Design, synthesis, characterization and anti-microbial screening of some novel 2,4-dithiobiueret based chalcones

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ABSTRACT

The interactions of 1:1 molar proportion of (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (Ia) and various alkyl/arylisothiocynates (IIa-e) in acetone medium have been investigated. The synthesized compounds from these reaction conditions were characterized on the basis of conventional elemental analysis, chemical characteristic and IR, NMR, spectral data.

Keywords-(2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one(Ia), various alkyl/aryl isothiocynates (IIa-e), acetone, antibacterial, ciprofloxin etc.

INTRODUCTION

Tayade[1], Murhekar[2] and Paranjape[3] reported acyclic 2,4-dithiobiurets as an excellent and potent biological moiety. Synthesis and biological evaluation of novel 2,4-dithiobiurets is interesting field in the organic chemistry. These 2,4-dithiobiurets are especially good class of organic intermediates[4-7] for the synthesis of various active heterocycles. More especially, nitrogen and sulphur containing and derived compounds from the chalcones possess a variety of anti-microbial8, anti-viral9 anti-bacterial activities[10].

Recently in the present research, a novel series of chalcone based 2,4-dithiobiurets were synthesized by the interactions of (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (Ia) with various substituted alkyl/arylisothiocynates (IIa-e) had been investigated for isolation of important nitrogen and sulphur containing heteroacycles having medicinal, agricultural, pharmacological and biological importance[11-12]. These compounds were also cyclised successfully into medicinal[13-14], biological[15-16] and agricultural[17] important 1,2,4-dithiazolo[12-18], 1,3,5-thiadiazines[12-18]. 1,3,5-thiadiazines were then isomerised into 1,3,5-triazines[12-18]. Contemplating the literature data, it was planned to design, synthesize and to investigate reactions of (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (Ia) with different alkyl/arylisothiocyanates (IIa-e). Considering the aims and objectives the interaction of (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxy phenyl)prop-2-en-1-one (Ia) and various alkyl/arylisothiocynates (IIa-e) in acetone medium were investigated.

MATERIALS AND METHODS

Materials:
All chemicals used were of Mercks Millipore (Indian made). (2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (Ia) were prepared by known literature method[12-18].
Method:
Method employed in the present experiments for the synthesis of various substituted 2,4-dithiobiureto based chalcones is conventional refluxing under water bath for different hours for different experiments.

EXPERIMENTAL
The melting points of synthesized compounds were recorded using hot paraffin bath. The carbon and hydrogen analysis was carried out on Carlo-Ebra-1106 analyzer while Nitrogen estimation was carried out on Colman-N-analyzer-29. IR spectra were recorded on Perkin Elmer spectrometer in the range 4000-400 cm$^{-1}$ in KBr pellets. PMR spectra were recorded on BRUKER AIIANCE II 400 NMR spectrometer with TMS as an internal standard using CDCl$_3$ and DMSO-d$_6$ as a solvent. The purity of the compounds was checked on silica gel – G plates by TLC with layer thickness of 3mm.

Experiment No. 1
$(2E)$-1-{4-[5-(prop-1-en-3-yl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIa)
$(2E)$-1-{4-[5-(prop-1-en-3-yl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIa) was prepared by refluxing a mixture of $(2E)$-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (Ia) and allylisothiocynate (IIa) and in acetone medium for 4 hours on water bath. The remaining solvent was distilled off. Separated Yellow crystals were washed with petroleum ether. These yellow crystals on basification with dilute ammonium hydroxide solution giving pale yellow crystals and recrystallized with aqueous ethanol.
Yield 82%, M.P. – 184°C

Similar method has been adopted for the synthesis of remaining members of the series (IIIb to IIIe).

Reaction Scheme:

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\begin{align*}
(2E)-1-(4-\text{Substituted thiocarbamidophenyl})-3-(3,4-\text{dimethoxyphenyl})\text{prop-2-en-1-one} \\
+ \quad \text{Substituted Isothiocynate} \\
\text{Acetone} \\
(2E)-1-[4-(5-\text{Substituted-2,4-dithiobiureto})\text{phenyl}]-3-(3,4-\text{dimethoxyphenyl})\text{prop-2-en-1-one} \\
(\text{Va-e})
\end{align*}
\]

Where $R_2 =$ -allyl, ethyl, -t-butyl, -phenyl, -p-cl-phenyl

Data Analysis:
$(2E)$-1-{4-[5-(prop-1-en-3-yl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIa)
Pale Yellow solid, C$_{22}$H$_{23}$N$_3$O$_3$S$_2$, Yield 82%, M.P. 184°, % Composition-found(calculated) C-59.02(59.84), H-5.47(5.25), N-9.12(9.52), O-10.50(10.87), S-15.09(14.52), FTIR (KBr) ν cm$^{-1}$ 3012.21 (Ar C-H stretching), 1154.26-1148.95 (C=S stretching), 3352.29-3315.28 (NH Stretching), 1027.45 (C-O-CH$^3$ Strching), 1667.19 (C=O Stretch amido), 1578.36 (N-H Bend); $^1$H NMR (400 MHz CDCl$_3$, δ ppm) singlet of 3H of NH at δ 3.51, 4.01,
8.40 ppm, singlet of 6H of -OCH₃ at δ 3.79, 3.80 ppm, doublet of 2H of -CH=CH- at δ 2.48, 3.74 ppm, multiplets of 7 H of ph δ 6.64-7.81 ppm, peentate of 1H, doublet 2H and doublet of 2H of allyl at δ 2.54, 1.82 and 2.43 ppm respectively Mol. Wt.: 441.

