Antimicrobial studies of novel 2, 5 –Dimercapto-1, 3, 4 –thiadiazole derivatives

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Available online at: www.isca.in, www.isca.me

Received 23rd November 2014, revised 18th December 2014, accepted 10th January 2015

Abstract

A series of novel chalcone derivatives of 2, 5 –Dimercapto-1, 3, 4 –thiadiazole (3a-h) were synthesized by Claisen-Schmidt condensation between terephthaldehydyl -2, 5 –dimercapto (acetichydrazide)-1, 3, 4 –thiadiazole (1) and substituted aromatic ketones (2a-h). All the synthesized compounds (3a-h) were characterized by UV, IR, 1H-NMR, 13C-NMR and mass spectral data. The synthesized compounds were subjected to antibacterial studies against Staphylococcus aureus, Bacillus subtilis (gram-positive), Escherichia coli and Salmonella enteritidis (gram-negative) bacteria and antifungal studies against Candida albicans, Trichophyton rubrum, Trichoderma viride and Aspergillus niger and the Minimum Inhibitory concentration of each compound was determined by liquid broth method. The results indicated that all the synthesized compounds 3a-h showed considerable antibacterial and antifungal activities. 

Keywords: 2, 5 –Dimercapto-1, 3, 4 –thiadiazole, anti-fungal and anti-bacterial activity.

Introduction

Chalcones are a major class of natural products belonging to the flavonoid family. They are considered as the precursors of flavonoids and isoflavonoids. They are also the precursors of a number of biologically important heterocycles such as benzothiazepines, pyrazolines, and flavones. They are widely distributed in fruits, vegetables, tea, spices, soy based foods and other plant products. From a chemical point of view an important feature of chalcones and their heteroanalogs is the ability to act as activated unsaturated systems in conjugate addition reactions of carbanions in presence of base catalysts. Chalocnes have been popular substrates for the generation of variety of heterocyclic, carbocyclic and flavonoids.

The compounds with the backbone of chalcones have been reported to possess various biological activities such as antibacterial, antifungal, insecticidal, anaesthetic, anti-inflammatory, analgesic, antilucergenic, antiplatelet, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antituberculosis, anti hyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of tyrosinase and inhibition of aldose reductase activities. 

In the present work we report the reaction of terephthaldehydyl-2, 5 -dimercapto (acetichydrazide)-1,3,4 –thiadiazole with different substituted aromatic ketones to form chalcones (3a-h). Many reports were available for the preparation of chalcones but the reports on antibacterial and antifungal activity of chalcones associated with thiadiazole nucleus are rarely found. This prompted us to synthesize chalcones containing 1, 3, 4 –thiadiazole moiety and to carry out the antibacterial and antifungal activity.

Material and Methods

Chemistry: All melting points (uncorrected) were determined using a Guna melting point apparatus. UV spectra were obtained UV 2460 shimadzu spectrophotometer. IR spectra were carried out on a Perkin-Elmer 1650 spectrophotometer. NMR spectra were recorded in CDCl3 on a Bruker AM 400 MHz spectrometer, using residual CHCl3 and TMS as an internal standard. Mass spectra were recorded on a VG-70-S instrument. Elemental analysis was carried out in a Perkin Elmer 240C model instrument. The purity of the compound was checked by TLC using silica gel ‘G’ plates. All the chemicals used are of AR grade.

General procedure for the preparation of compounds 3a-h:
Terephthaldehydyl 2,5 –dimercapto (Acetichydrazide)-1,3,4 –thiadiazole. I (0.01 mol) was dissolved in 100 ml ethanol and the substituted aromatic ketones (2a-h) (0. 02mol) were added and heated for 7-8 hrs with constant stirring in a magnetic stirrer and a catalytic amount of NaOH was added in drops. The reaction was poured into ice-cold water, neutralized with con.HCl and left over night in a refrigerator. The precipitate formed was filtered, dried and the purity of the compound was checked by TLC using chloroform as the solvent.

