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Microwave assisted synthesis of 4,6- diphenyl substituted thiazine derivatives and its characterisation

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ABSTRACT

Hetero atom containing compounds possess considerable attention in the design of biologically active molecules and organic materials. In this study 4,6-diphenyl substituted thiazine derivatives were prepared by two steps. In a first step substituted chalcone were synthesized by direct condensation between substituted benzaldehyde with substituted acetophenone, using 40% sodium hydroxide in PEG-400 as a solvent. In a second step substituted chalcone derivatives were allowed to react with thiourea in the presence of sodium hydroxide in ethanol as catalyst which gives thiazine as product. The substituted chalcones and thiazine derivatives were synthesized by both conventional and microwave irradiation methods. The progress of the reaction was monitored by TLC and separated the compound using column chromatography. Structures of synthesized compounds were confirmed by UV, FT-IR, ^{1}H-NMR and Mass spectral analysis. The anti-microbial activities of compounds have also been tested using Minimum Inhibitory concentration (MIC) method with two different micro-organisms *Staphyloccocous aures* (MTCC3381), and *Escheriochia coli* (MTCC739). The results of the antimicrobial activity clearly shown that the substituted 4,6-diphenyl substituted thiazine derivatives has excellent inhibiting nature against both types of bacteria than corresponding chalcone derivative.

KEYWORDS

Chalcones;
Thiazine;
Antimicrobial activity;
PEG–400;
Thio-urea;
MWI.

INTRODUCTION

Thiazine is a Six membered Hetero cyclic ring system which contains two hetero atoms (N&S) placed at1,3 – positions[1]. Structure of 1,3 thiazine ring substituted with two phenyl rings at 4,6th position possesses an N-C-S linkage,that is believed to be very useful units in the fields of medicinal and pharmaceutical chemistry[2] and have been reported to exhibit a variety of biological activities like Antibacterial[3], Anti-fungal[4], Anti-tubercular[5], Anti-Histamine, Anti-inflammatory[6] and anti-microbial[7] activities etc. In Previously Chalcones (benylidene acetophenone or 1,3diphenyl-2-propen-1-one)were prepared by Claisen Schmidt condensation of substituted benzaldehyde with substituted acetophenone in presence of suitable condensing agent (ethanolic NaOH/KOH)[8,9,10].

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The presence of a reactive α, β- unsaturated keto group in substituted chalcones is found to be responsible for their Biological activities[11,12]. Here with Green Chemistry approach,simple and convenient method for the synthesis of Substituted chalcones using poly ethylene glycol (PEG) has been found to be an interesting solvent system[13,14]. because PEG-400 is an environmentally benign reaction solvent, it is inexpensive, potentially recyclable and water soluble, which facilitates its removal from there action product.

Microwave-assisted synthesis is an eco-friendly and efficient method of synthesis of organic compounds as compared to the conventional method of synthesis. In this method, reaction occurs more rapidly, safely and with higher chemical yields due to which this method becomes superior to the conventional method. The conventional method, requiring a longer reaction time and larger quantities of solvents and reagents, causes environmental pollution and contributes to the health hazards.

Based on the careful analysis of the literature, present investigation focused on the PEG-400, the series of chalcones and diphenyl substituted 1,3 thiazine compounds were synthesized by both conventional and microwave irradiation methods.

The synthesized compounds were characterized on the basis of UV-Visible, FTIR, ^{1}HNMR and mass spectral data. All the compounds were screened for their in vitro antibacterial activity against Gram positive strains (Staphylococcus aureus) and Gram negative strains (Escherichia coli) respectively[17].

EXPERIMENTAL

Methods and Materials

The chemicals 4-hydroxy acetophenone(1),4-hydroxy benzaledehyde (2), PEG-400(3) thio urea (5), and sodium hydroxide were obtained from Avra chemicals, Hyderabad and were used as such without further purification. Silica gel (TLC and Column grade) were purchased from Merck. The solvents were purified as per the standard procedure reported elsewhere.

