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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 conIIIentional 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 isothio -cynates **(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-thidiazines[12-18]. 1,3,5-thidiazines 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/arylisothiocynates **(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].

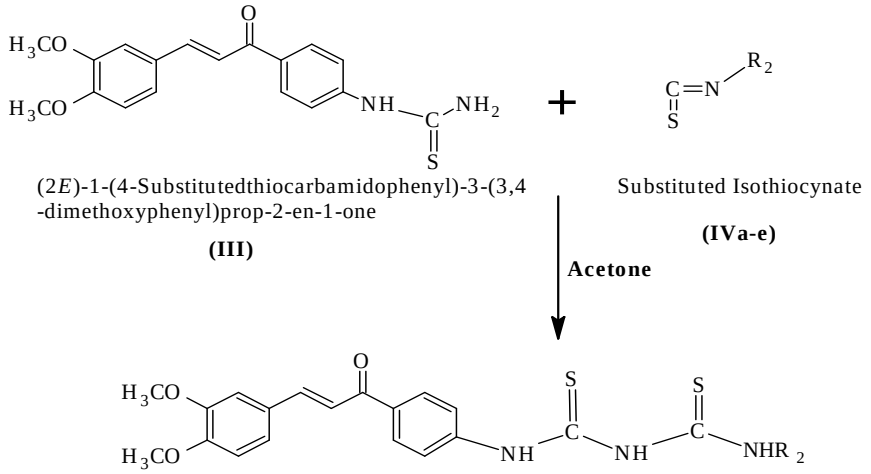
Method:
Method employed in the present experiments for the synthesis of various substituted 2,4-dithiobiuerto based chalcones is conventional refluxing under water bath for different hours for different experiments**.**

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 AIIIANCE 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
(2*E*)-1-{4-[5-(prop-1-en-3-yl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIa)
(2*E*)-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. – 184^0C

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

Reaction Scheme:



(2*E*)-1-(4-Substitutedthiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one

(III)

Substituted Isothiocynate

(IVa-e)

(2*E*)-1-[4-(5-Substituted-2,4-dithiobiureto)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one

(Va-e)

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

Reaction Scheme

Data Analysis:
(2*E*)-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, $C_{22}H_{23}N_3O_3S_2$, 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**-3012.21 (Ar C-H stretching), 1154.26-1148.95 (C=S stretching), 3352.29-3315.28 (NH Stretching), 1027.45 (C-O-CH_3Strching), 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,

8.40ppm, singlet of 6H of -OCH_3 at δ 3.79, 3.80ppm , doublet of 2H of -CH=CH- at δ 2.48, 3.74ppm, multiplets of 7 H of ph δ 6.64-7.81ppm, peentate of 1H, doublet 2H and doublet of 2H of allyl at δ 2.54, 1.82 and 2.43ppm respectively Mol. Wt.:441.

(2E)-1-[4-(5-ethyl-2,4-dithiobiureto)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIb)
Yellow solid, $C_{21}H_{23}N_3O_3S_2$, Yield 85%, M.P. 187, % Composition-found(calculated) C-58.02(59.72), H-5.62(5.40), N-9.88(9.78), O-11.02(11.17), S-15.08(14.93), **FTIR (KBr) ν cm**-3005.22 (Ar C-H stretching), 1162.35-1152.85 (C=S stretching), 3355.46-3332.08 (NH Stretching), 2018.01 (C-O-CH_3Strching), 1672.09 (C=O Stretch amido), 1589.08 (N-H Bend); **^{1}H NMR (400 MHz $CDCl_3$ δ ppm)** singlet of 3H of NH δ 3.40, 3.67, 8.21ppm, singlet of 6H of -OCH_3 at δ 3.60, 3.62ppm, doublet of 2H of -CH=CH- at δ 3.37, 3.48ppm , multiplets of 7 H of ph δ 6.67-7.91ppm and quartet of 2H and triplet of 3H of ethyl at δ 1.45 and 1.32 respectively Mol. Wt.:429.

