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Design, Synthesis, Characterization and Anti-Microbial Screening of Some Novel Thiocarbamidochalcones

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ABSTRACT

Interactions of (2*E*)-1-(4-chlorophenyl)-3-(3,4 dimethoxyphenyl)prop-2-en-1-one with various substituted thioureas such as thiourea, N-phenylthiourea, 2-chlorophenylthiourea, 3-chlorophenylthiourea and 4-chlorophenylthiourea in presence of isopropanol as a medium. The products isolated in these reactions were characterized on the basis of conventional elemental analysis, chemical characteristics and spectral data. All the synthesized compounds screened against various microorganisms such as gram positive *Staphylococcus aureus*, gram-negative *Escherichia coli*. Ciprofloxacin was used as a standard drug for the antimicrobial screening.

Keywords: (2*E*)-1-(4-chlorophenyl)-3-(3,4 dimethoxyphenyl)prop-2-en-1-one, substituted thioureas, isopropanol, antibacterial, ciprofloxin etc.

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INTRODUCTION

(2*E*)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-oneis an chalcone derived from 4-chloroacetophenone with 3,4-dimethoxyaldehydes in NaOH and ethanol. Chalcones are well known very potent intermediates[1] for synthesizing various heterocyclic compounds as well as for their various biological activities. The compounds with the chalcone backbone have been reported to possess various biological activities such as anti-mitotic[2,7], inhibition of chemical mediators release[3], anti-inflammatory[4], anti-vascular[4,5], antii-cancer[5,7,8,9], analgesic[7], inhibition of leukotriene B4[7,8], antimicrobial[9], inhibition of tyrosinase and inhibition of aldose reductase activities[9]. Chalcones had proved subject of great attention for due to numerous reasons[9]; their ease of synthesis, simplest intermediate in synthetic chemistry[1-5], potent biologicalactivities[1-11].

Literature study displayed chalcones[10-14] gives different reactions with different types of reagents, hence reflects overall diverse scope. Reactivity of chalcone changes with change in the medium *viz*, acidic, basic and neutral. Acidic and basic medium reactions are reported the synthesis of different biological potent heterocylic compounds. The reactions of halochalcones in a neutral medium proceeds with the orbital interaction of halo group with the thioureas. Holding the sense of information in mind, it is decided to investigate the interactions of (2*E*)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one with different thioureas to synthesize the novel series of thiocarbamides (2*E*)-1-(4-substitutedthiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one. All the synthesized substitutedthiocarbamides[14-16] are important class of compounds which posses antibacterial[14], fungicial[15], anesthetic, antiviral activities[14,16]. These are widely used commercial pesticides mainly herbicides[12-15]. Believing all the above objectives in mind, it was planned to carry out the interaction of chalcones and different substituted thioureas.

MATERIALS AND METHOD

Materials

All chemicals used were of Mercks Millipore (Indian made). (2*E*)-1-(4-chlorophenyl)-3-(3, 4-dimethoxyphenyl)prop-2-en-1-one were prepared by known literature method[2].

Method

Method employed in the present experiments for the synthesis of various substituted thiocarbamidochalcones 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. 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 AVANCE 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 were checked on silica gel – G plates by TLC with layer thickness of 3mm.

Experiment No. 1

(2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIa)

A mixture of (2E)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one **(I)** 5.996gm (0.01982M) and thioureas **(IIa)** 1.506gm (0.01982M) was refluxed over water bath in isopropanol (40ml) medium for 5 hours. After the new product was found to be gradually separated out, which on basification with dilute sodium bicorbonate afforded white crystals. It was recrystallized with aqueous ethanol.

Yield- 96% M.P. - 198^0C

Experiment No.2

(2*E*)-1-[4-(3-phenylthiocarbamido)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIb)

A mixture of (2E)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one **(I)** 5.996gm (0.01982M) and 1-phenylthiourea **(IIb)** 3.012gm (0.01982M) was refluxed over water bath in isopropanol (40ml) medium for 3-4 hours. After the new product was found to be gradually separated out, this on basification with dilute sodium bicorbonate afforded white crystals. It was recrystallized with aqueous ethanol.

Yield- 89% M.P. - 192^0C

Experiment No.3

(2*E*)-1-{4-[3-(2-chlorophenyl)thiocarbamido]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIc)

A mixture of (2E)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one **(I)** 5.996gm (0.01982M) and 1-(2-chlorophenyl)thioureas **(IIc)** 3.69gm (0.01982M) was refluxed over water bath in isopropanol (40ml) medium for 4 hours. After the new product was found to be gradually separated out, which on basification with dilute sodium bicorbonate afforded white crystals. It was recrystallized with aqueous ethanol.