Terephthalphenyl-2,5 –dimercapto (Acetichydrazide)-1,3,4 –thiadiazole -(3-nitrophenyl)-prop-2-en-1-one (3a):

Yield 65%; m.p.: 201–203 °C; UV λ max: 651.50,561.50; 333.00;IR (KBr) cm-1: 3466, 1697, 1458; 1H-NMR (400MHz CDCl3) δ: 7.11 (d, 1H, J=16Hz, H-2), 7.38 (dd, 1H, J=8Hz,1.6Hz, H-3', 6.88 (d, 1H, J=8Hz, H-4'), 6.98 (d, 1H, J=8Hz, H-5'), 6.76 (td, 1H, J=8, 1.6Hz, H-8'), 7.68 (d, 1H, J=16Hz, H-2),7.23 (d, 1H, J=16Hz, H-3), 7.08 (d, 1H, J=16Hz, H-4), 5.68 (td, 1H, J=8Hz, H-5'), 6.76 (td, 1H, J=8Hz, H-6'), 6.93 (dd, 1H, J=8, 1.6Hz, H-7), 6.48 (dd, 1H, J=8, 1.6Hz, H-8'), 7.68 (d, 1H, J=16Hz, H-2),7.23 (d, 1H, J=16Hz,
Terephthalphenyl-2.5 – Dimercapto (Acetichydrazide)-1,3,4-thiadiazole --(4-Fluorophenyl)-prop-2-en-1-one(3b) :: Yield 64%; m.p.: 198; 1H-NMR(400MHz CDCl₃): δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.46 (m, 1H,H-3'), 7.09 (d, 1H, J=7.8Hz, H-4'), 6.91 (d, 1H, J=7.8Hz, H-5'),6.77 (t, 1H, J=7.8Hz, H-6'), 6.99 (td, 1H, J=7.8Hz, H-7'), 6.67(d, 1H, J=7.8Hz, H-8'), 7.46 (m, 2H, 2'H, 3'''), 7.87 (m, 2H, H-2', 6''), 6.73 (d, 1H, H-4'), 7.77 (d, 2H, J=16Hz, H-2,3), 8.89 (s,1H, NH). 13C-NMR δ: 131.60, 131.38, 127.94, 126.84, 126.83, 126.54, 124.78, 124.76, 123.47, 123.36, 123.23, 113.07, 112.90, 103.15, 103.08, 101.23, 101.20, 101.12, 78.97 (s, 1H, NH). Anal. Calcd.for C₂₆H₃₈N₂O₂S₂Cl: C, 65.69%; H, 4.55%; N, 4.25%; Found: C, 67.67%; H, 4.44%; N, 4.34%.

Terephthalphenyl-2.5 – Dimercapto (Acetichydrazide)-1,3,4-thiadiazole --(4-Chlorophenyl)-prop-2-en-1-one(3c) : Yield 66%; m.p.: 210°C. UV λ max: 570.50,328.50,259.50;IR (KBr) cm⁻¹: 3450, 1640, 1451; 1H-NMR (400 MHz CDCl₃): δ: 7.30 (d, 1H, J=1.6Hz, H-2'), 7.63 (dd, 1H, J=1.6Hz, H-3'),7.09 (d, 1H, J=1.6Hz, H-4'), 6.93 (dd, 1H, J=8Hz, H-5'), 6.78 (dt,1H, J=8Hz, H-6'), 6.60 (td, 1H, J=1.6Hz, H-7'), 5.53 (dd, 1H, J=1.6Hz, H-8'), 8.79 (s, 1H, NH). 13C-NMR δ: 193.71, 184.00, 150.0, 169.92, 161.12, 129.73, 40.58. MS (El/mz) = 798.03. Anal. Calcd.for C₂₆H₃₈N₂O₂S₂Cl: C, 69.34%;H, 3.85%; N, 3.85%; Found: C, 69.29%; H, 3.80%; N, 3.91%.