FTIR spectra (KBr pellets) were measured using Alpha Bruker FTIR instrument scanning with the entire region of 4000 - 400 cm^{-1} with typical resolution of 1.0 cm^{-1}. UV-Visible spectra were also recorder using Alpha Bruker UV spectrophotometer. The NMR spectra of the compounds have been recorded on Bruker AV400 spectrometer operating at 400 MHz for recording ^{1}H spectra in DMSO solvent using TMS as internal standard. Mass spectra have been recorded on SHIMADZU spectrometer using chemical ionization technique. Melting points of all synthesized compounds have been determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected. Microwave reactions are carried out commercially available IFB domestic microwave oven having a maximum power output of 110W operating at 450Hz.

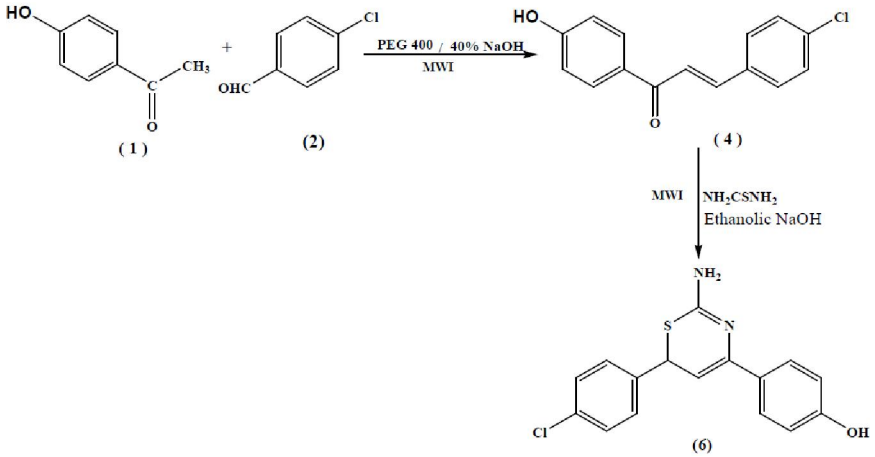
Synthesis of 3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (4)

Method – A (Conventional method)

A mixture of 4-hydroxy acetophenone (1) (0.01mol) and 4-chlorobenzaldehyde (2) (0.01mol) and NaOH (0.02 mol) were stirred in PEG-400 (20mL) as solvent at 65°C for an hour. The completion of the reaction was monitored by TLC and the crude mixture was worked up in ice-cold water (100mL). The product was separated out and filtered. The filtrate was evaporated to dryness to remove water leaving behind PEG-400. The recovered PEG-400 has been utilized for the synthesis of chalcones. Synthesized compounds were recrystallized from ethanol to afford pure compound (5). (Yield – 82% & melting point: 100-104 °C).

Method - B (Micro wave irradiation method)

A mixture compounds 1(0.01mol) and 2 (0.01mol) and NaOH (0.02mol) were grinded in to the mortar. Then it was mixed with 10mL of PEG – 400. The mixed compounds were taken in a 100mL beaker and it was irradiated in a microwave oven for the 3-5 minutes at 110W operating at 2450Hz at 30 seconds of intervals. After completion of reaction as followed by T.L.C examination, cold water was added to the reaction mixture and neutralized by dil. HCl. The solid product was obtained, which was filtered, dried and crystallized from an ethanol.



Scheme 1 : Synthesis of 4,6- diphenyl substituted thiazine derivative

The filtrate was evaporated to dryness to remove water leaving behind PEG-400. (Yield – 96% & melting point: 101-105°C).

Synthesis of 4-(2-amino-6-(4-chlorophenyl)-6H-1,3-thiazin-4-yl)phenol (6)

i) Conventional method

A mixture of compound 4 (0.01mol) and thio urea 5 (0.01 mol) were dissolved in ethanolic sodium hydroxide (10 ml) was stirred about 2-3 hours with a magnetic stirrer. This was then poured into 100 ml of cold water with continuous stirring for an hour and then kept in refrigerator for 24 hours. The crude mixture was poured into ice cold water and neutralized by an acid. The precipitate obtained was filtered, washed and recrystallized. The completion of the reaction was monitored by TLC. The solid product was obtained.(Yield: 62% & melting point: 131-134°C)

ii) Microwave method

A mixture of compound 4 (0.01mol) and thio urea 5 (0.01 mol) and sodium hydroxide (0.005mol) were mixed thoroughly in mortar. Then it was dissolved into minimum amount of ethanol. The mixed compounds were taken in a 100mL beaker and it was irradiated in a microwave oven for the 5-7 minutes at 110 W operating at 2450Hz at 30 seconds of intervals. The completion of the reaction was monitored by TLC and the crude mixture was worked up in ice-cold water (100 mL). Acidified with Dil. HCl, the product was separated out and filtered. (Yield: 89% & 132-135°C)