Yield- 90% M.P. - 182^0C

Experiment No. 4

(2E)-1-{4-[3-(3-chlorophenyl)thiocarbamido]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIId)

A mixture of (2E)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one **(I)** 5.996gm (0.01982M) and 1-(3-chlorophenyl)thioureas **(IId)** 3.69gm (0.01982M) was refluxed over water bath in isopropanol (40ml) medium for 4 hours. After the new product was found to be gradually separated out, which on basification with dilute sodium bicorbonate afforded white crystals. It was recrystallized with aqueous ethanol.

Yield- 88% M.P. - 185^{0}C

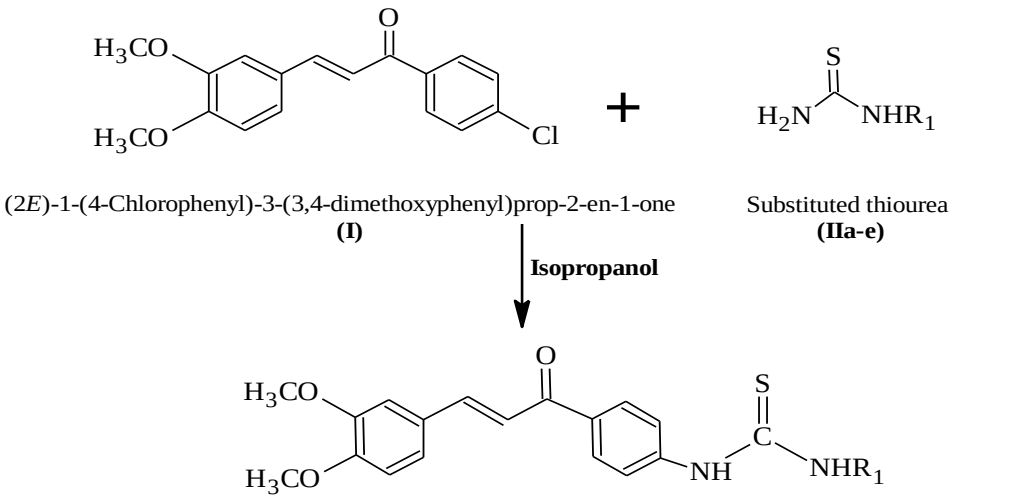
Experiment No.5

(2E)-1-{4-[3-(4-chlorophenyl)thiocarbamido]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIe)

A mixture of (2E)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one **(I)** 5.996gm (0.01982M) and 1-(4-chlorophenyl)thioureas **(IIe)** 3.69gm (0.01982M) was refluxed over water bath in isopropanol (40ml) medium for 5 hours. After the new product was found to be gradually separated out, this on basification with dilute sodium bicorbonate afforded white crystals. It was recrystallized with aqueous ethanol.

Yield- 83% M.P. - 187^{0}C

Reaction Scheme:



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

Substituted thiourea **(IIa-e)**

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

(IIIa-e)

Where R^1 = H, -ph,-2-cl-ph,-3-cl-ph,4-cl-ph

Scheme-I

RESULTS AND DISCUSSION

Spectral data obtained from the present research support the formation of designed or target products. Spectral characterization and pharmacological study results of all the synthesized compounds are also given below:

Spectral Characterization-

(2E)-1-(4-thiocarbamidophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIa)

Yellow solid, $C_{18}H_{18}N_2O_3S$, Yield 94%, M.P. 186, % Composition-found(calculated) C-6.07(63.14), H-5.25(5.30), N-8.23(8.18), S-9.33(9.36), FTIR (KBr) ν cm-3032.30-3118.03 (Ar C-H stretching), 1137.23 (C=S stretching), 3460.22-3444.12 (NH_2 Stretching), 1028 (C-O-CH_3Strching), 1667.82 (C=O Strech amido), 1587.23 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) 9.59 amido, 8.28, 3.54 (s, 3H, NH), 3.32(s, 6H, CH_3), 2.60, 3.74(d, 2H, CH), 6.543-7.90 (m,7 H of ph)ESI-MS (m/z) 303.10(M+), Mol. Wt.:342.41.

(2*E*)-1-[4-(3-phenylthiocarbamido)phenyl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIb)

Shining Yellow solid, $C_{24}H_{22}N_2O_3S$, Yield-89%, M.P. 192^oC, Composition-found(calculated) C-67.92 (68.84), H-5.28 (5.32), N-6.62 (6.68), S-7.65 (7.69), FTIR (KBr) ν cm-3055.03-3035.75 (Ar C-H stretching), 1091.63 (C=S stretching), 3286.48 (NH Stretching), 1014.49 (C-O-CH_3Strching), 1675.08 (C=O Strech amido), 1593.09 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) 9.69 amido, 8.17 (s, 2H, NH), 3.42 (s, 6H, CH_3), 2.53, 3.89 (d, 2H, CH), 6.63-8.17 (m,12 H of ph)ESI-MS (m/z) 303.10(M+), Mol. Wt.:418.50.