(2*E*)-1-{4-[5-(2-methylprop-2-yl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIc)
Dark Yellow, $C_{23}H_{27}N_3O_3S_2$, Yield-79%, M.P. 192^{o}C, Composition-found(calculated) C-60.27 (60.37), H-6.01 (5.95), N-9.20 (9.18), S-14.08 (7.08), FTIR (KBr) ν cm-3004.80 (Ar C-H stretching), 1145.64, 089.71 (C=S stretching), 3380.98, 3371.34 (NH Stretching), 1027.99 (C-O-CH_3Strching), 1658.67 (C=O Strech amido), 1589.23 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) Singlet of 3H of NH at δ 3.47, 3.57, 8.13ppm, Singlet of 6H of CH_3 δ 3.81, 3.86ppm, doublet of 2H of -CH=CH- at δ 2.50, 3.64ppm, Multiplets of 7 H of ph δ 6.62-7.70ppm, singlet of 9H-CH_3at δ 1.38ppm, ESI-MS (m/z) m/z+=303.10, 305.12, 306.13 and molecular ion i.e. molecular weight is 457.

(2*E*)-1-{4-[5-(2-methylprop-2-yl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIc)
Dark Yellow, $C_{25}H_{23}N_3O_3S_2$, Yield-81%, M.P. 189^{o}C, Composition-found(calculated) C-62.84 (62.87), H-4.93 (4.85), N-8.60 (8.80), S-13.38 (13.43), FTIR (KBr) ν cm-3070.46 (Ar C-H stretching), 1150.01,1089.71 (C=S stretching), 3379.05 (NH Stretching), 1027.99 (C-O-CH_3Strching), 1658.67 (C=O Stretch amido), 1589.23 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) 3H of -NH at 3.49ppm, 8.14ppm, singlet of 6H of -OCH_3 at 3.84ppm, 3.87ppm, doublet of 2H –CH=CH- at 2.51ppm, 3.80ppm, Multiplets of 11 H of ph at 6.63-7.71, ESI-MS (m/z) 303.1, 303.12, 479.15 and molecular ion i.e. molecular weight is 477**.**

(2*E*)-1-{4-[5-(4-chlorophenyl)-2,4-dithiobiureto]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIe)
Dark yellow solid, $C_{22}H_{22}N_3O_3S_2Cl$, Yield 78%, M.P. 180, % Composition-found(calculated) C-58.80(58.54), H-4.28(4.33), N-8.42(8.21), O-9.68(9.37), S-6.97(6.92), **FTIR (KBr) ν cm**-3082.16 (Ar C-H stretching), 1148.54-1156.25 (C=S stretching), 3370.15 (NH Stretching), 1029.01 (C-O-CH_3Strching), 1685.71 (C=O Stretch amido), 1591.25 (N-H Bend); **^{1}H NMR (400 MHz $CDCl_3$ δ ppm)** singlet of 3H of –NH at δ 3.45, 310, 8.13ppm, singlet of 6H of -OCH_3 at δ 3.71, 3.68ppm, doublet of 2H of -CH=CH- at δ 2.42, 3.75ppm and multiplets of 11 H of ph at δ 6.64-7.7.70ppm, Mol. Wt.:511.5.

PHARMACOLOGICAL STUDIES

Antimicrobial Activity

All the synthesized compounds **(IIIa)** to **(IIIe)** were screened for their *in Vitro* antibacterial activity against IIIarious 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).

	Diameter of zone of inhibition (mm)			
	Escherichia coli		***Staphylococcus aureus***	
Compounds	**25mg/ml**	**50mg/ml**	**25mg/ml**	**50mg/ml**
IIIa	7±0.1	9 ±1	10 ±0.6	11 ±1.0
IIIb	5 ±2.0	5 ±1.0	--	--
IIIc	7 ±2.0	13 ±2.0	11±1	16±1
IIId	14 ±11	15 ±2.0	9±2.0	11 ±1.5
IIIe	11 ±1.0	11 ±1.0	8 ±1.0	13 ±1.0
Ciprofloxacin	17 ±08	26 ±	19 ±11	28 ±13

RESULTS AND DISCUSSION

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-dithiobiurets 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.

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