RESULTS AND DISCUSSION

Spectral details of 3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (4)

Melting Point	: 101-105°C
UV-Visible ($\lambda_{max,}$ nm)	: 230(* transition), 345 (* transition) (Figure 1)
FTIR (cm^{-1})	: 3222 (O-H), 3029 (Aromatic C-H str), 2899 (C-H), 1677 (C=O), 1580 (C=C str), 1089 (C-Cl chloro aromatic), 815 (C- H out plane bending) (Figure 2)
^{1}H NMR (ppm)	: 6.25 - 6.54 (2d, 2H, -CH=CH-), 6.95-8.01(m, 8H, Ar-H),11.106 (s, 1H, Ar-OH) (Figure 3)
Mass (m/z)	: Calculated M.W 258.0448. Observed M.W 259.6 (M+1)

Spectral details of 4-(2-amino-6-(4-chlorophenyl)-6H-1,3-thiazin-4-yl)phenol (6)

Melting Point	: 131-134°C9
UV-Visible ($\lambda_{max,}$ nm)	: 227 (* transition), 267 (* transition) (Figure 4)
FTIR (cm^{-1})	: 3064 (NH str.), 3015 (O-H str), 2937(Aromatic C-H str.), 1643 (C=N str.), 1338 (C=C str), 2311(C-S-C str.). (Figure 5)
^{1}H NMR (ppm)	: 9.35(s, 1H, Ar-OH), 7.26 –

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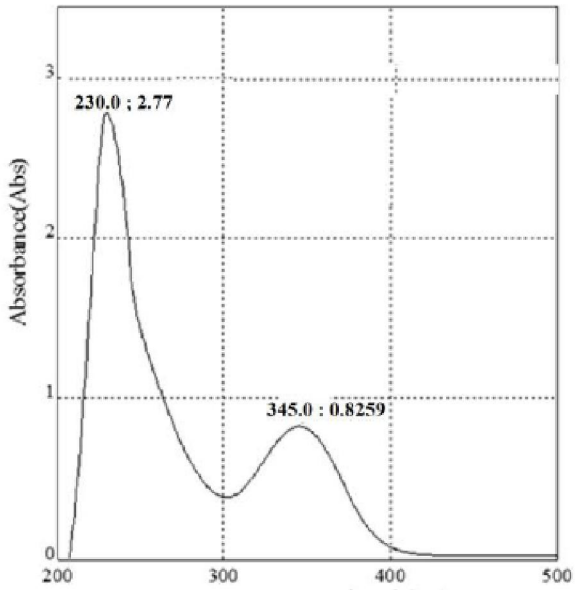

Fig. 1 UV-Vis. spectrum of 3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2- en-1-one

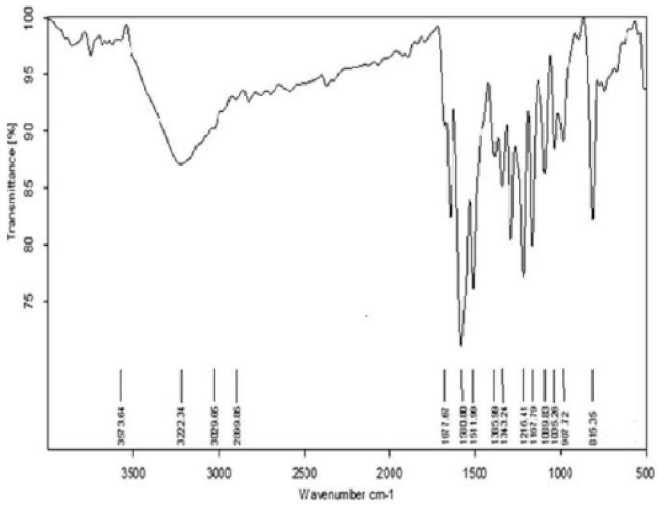

Fig. 2 FTIR spectrum of 3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one

