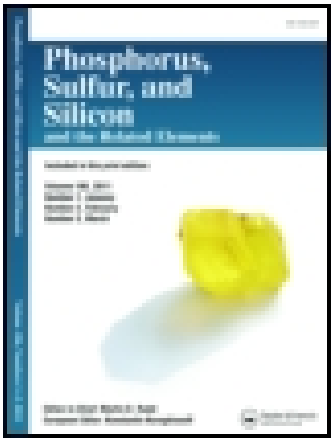

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# Isocoumarin Thioanalogues as Potential Antibacterial Agents

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# Isocoumarin Thioanalogues as Potential Antibacterial Agents

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*A series of 3-substituted-1H-isochromene-1-thiones (**3**) were prepared by the reaction of 3-substituted isocoumarins (**2**) with Lawesson's reagent in the presence of toluene under a nitrogen atmosphere. The antimicrobial activities of the newly synthesized products were measured using Gram-negative (*Escherichia coli*,* Salmonella typhi*, and* Proteus mirabilis*) and Gram-positive bacteria (*Staphylococcus aureus *and* Bacillus cereus*). Synthesized thioanalogue of isocoumarins showed good antibacterial activity against* Proteus mirabilis.

**Keywords** Isochromene-1-thione; isocoumarins; Lawesson's reagent

## INTRODUCTION

Most methods developed for the chemical preparation of thionolactones involve an oxygen–sulfur exchange from the corresponding carbonyl compounds, and usually proceed from thermal processes. Resulting from the pioneering work of Lawesson and co-workers,[1,2] 2,4-bis(4-methoxy-phenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide, known as Lawesson's reagent (LR), was designed to perform, under defined conditions, a single sulfurization of lactones selectively resulting in the corresponding thionolactones.[3] Isocoumarins possess important biological properties.[4–8] With the intension of improving the biological properties of isocoumarins, the thionation reaction was attempted. In previous studies, Lawesson's reagent proved to be an efficient sulfur transfer

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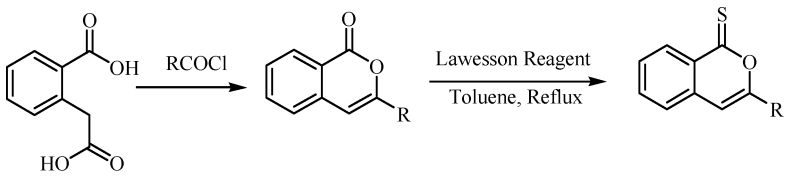


**1** **2** **3**

R = Alkyl, Aryl, Aralkyl, cycloalkyl, etc

**SCHEME 1** Synthesis of 3-substituted-1H-isochromene-1-thione from isocoumarins.



reagent in the case of chromones, thiochromones, flavones, isoflavones, benzoxapines, etc.[9–14] Therefore this reagent has been utilized in our thioisocoumarin synthesis as a part of our research interest on isocoumarins.[15–17]

## RESULTS AND DISCUSSION

Our investigation began with an attempted synthesis of the precursor of 3-substituted isochromen-1-ones derived from homophthalic acid, followed by thionation of 3-substituted isochromen-1-ones with Lawesson's reagent (Scheme 1). The 3-substituted isocoumarins were prepared by a previously reported procedure.[7,15] The reaction was successfully completed in just a few hours with excellent yields. The purified isocoumarins were then allowed to react with Lawesson's reagent in the presence of toluene under nitrogen atmosphere to afford the corresponding 3-substituted-1H-isochromene-1-thiones. The reaction producing 3-substituted-1H-isochromene-1-thione derivatives by a simple and an efficient route gave modest to good yields, thereby providing a convenient route for the synthesis of variety of thioisocoumarins. The products of the reaction were isolated, purified, and characterized by various spectral techniques such as FTIR, LC-MS, $^{1}$H-NMR, and $^{13}$C-NMR. All synthesized compounds exhibited excellent antibacterial activity against *Proteus mirabilis*, whereas, except compound **3e**, all other compounds showed good activity against *Bacillus cereus*.

## CONCLUSIONS

In the present study, thionation of isocoumarins was successfully carried out by Lawesson's reagent, and from antibacterial activity, we

conclude that all thioanalogues of 3-substituted-1H-isochromene-1-one have good activity against *Proteus mirabilis*.

## EXPERIMENTAL

Melting points were taken in open capillary tubes and corrected with reference to benzoic acid. IR spectra, as KBr pellets, were recorded on a Nucon Infrared spectrophotometer. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO (with TMS for $^{1}H$ and DMSO for $^{13}C$ NMR as internal references).