Terephthalphenyl-2.5 – Dimercapto (Acetichydrazide)-1,3,4-thiadiazole --(4-Methylphenyl)-prop-2-en-1-one(3d) : Yield 61%; m.p.: 204°C. UV λ max: 765.00,758.00,334.50; IR (KBr) cm⁻¹: 3450, 1685, 1456; 1H-NMR (400 MHz CDCl₃): δ: 7.30 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd, 1H,J=1.6Hz, H-3'),7.09 (d, 1H, J=1.6Hz, H-4'), 6.91 (dd, 1H, J=1.6Hz, H-5'), 6.77 (td, 1H, J=8Hz, H-6'), 6.70 (td, 1H, J=1.6Hz, H-7'), 6.68 (dd, 1H, J=1.6Hz, H-8'). 7.67 (m, 1H, J=16Hz, H-2), 7.83 (m, 1H, J=16Hz, H-3), 7.80 (m, 2H, H-2',3''), 6.76 (m, 2H, H-2',3''), 8.78 (s, 1H, NH). 13C-NMR δ: 173.12,149.58,134.15,126.02,118.79; MS (El/mz) = 889.97. Anal. Calcd.for C₃₂H₂₄N₇O₈S₄Br₂: C, 61.78%; H, 3.43%; N, 3.43%; Found: C,61.84%; H, 3.51%; N, 3.45%.

Terephthalphenyl-2.5 – Dimercapto (Acetichydrazide)-1,3,4-thiadiazole --(4-Nitrophenyl)-prop-2-en-1-one(3g) : Yield 62%; m.p.: 213°C. UV λ max: 583.50,576.00,328.50; IR (KBr) cm⁻¹: 3462, 1692, 1452; 1H-NMR (400 MHz CDCl₃): δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.61 (dd, 1H, J=1.6Hz, H-3'), 7.09 (d, 1H, J=1.6Hz, H-4'), 6.91 (dd, 1H, J=1.6Hz, H-5'), 6.78 (td, 1H, J=8Hz, H-6'), 6.65 (dd, 1H, J=1.6Hz, H-7'), 5.79 (d, 1H, J=16Hz, H-2'), 7.83 (m, 1H, J=16Hz, H-3), 7.80 (m, 2H, H-2',3''), 6.77 (m, 2H, H-2',3''), 8.78 (s, 1H, NH). 1005 (s, 1H, CHO). 13C-NMR δ: 173.12,149.58,134.15,126.02,118.79; MS (El/mz) = 820.94. Anal. Calcd.for C₃₂H₂₄N₇O₈S₄: C, 73.39%; H, 4.20%; N, 3.91%; Found: C, 73.47%; H, 4.25%; N, 4.31%.

Terephthalphenyl-2.5 – Dimercapto (Acetichydrazide)-1,3,4-thiadiazole --(3-Bromophenyl)-prop-2-en-1-one(3e) : Yield 63%; m.p.: 199°C. UV λ max: 657.00,630.30,329.00; IR (KBr) cm⁻¹: 3452, 1685, 1456; 1H-NMR (400 MHz CDCl₃): δ: 7.31 (d, 1H, J=1.6Hz, H-1'), 7.68 (dd, 1H, J=1.6Hz, H-3'), 7.08 (d, 1H, J=8Hz, H-4'), 6.93 (dd, 1H, J=1.6Hz, H-5'), 6.79 (td, 1H, J=8, 1.6Hz, H-6'), 6.99 (td, 1H, J=8, 1.6Hz, H-7'), 6.67 (d, 1H, J=1.6Hz, H-8'), 7.80 (d, 1H, J=1.6Hz, H-9'). 7.02 (d, 1H, J=8Hz, H-4'), 8.26 (dd, 1H, J=1.6Hz, H-5'), 7.74 (t, 1H, J=8Hz, H-5'), 8.28(m, 1H, H-6'), 8.75 (s, 1H, NH). 13C-NMR δ: 173.14, 160.78, 153.42, 149.62, 133.32, 129.72, 126.56, 126.35,119.30,40.47; MS (El/mz) = 850.68. Anal. Calcd.for C₂₆H₂₄N₇O₈S₄: C, 73.39%; H, 4.20%; N, 3.91%; Found: C, 73.47%; H, 4.25%; N, 4.31%.