(2E)-1-[4-(5-ethyl-2,4-dithiobisureto)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIb)
Yellow solid, C₁₉H₁₉N₂O₂S₂, Yield 85%, M.P. 187°C, % Composition found (calculated) C 58.02(59.72), H 5.62(5.40), N-9.88(9.78), S-11.02(11.07), FTIR (KBr) ν cm⁻¹: 3005.22 (Ar C-H stretching), 1152.85 (C=O-CH₃), 1589.08 (N-H Bend); ¹H NMR (400 MHz CDCl₃ δ ppm) singlet of 3H of NH at δ 3.40, 3.67, 8.21 ppm, singlet of 6H of -OCH₃ at δ 3.60, 3.62 ppm, doublet of 2H of -CH=CH- at δ 2.50, 3.74 ppm, Multiplets of 7 H of ph δ 6.67-7.91 ppm and quartet of 2H and triplet of 3H of ethyl at δ 1.45 and 1.32 respectively Mol. Wt.: 429.

(2E)-1-[4-(5-(2-methylprop-2-yl)-2,4-dithiobisureto)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIc)
Dark Yellow solid, C₁₉H₁₇N₂O₂S₂, Yield-79%, M.P. 192°C, Composition found (calculated) C 60.27(60.37), H-6.01 (5.95), N-9.20 (9.18), S-13.38 (13.43), FTIR (KBr) ν cm⁻¹: 3030.10, 3051.12, 3066.13 and molecular ion i.e. molecular weight is 457.

(2E)-1-[4-(5-(4-chlorophenyl)-2,4-dithiobisureto)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIe)
Yellow solid, C₁₉H₁₅N₂O₂S₂Cl, Yield-81%, M.P. 189°C, Composition found (calculated) C 58.80(58.54), H 4.93 (4.85), N-8.60 (8.80), S-13.18 (13.43), FTIR (KBr) ν cm⁻¹: 3375.52, 3070.46 (Ar C-H stretching), 1672.09 (C=O Stretch amid), 1589.23 (N-H Bend); ¹H NMR (400 MHz CDCl₃ δ ppm) singlet of 3H of NH at δ 3.47, 3.57, 8.13 ppm, Singlet of 6H of CH₃ δ 3.81, 3.86 ppm, doublet of 2H of -CH=CH- at δ 2.50, 3.64 ppm, Multiplets of 7 H of ph δ 6.62-7.70 ppm, singlet of 9H-CH₃ at δ 1.38 ppm, ESI-MS (m/z) m/z+=303.10, 305.12, 306.13 and molecular ion i.e. molecular weight is 477.

PHARMACOLOGICAL STUDIES
Antimicrobial Activity
All the synthesized compounds (IIIa) to (IIIe) were screened for their in vitro antibacterial activity against Illarious microorganisms such as gram positive Staphylococcus aureus, gram negative Escherichia coli by Disc diffusion method was performed using Nutrient agar medium. Each compound was tested at concentration 50 µg/mL in DMSO. The zone of inhibition of tall the synthesized compounds were measured after 24 h incubation at 37°C. Standard drug used to compare the activity was Ciprofloxacin (25 µg/mL).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Diameter of zone of inhibition (mm)</th>
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<tbody>
<tr>
<td></td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>IIa</td>
<td>7.4 ± 0.1</td>
</tr>
<tr>
<td>IIb</td>
<td>5 ± 0.2</td>
</tr>
<tr>
<td>IIc</td>
<td>7 ± 0.2</td>
</tr>
<tr>
<td>IIId</td>
<td>14 ± 1.1</td>
</tr>
<tr>
<td>IIe</td>
<td>11 ± 1.1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>17 ± 0.8</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

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In the present research of synthesis of compounds (IIIa-IIIe), percentage of yield of compound (IIIb) is highest i.e. 85%. Variation in the yield of each compound is due to substitution at Nitrogen in the alky/aryl thiocynate (IIa-e). It is also observed that, change in the substituent at nitrogen leads not only the yield of product but also it affects the melting point and antibacterial activities against the gram positive and gram negative bacteria more specially, Escherichia coli and Staphylococcus aureus respectively. IIIc and IIId active against E. Coli while IIIc and IIIe are active against S. Coccus aureus.

CONCLUSION

Among synthesized series of compounds of 2,4-dithiobisures i.e. (IIIa-IIIe), it can conclude that compound (IIIc) and (IIIe) displayed the excellent anti-microbial results in compare with the ciprofloxacin as a standard drug. After studying the toxicities of the (IIIc) and (IIIe), these compounds may be act as good drugs for the living beings.

REFERENCES