds **3** (MIC= 100 µg/mL against *A. flavus* and *A. niger*,) were less active from the synthesized series. None of the synthesized compounds showed comparable activity with that of Fluconazole (MIC= 4.25 µg/mL).

CONCLUSION

With the pervasive applicability and pharmacoactivity of these derivatives, we have herein devised an energy efficient, general, cost effective and eco sustainable method for the synthesis of a series of rhodanine derivatives **3**, **4** and **6a-l**. The promising salient features of this strategy are minimization of waste, ease of product isolation, rapid, avoids laborious column purification steps, economically viable, easy to operate, rate and yield enhancements. The present method will permit a further increase of the diversity within rhodanine derivatives. It is envisaged that, the utility of sonication in combination with ethanol as solvent and potassium carbonate as a catalyst will make further development and good prospects for industrial application, synthetic chemistry and chemical science. Amongst these

synthesized compounds **6a, 6h**, **6j**, **6h** were shows most antibacterial and antifungal activities.

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REFERENCES

1. E.L. Luzina, A.V. Popov, Eur. J. Med. Chem., 2009; 44: 4944–4953.
2. S. Carradori, D. Secci, A. Bolasco, C. De Monte, M. Yanez, Arch. Pharm., 2012; 345: 973–979.
3. B.S. Holla, K.V. Malini, B.S. Rao, B.K. Sarojini, N.S. Kumari, Eur. J. Med. Chem. 2003; 38: 313–318.
4. K. Toyoshi, A. Misako, K. Masako, O. Katsuya, K. Shigekatsu, M. Tamatsu, I. Takeshi, Chem. Pharm. Bull., 1985; 33: 4878–4888.
5. R. Murugan, S. Anbazhagan, S. Lingeshwaran, S. Narayanan, Eur. J. Med. Chem., 2009; 44: 3272–3279.
6. S. Chandrappa, C.V. Kavitha, M.S. Shahabuddin, K. Vinaya, C.S. Ananda, S.R. Ranganatha, S.C. Raghavan, K.S. Rangappa, Bioorg. Med. Chem., 2009; 17: 2576–2584.
7. 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.
8. B.P. Mallikarjuna, B.S. Sastry, G.V. Suresh, Y. Rajendraprasad, S.M. Chandrashekar, K.Sathisha, Eur. J. Med. Chem., 2009; 44: 4739–4746.
9. J. Balzarini, B. Orzeszko, J.K. Maurin, A. Orzeszko, Eur. J. Med. Chem., 2007; 42: 993–1003.
10. V. Murugesan, V.S. Tiwari, R. Saxena, R. Tripathi, R. Paranjape, S. Kulkarni, N. Makwana, R. Suryawanshi, S.B. Katti, Bioorg. Med. Chem., 2011; 19: 6919–6926.
11. R.K. Rawal, R. Tripathi, S.B. Katti, C. Pannecouque, E.D. Clercq, Bioorg. Med. Chem., 2007; 15: 3134–3142.
12. X. Zhang, X. Li, D. Li, G. Qua, J. Wang, P.M. Loiseau, X. Fan, Bioorg. Med. Chem. Lett., 2009; 19: 6280–6283.