### General Procedure of the Synthesis of 3-Substituted-1H-isochromene-1-thione (3a–f)

The title compounds were synthesized from a mixture of isocoumarins, **2** (10 mmol), and Lawesson's reagent (12 mmol). The mixture was placed in a glass tube fitted with a tightened rubber septum and was refluxed at 110°C using toluene as a solvent under a nitrogen atmosphere. The progress of the reaction was monitored by TLC using a hexane:ethyl acetate (9:1 v/v) mixture. After the completion of the reaction, the mixture was dissolved in dichloromethane and adsorbed on silica gel. The compounds were purified by column chromatography using a mixture of hexane:ethyl acetate (9:1 v/v). The products obtained were characterized by FTIR, LC-MS, $^{1}H$-NMR, and $^{13}C$-NMR techniques. The reactions of Lawesson's reagent with various isocoumarins **2a–f** are tabulated (Table I). The spectral data of the compounds **3a–f** are given below.

**TABLE I Synthesis of 3-Substituted Isochromene-1-thiones[a]**

| Isocoumarins 2\Isochromene-1-thione 3 R | Yield%[b] |
|---|---|
| n—$C_4H_9$, 2a, 3a | 96 |
| Ph, 2b, 3b | 92 |
| p-$CH_3$-$C_6H_4$, 2c, 3c | 94 |
| p-$OCH_3$-$C_6H_4$, 2d, 3d | 89 |
| 2—furyl, 2e, 3e | 90 |
| Cyclo $C_6H_{11}$, 2f, 3f | 87 |

[a]Isocoumarins, **2a–f** (10 mmol) in toluene (50mL), Lawesson's reagent, (12 mmol).

[b]Isolated yield for isochromene-1-thione, **3**.

### *3-Butylthioisocoumarin (3a)*

Yellow solid, mp 71.2–73°C, IR ($\nu$ $cm^{-1}$) 2955, 2923, 2852, 1650, 1551, 1474, 1457, 1428, 1381, 1327, 1287, 1208, 1170, 1085, 1022, 999, 836, 758, 576, 464. $^1$H NMR ($CDCl_3$): $\delta$ 8.69 (m, 1H), 7.68–7.72 (m, 1H), 7.44–7.49 (m, 1H), 7.35 (m, 1H), 6.49 (s, 1H), 2.64 (t, $J$ = 7.52 Hz, 2H), 1.71–1.79.66 (m, 2H), 1.49–1.39 (m, 2H), 0.95 (t, $J$ = 7.52 Hz, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 201.53, 161.65, 135.05, 132.78, 132.25, 129.79, 128.58, 125.52, 105.44, 33.176, 29.23, 22.1, 13.7, LCMS—218.7. $C_{13}H_{14}OS$ requires Mol. Wt.: 218.3.

### *3-Phenylthioisocoumarin (3b)*

Yellow solid, mp 115–117°C, IR ($\nu$ $cm^{-1}$) 3061, 2923, 2853, 1634, 1551, 1473, 1457, 1428, 1341, 1296, 1204, 1111, 1085, 1026, 999, 838, 761, 686, 517, 474. $^1$H NMR ($CDCl_3$): 8.72 (d, 1H), 7.94–7.96 (m, 2H), 7.71–7.75 (m, 1H), 7.46–7.51 (m, 5H), $\delta$ 7.14 (s, 1H), $^{13}$C NMR ($CDCl_3$): $\delta$ 200.41, 156.7, 135.14, 132.87, 132.16, 131.27, 130.37, 130.19, 129.17, 128. 97, 126.47, 125.42 104.66, LCMS—238.7. $C_{15}H_{10}OS$ requires Mol. Wt.: 238.3.

### *3-p-Tolylthioisocoumarin (3c)*

Yellow solid, mp 133.1–134°C, IR ($\nu$ $cm^{-1}$) 2922, 2852, 1630, 1548, 1474, 1447, 1340, 1283, 1219, 1198, 1172, 1113, 1033, 989, 814, 746, 519, 474. $^1$H NMR ($CDCl_3$): 8.72 (d, 1H), 7.71–7.86 (m, 3H), 7.47 (m, 2H), 7.29 (d, 2H), $\delta$ 7.10 (s, 1H), 2.48 (s, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 200.50, 156.99, 140.77, 135.09, 132.87, 132.41, 130.08, 129.68, 128.93, 128.52, 126.33, 125.35, 103.95, 21.45, LCMS—252.9. $C_{16}H_{12}OS$ requires Mol. Wt.: 252.3.

### *3-p-Anisylthioisocoumarin (3d)*

Yellow solid, mp 151.3–152°C, IR ($\nu$ $cm^{-1}$) 3055, 2921, 2852, 1620, 1553, 1432, 1381, 1375, 1344, 1261, 1195, 1153, 1088, 1019, 972, 823, 769, 629, 520, 466. $^1$H NMR ($CDCl_3$): $\delta$ 8.71 (m, 1H), 7.83–7.92 (m, 2H), 7.73–7.69 (m, 1H),7.45–7.49 (m, 2H), 7.03–6.98 (m, 3H), 6.85 (s, 1H), 3.84 (s, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 200.50, 161.41, 156.89, 135.09, 132.62 129.85, 128.69, 127.05, 126.20, 123.86, 114.38, 103.14, 55.45, LCMS—269.2. $C_{16}H_{12}O_2S$ requires Mol. Wt.: 268.3.