Antibacterial and antifungal activity: The results of the antibacterial and antifungal activity of the tested compounds were given in table 1 and 2. Significant inhibitory activity with a
MIC value of 15 to 20 µg/mL was observed against the studied pathogenic bacteria. *B. subtilis, S. aureus* was the most sensitive strain. Tetracycline was used as a standard compound for screening the antibacterial activity. Most of the compounds had remarkable antifungal activity against the microorganisms employed in this study. Two out of eight studied compounds exhibited a good antifungal activity with a MIC value of 15 to 20µg/mL against *C. albicans, T. rubrum, T. viride,* and *A. flavus.* As it can be seen in Table 2, *A. flavus* was more susceptible than *C. albicans, T. rubrum, T. viride* to the studied compounds. Ketoconazole was used as a standard compound for screening antifungal activity. From the outcome of antimicrobial screening, it is apparent that the compounds 3a, 3c, 3d and 3g possess very good antibacterial and antifungal activity with MIC values ranging from 15 to 20µg/mL and the compounds 3b, 3e, 3f and 3h showed moderate antimicrobial and antifungal activity.

**Results and Discussion**

Compounds 3a-h were synthesized by the reaction between terephthalphenyl -2,5 –dimercapto (acetichydrazide)-1,3,4 – thiadiazole with various substituted aromatic ketone by Claisen-Schmidt condensation reaction as shown in scheme 1. For the compounds 3a-h, IR spectra showed characteristic absorption bands to show the presence of carbonyl group at 1670 cm⁻¹, C=C at 1600 cm⁻¹ and NH stretching at 3450 cm⁻¹. For all the synthesized compounds, the signals for the aromatic carbons and protons were assigned using known effects of substituents, position, multiplicities and integral values. In ¹H-NMR spectra for the compound 3a-h the H-2 and H-3 protons are found to be in the Trans positions by appearing as doublets at δ 7.30 and 7.77 with a coupling constant of 16Hz. NH proton appeared as a singlet at δ 8.79. In compound 3a, the methoxy protons appeared as a single t δ 1.18, similarly in 3d, CH₃ appeared at δ 2.35. In 3g, the singlet at δ 10.05 is due to CHO group and all the aromatic protons appeared between δ 6.50- 8.28. The ¹³C–NMR spectrum were recorded in CDCl₃ and spectral signals were in good agreement with the proposed structures; C=O group appeared at δ 187.92. In the compound 3a, the methoxy carbon appeared at δ 55.42 and in compound 3d, the methyl carbon appeared at δ 21.05. For 3g, the keto carbon appeared at δ192.59 and all the aromatic carbons and unsaturated Carbons appeared between 100-160. Characteristic molecular ion peaks were observed in the mass spectra of the compounds 3a-g and shown in experimental section.

### Table-1

**Antibacterial activity of the compounds 3a-h**

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<tr>
<th>Tested compound</th>
<th>Minimum inhibitory concentration expressed in µg/mL</th>
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<tr>
<td></td>
<td>B. subtilis</td>
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<tr>
<td></td>
<td>Gram positive</td>
</tr>
<tr>
<td>3a</td>
<td>20</td>
</tr>
<tr>
<td>3b</td>
<td>45</td>
</tr>
<tr>
<td>3c</td>
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</tr>
<tr>
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<td>3h</td>
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</tr>
<tr>
<td>Tetracycline</td>
<td>20</td>
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### Table-2

**Antifungal activity of the compounds 3a-h**

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<th>Tested compound</th>
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</thead>
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<td>Candida albicans</td>
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<td>3a</td>
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</tr>
<tr>
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<td>40</td>
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<tr>
<td>3c</td>
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<td>3g</td>
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<tr>
<td>3h</td>
<td>30</td>
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</table>

Ketoconazole 10 10 10 10
Scheme-1
Synthesis of Chalcones 3a-h

Figure-1
IR Spectral data of compound 3a
Figure-2

$^1$H - NMR Spectral data of compound 3a

Figure-3

$^{13}$C- NMR Spectral data of compound 3a
Conclusion

In conclusion, a series of chalcones (3a-h) were synthesized and characterized by Claisen-Schmidt condensation reaction. They were screened for their potential antimicrobial activities in comparison with the standard drugs tetracycline and ketoconazole. The compounds 3a and 3c,3d exhibited the most intensive and consistent antimicrobial activity with a MIC value of 15-20 µg/mL.

Acknowledgements

We are thankful to the Management, Vice-chancellor, Registrar and HOD, Dept. of Chemistry, Karpagam University, Coimbatore, Tamil Nadu, India for providing the facilities to carry out the research work.

References