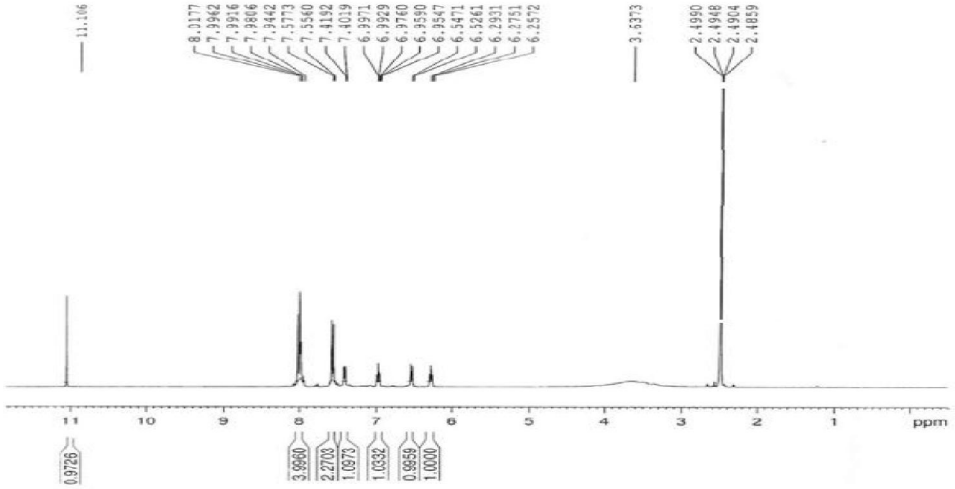

Fig. 3 ^{1}HNMR spectrum of 3-(4-chlorophenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one

8.03 (m, 8H, Ar-H), 6.12(s, 1H, Ethylinic proton), 3.51(s, 2H, amine proton) (Figure 6)

Mass (m/z) : Calculated M.W 317.0, Observed M.W 316.04

Figure (1-3) revealed the UV-Visible, FTIR and ^{1}HNMR spectra of 3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one respectively using compound 1, and 2 in the presence of sodium hydroxide has been shown in the scheme 1. Figure (4-6) revealed the UV-Visible, FTIR and ^{1}HNMR spectra of 4-(2-amino-6-(4-chlorophenyl)-6H-1,3-thiazin-4-yl) phenol respectively using compound 4 with compound 5 in the presence of ethanolic Sodium hydroxide has also been presented in the scheme 1.

UV-Visible and FTIR spectra of compound 4 have been provided a preliminary idea in confirmation the formation of product. According to the UV spectrum, represented in Figure (1), presence of peaks at 230 and 345 nm clearly showed that the compound (5) has -CH=CH- group and hetero atom respectively. According to the FTIR, represented in Figure (2), presence of peak at 1580 cm^{-1} has clearly noticed the utilization of starting materials transforms into the product. Further, the corresponding peaks at 3222, 3029 and 2899, 1677 cm-1 have been related to –OH, C-H aromatic stretching and aliphatic C-H stretching respectively in the compound 4. The concerned mass of compound 4 is in good agreement with the observed (258.0448m/z) and calculated value (259.2 m/z). Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 11.10, 6.95-8.05, and 6.25-6.54 ppm corresponding to the O-H, Ar-H and –CH=CH- protons of compound 4 were mentioned in Figure (3).

UV-Visible and FTIR spectra of compound 6 have provided a preliminary idea in confirmation the formation of product. According to the UV spectrum of compound 6, presence of peaks at 227 and 278 nm has been related to aromatic double bond and hetero atom respectively shown in Figure (4). According to the FTIR, represented in Figure (5), absence of peak at 1677 cm^{-1} clearly observed the complete utilization of starting materials transformed into the product. Further, the corresponding peaks at 3064,