### *3-(Furan-2-yl)-1H-isochromene-1-thione (3e)*

Yellow solid, mp 112–114°C, IR ($\nu$ $cm^{-1}$) 3067, 2923, 2853, 1650, 1542, 1472, 1458, 1384, 1340, 1285, 1204, 1169, 1092, 1030, 989, 839, 744, 591, 470. $^1$H NMR ($CDCl_3$): $\delta$ 8.72–8.70 (d, 1H), 7.74–7.70 (m, 1H), 7.55–7.46 (m, 3H), 7.11–7.06 (m, 1H), 6.98–6.89 (m, 1H), 6.57 (s,

**TABLE II Antimicrobial Activity of Synthesized Compounds (Zones of Inhibition in mm)**

| | Synthesized Compounds | | | | | | | | | | | | Standard Strepto-mycin 100 μL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3a (μL) | | 3b (μL) | | 3c (μL) | | 3d (μL) | | 3e (μL) | | 3f (μL) | | |
| | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | |
| al Strains | Zone of inhibition in mm | | | | | | | | | | | | |
| *Escherichia coli* | 18 | 22 | – | 14 | – | 15 | – | 14 | – | 13 | – | – | 31 |
| *Proteus mirabilis* | – | 16 | 12 | 14 | 10 | 14 | 13 | 15 | 12 | 14 | 12 | 16 | 29 |
| *Staphylococcus aureus* | – | – | – | – | 13 | 15 | 12 | 14 | – | – | – | – | 28 |
| *Salmonella typhi* | – | 16 | – | 13 | – | – | – | – | – | 17 | 12 | 15 | 38 |
| *Bacillus cerus* | 12 | 16 | 13 | 15 | 12 | 15 | 13 | 15 | – | – | – | 17 | 28 |

1H), $^{13}$C NMR ($CDCl_3$) $\delta$ 199.58, 149.07, 144.32, 135.18, 133.10, 131.79, 128.98, 126.41, 125.97, 112.29, 112.15, 110.90, 102.79. LCMS-228.0. $C_{13}H_8O_2S$ requires Mol. Wt.: 228.2.

### *3-Cyclohexyl-1H-isochromene-1-thione (3f)*

Yellow solid, mp 68–70°C, IR ($\nu$ cm$^{-1}$) 3015, 2921, 2849, 1657, 1548, 1464, 1426, 1379, 1333, 1277, 1216, 1168, 1072, 1036, 989, 829, 758, 474. $^1$H NMR ($CDCl_3$): $\delta$ 8.71–8.69 (d, 1H), 7.72–7.67 (m, 1H), 7.49–7.44 (m, 1H), 7.38–7.36 (m, 1H), 6.49 (s, 1H), 2.62–2.57 (t, 1H), 2.12–2.09 (m, 2H), 1.90–1.86 (m, 2H), 1.79–1.74 (m, 1H), 1.52–1.26 (m, 5H). $^{13}$C NMR ($CDCl_3$): $\delta$ 201.50, 165.70, 134.98, 132.72, 132.36, 129.9, 128.54, 125.76, 104.00, 41.68, 30.81, 25.91, 25.80, LCMS-243.08. C15H16OS requires Mol. Wt.: 244.3.

## IN VITRO ANTIMICROBIAL ACTIVITIES EVALUATION

The in vitro antibacterial screening of synthesized compounds were evaluated against selected Gram-positive organisms viz. *Bacillus cereus* and *Staphylococcus aureus* and three Gram-negative organisms viz. *Escherichia coli*, *Salmonella typhi*, and *Proteus mirabilis* by the Agar well diffusion method.[18] Cultures of bacteria were grown on nutrient broth (HiMedia) at 37°C for 12–14 h and were maintained on respective agar slants at 4°C. Nutrient agar was poured onto a plate and allowed to solidify. The test compounds (DMSO solutions) were added dropwise to a 10 mm diameter well placed in the agar plate. The compounds of 4mg/mL concentration were used as stock solution from this 100 $\mu$L was loaded to each well. The plates were then kept at 5°C for 1 h then transferred to an incubator maintained at 36°C. The width of the growth inhibition zone was measured after 24 h incubation. The activity studies have been carried out with two different concentration and triplicate measurements (Table II). The results indicate that all the thioanalogue of 3-substituted-1H-isochromene-1-ones have good antibacterial activity against *Proteus mirabilis*.

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