13. A. Verma, S.K. Saraf, Eur. J. Med. Chem., 2008; 43: 897–905.
14. F.L. Gouveia, R.M.B. de Oliveira, T.B. de Oliveira, I.M. da Silva, S.C. do Nascimento, K.X.F.R. de Sena, J.F.C. de Albuquerque, Eur. J. Med. Chem., 2009; 44: 2038–2043.
15. R. Ottana, S. Carotti, R. Maccari, I. Landini, G. Chiricosta, B. Caciagli, M.G. Vigorita, E. Mini, Bioorg. Med. Chem. Lett., 2005; 15: 3930–3933.
16. T.J. Shah, V.A. Desai, ARKIVOC., 2007; xiv: 218–228.
17. M. Gualtieri, L. Bastide, P.V. Latouche, J.P. Leonette, J. Antimicrob. Chemother., 2006; 58: 778–783.
18. M.M. Sim, S.B. Ng, A.D. Buss, S.C. Crasta, K.L. Goh, S.K. Lee, Bioorg. Med. Chem. Lett., 2002; 12: 697–699.
19. V. Petrikaite, E. Tarasevicius, A. Pavilonis, Medicina (Kaunas)., 2007; 43: 657–663.
20. M. Sortino, P. Delgado, S. Juarez, J. Quiroga, R. Abonia, B. Insuasty, M. Nogueras, L. Rodero, F.M. Garibotto, R.D. Enriz, S.A. Zacchino, Bioorg. Med. Chem., 2007; 15: 484–494.
21. X. Jin, C.J. Zheng, M.X. Song, Y. Wu, L.P. Sun, Y.J. Li, L.J. Yu, H.R. Piao, Eur. J. Med. Chem., 2012; 56: 203–209.
22. W.K. Coulibaly, L. Paquin, A. Benie, Y.A. Bekro, E. Durieux, L. Meijer, R. L.Guevel, A.Corlu, J.P. Bazureau. Sci Pharm., 2012; 80: 825–836.
23. D. Kaminskyy, D. Khyluk, O. Vasylenko, R. Lesyk, Tetrahedron Lett., 2012; 53: 557–559.
24. J.M. Guernon, Y.J. Wu, Tetrahedron Lett., 2011; 52: 3633–3635.
25. N.G. Khaligh, F. Shirini, Ultrason. Sonochem., 2013; 20: 19–25.
26. J.T. Li, Y. Yin, L. Li, M.X. Sun, Ultrason. Sonochem., 2010; 17: 11–13.
27. R.M. Srivastava, R.A.W.N. Filho, C.A. Silva, A. Bortoluzzi, Ultrason. Sonochem., 2009; 16: 737–742.
28. K. Prasad, D.V. Pinjari, A.B. Pandit, S.T. Mhaske, Ultrason. Sonochem., 2010; 17: 409– 415.
29. K.J. Parag, D.V. Pinjari, A.B. Pandit, G.S. Shankarling, Ultrason. Sonochem., 2011; 18: 617–623.
30. L.H. Fu, Y.Y. Dong, M.G. Ma, S.M. Li, R.C. Sun, Ultrason. Sonochem., 2013; 20: 839–845.
31. K.S. Suslick, S.B. Choe, A.A. Cichowlas, M.W. Grinstaff, Nature., 1991; 353: 414–416.
32. K. Chatakondu, M.L.H. Green, M.E. Thompson, K.S. Suslick, Chem. Commun., 1987; 900–901.

33. A. Duarte, W. Cunico, C.M.P. Pereira, A.F.C. Flores, R.A. Freitag, G.M. Siqueira, Ultrason. Sonochem., 2010; 17: 281–283.
34. (a) J.P. Lorimer, T.J. Mason, Chem. Soc. Rev., 1987; 16: 239–274; (b) L.C. Bretanha, V.E. Teixeira, M. Ritter, G.M. Siqueira, W. Cunico, C.M.P. Pereira, R.A. Freitag, Ultrason. Sonochem., 2007; 18: 704–707; (c) J.D. Sweet, D.J. Casadonte Jr., Ultrason. Sonochem., 2001; 8: 97–101.
35. (a) D.N. Pansare, N.A. Mulla, C.D. Pawar, V.R. Shende, D.B. Shinde, Bioorg. Med. Chem. Lett., 2014; 24: 3569–3573; (b) S.N. Darandale, D.N. Pansare, N.A. Mulla, D.B. Shinde, Bioorg. Med. Chem. Lett., 2013; 23: 2632–2635; (c) S.N. Darandale, N.A. Mulla, D.N. Pansare, J.N. Sangshetti, D.B. Shinde, Eur. J. Med. Chem., 2013; 65: 527–532.
36. (a) http://dx.doi.org/10.1016/j.jscs.2015.10.005J.G. (b) D.N. Pansare, D.B. Shinde, Tetrahedron Lett., 2014; 55: 1107–1110; (c) D.N. Pansare, D.B. Shinde, Open Chem. Journal., 2015; 2: 20-26.
37. Cappuccino, N. Sherman, Microbiology- a laboratory manual, Addison Wesley, California, 1999.
38. A.H. Collins, Microbiological Methods, 2nd ed.; Butterworth: London, 1976.
39. Z.K. Khan, In vitro and in vivo screening techniques for bioactivity screening and evaluation, Proc. Int. Workshop UNIDO-CDRI, 1997; 210.
40. B. Duraiswamy, S.K. Mishra, V. Subhashini, S.A. Dhanraj, B. Suresh, Indian J. Pharm. Sci., 2006; 68: 389–391.