(2*E*)-1-{4-[3-(2-chlorophenyl)thiocarbamido]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIIc)

Dark Yellow solid, $C_{24}H_{21}N_2O_3SCl$, Yield-90%, M.P. 182^oC, Composition-found(calculated) C-63.60 (63.65), H-4.65 (4.67), N-6.15 (6.20), S-6.88 (7.08), Cl-7.80(7.84), FTIR (KBr) ν cm-3267.19-3186.18 (Ar C-H stretching), 1153.35 (C=S stretching), 3415.70 (NH Streching), 1020 (C-O-CH_3Strching), 1658.67 (C=O Strech amido), 1620.09 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) 9.73 amido, 8.14 (s, 2H, NH), 3.42 (s, 6H, CH_3), 2.54, 3.87 (d, 2H, CH), 6.9-7.71 (m,12 H of ph) ESI-MS (m/z) 303.10(M+), Mol. Wt.:443.

(2E)-1-{4-[3-(3-chlorophenyl)thiocarbamido]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (IIId)

Yellow solid, $C_{24}H_{21}N_2O_3SCl$, Yield-88%, M.P. 185^oC, Composition-found(calculated) C-63.32 (63.65), H-4.80 (4.67), N-6.44 (6.20), S-7.14 (7.08), Cl-7.76 (7.84), FTIR (KBr) ν cm-3254.23-3125.21 (Ar C-H stretching), 1165.21 (C=S stretching), 3350.12 (NH Streching), 1034.37 (C-O-

CH_3Strching), 1665.25 (C=O Strech amido), 1647.05 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) 9.68 amido, 8.09 (s, 2H, NH), 3.51 (s, 6H, CH_3), 2.64, 3.83 (d, 2H, CH), 6.8-7.71 (m,12 H of ph) ESI-MS (m/z) 303.10(M+), Mol. Wt.:443.

(2E)-1-{4-[3-(4-chlorophenyl)thiocarbamido]phenyl}-3-(3,4-dimethoxyphenyl)prop-2-en-1-one(IIIe)

Yellow solid, $C_{24}H_{21}N_2O_3SCl$, Yield-83%, M.P. 187^{o}C, Composition-found(calculated) C-6.35 (63.65), H-4.81 (4.67), N-6.32 (6.20), S-7.18 (7.08), Cl-7.74 (7.84), FTIR (KBr) ν cm-3257.23-3352.26 (Ar C-H stretching), 1647.05 (C=S stretching), 3352.29 (NH Streching), 1024.36 (C-O-CH_3Strching), 1655.26 (C=O Strech amido), 1590.65 (N-H Bend); 1H NMR (400 MHz $CDCl_3$ δ ppm) 9.68 amido, 8.09 (s, 2H, NH), 3.62 (s, 6H, CH_3), 2.54, 3.78 (d, 2H, CH), 6.8-7.74 (m,12 H of ph) ESI-MS (m/z) 303.10(M+), Mol. Wt.:443.

Pharmacological Studies-

Antimicrobial Activity

All the synthesized compounds **(IIIa)** to **(IIIe)** were screened for their *in vitro* antibacterial activity against various 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 all the synthesized compounds were measured after 24 h incubation at 37^{0}C. Standard drug used to compare the activity was Ciprofloxacin(25 µg/mL).

Table 1: Antibacterial results

	Diameter of zone of inhibition (mm)			
	Escherichia coli		***Staphylococcus aureus***	
Compounds	**25mg/ml**	**50mg/ml**	**25mg/ml**	**50mg/ml**
IIIa	9 ±10	17 ±08	7 ±06	12 ±10
IIIb	12 ±12	21 ±09	11 ±11	21 ±10
IIIc	13 ±08	21 ±	12 ±12	22 ±12
IIId	10 ±11	18 ±	6 ±07	14 ±12
IIIe	8 ±09	13 ±	8 ±13	18 ±10
Ciprofloxacin	17 ±08	26 ±	19 ±11	28 ±13

In the present research of synthesis of compounds **(IIIa-IIIe)**, percentage of yield of compound **(IIIa)** is highest i.e. 96%. Variation in the yield of each compound is due to substitution at Nitrogen in the thiourea. 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 grame possive and gram negative bacteria more specially, ***Escherichia coli and Staphylococcus aureus*** respectively.

CONCLUSION

In all the synthesized compounds **(IIIa-IIIe**), it can conclude that compound **(IIIb)** and **(IIIc)** displayed the excellent anti-microbial results in compare with the ciprofloxacin as a standard drug. After studying the toxicities of the **(IIIb)** and **(IIIc)**, these compounds may be act as good drugs for the living beings.

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