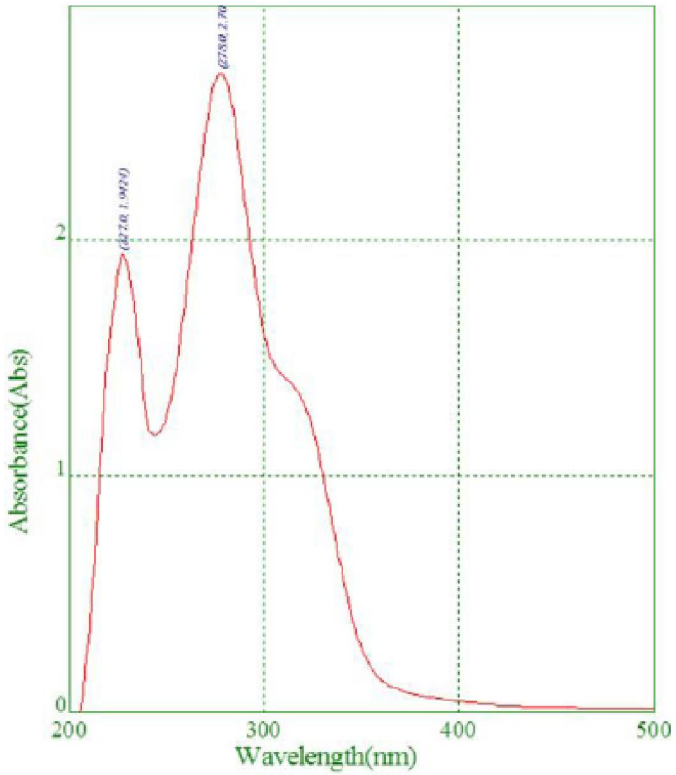

Fig. 4 UV-Vis. spectrum of 4-(2-amino-6-(4-chlorophenyl)-6H-1,3-thiazin-4-yl)phenol

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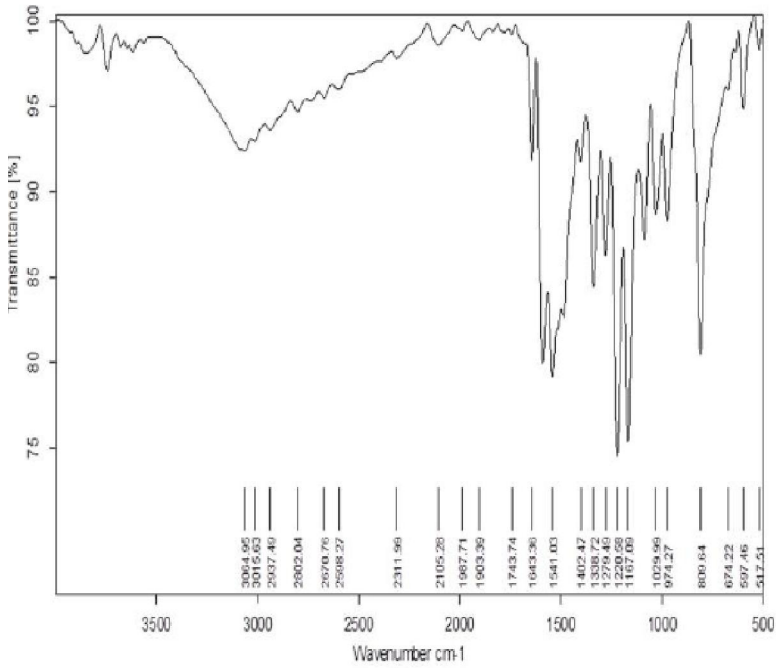

Fig. 5 FTIR spectrum of 4-(2-amino-6-(4-chlorophenyl)-6H-1,3-thiazin-4-yl)phenol

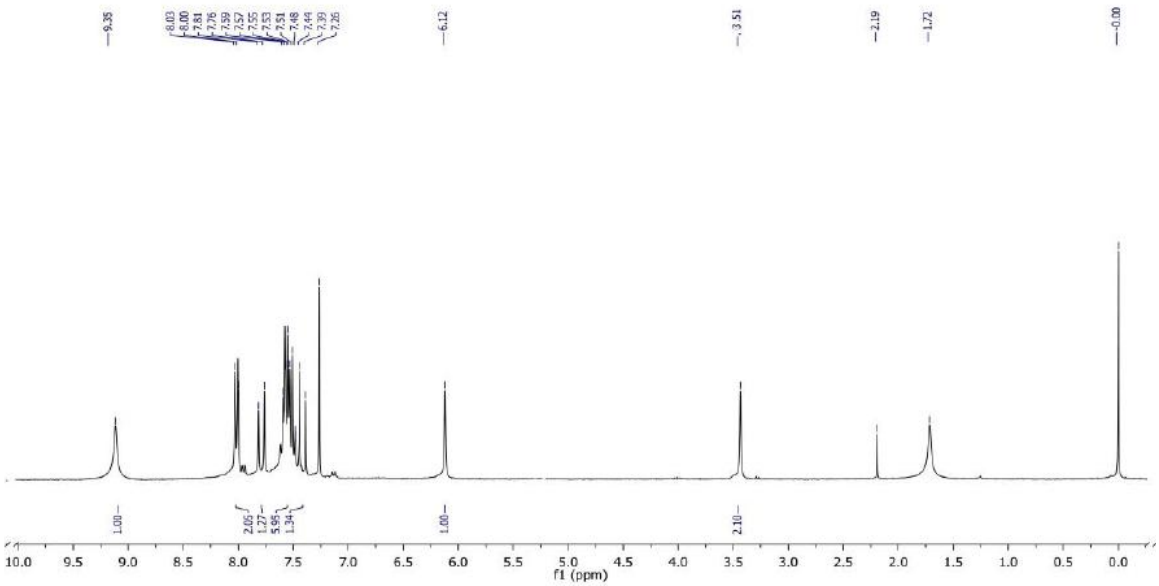

Fig.6 ^{1}HNMR spectrum of 4-(2-amino-6-(4-chlorophenyl)-6H-1,3-thiazin-4-yl)phenol

3015, 2937, 1643 and 1338cm^{-1} for –NH, -OH, C-H aromatic stretching, C=N stretching and C=C stretching vibrations respectively in the compound 6. All such stretching and bending peaks have also been supported for the formation of the product. The concern mass of compound 6 are in good agreement with the observed (316.04 m/z) and calculated value (317.0 m/z). Similarly, proton NMR strongly empowered for the formation of the product by its δ value at 9.35, 7.26-8.03, 6.12 and 3.51ppm corresponding to the O-H, Ar-H, Ethylinic proton, and NH_2 protons of compound 6 were mentioned in Figure (6).

Antimicrobial activity

The minimum inhibitory concentration (MIC), which is considered as the least concentration of the sample which inhibits the visible growth of a microbe was determined by the broth dilution method.

TABLE 1: Sample minimum inhibiting concentration (MIC) (µg/ml)

Compounds	Satphylococcus aureus (S. a)	Escherichia coli (E. c)
4	7.81	15.63
6	3.91	7.81

The compounds 5 and 6 were adopted for broth dilution method to evaluate the MIC values. The MIC values are given in the following table.

CONCLUSTION

In the present work 4,6-diphenyl substituted thiazine derivatives were synthesized successfully by Claisen-Schmidt condensation using both conventional and microwave irradiation methods. Generally most of the researchers have been synthesized chalcones using alcohol as solvent and catalyst like Na-OH or KOH. Synthesis of chalcones by using ethanol or methanol has generated organic solvent as waste and which cannot reuse once again. But, in our work the chalcones have been synthesized using PEG-400 as solvent, which is eco-friendly, inexpensive, water soluble, non-toxic and potentially recyclable.

Synthesizing of diphenyl substituted thiazine derivatives achieved by condensation between the substituted chalcones with thiourea in presence of ethanolic sodium hydroxide by a microwave assisted method.

Synthesizing of chalcones and thiazine compounds via microwave assisted method of reaction; it is shorter reaction time, mild reaction condition, eco-friendly, excellent yield as compared to conventional methods and reduces the use of volatile organic compounds (VOCs) and finally, it is agreement with the green chemistry protocols.

The chemical structures of compounds 4 and 6 have been confirmed using various spectral techniques viz., FTIR, UV-Visible, Mass and 1H-NMR spectra and were found to be in agreement with the chemical structures expected.

The microbial activities substituted chalcones and 4,6-diphenyl substituted thiazine derivatives were checked against the two microbes *Staphylococcus aureus* and *Escherichia coli.* The report of antimicrobial activity clearly showed that, the synthesized compounds of 6 has excellent activity towards the tested bacterial strains of both gram positive and gram negative. This is due to the compounds 6 has Presence Of Phenolic group and hetero atom like N & S, which enhance the Anti-Microbial activity.

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