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GREEN CHEMISTRY APPROACH TO SYNTHESIS OF 4-IODOPHENYL CHALCONES AND THEIR ANTIBACTERIAL ACTIVITY

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Abstract: The styryl-4-iodo phenyl chalcones were synthesized by microwave irradiation method and tested for antibacterial effects against various bacterial strains. The synthesized compounds were characterized using UV, IR, ^{1}H & ^{13}C NMR and MS data. The antibacterial screening of the synthesized compounds were performed in vitro by the Bauer-Kirby disc diffusion method.

I. INTRODUCTION

A number of chalcone compounds having hydroxy, methoxy groups in different position have been reported to possess versatile antimicrobial activity (N. Bhasker & B. Krishna, 2009). Chalcones (1, 3-diphenyl-2-propene-1-one) and related compounds "chalconoids" are those in which two aromatic rings are linked by a reactive keto ethylenic group (–CO–CH=CH–) that forms the central core for a variety of important biological compounds, and known collectively as chalcones. Chalcones has a conjugated double bonds and an entirely delocalized π-electron system on both benzene rings; such system has relatively low redox potentials and have a greater probability of undergoing electron transfer reactions (Patil CB & Mahajan, 2009). Chalcones having an α , β unsaturated carbonyl group are one of the important biocides and versatile synthons for various chemical transformations. Most of the chalcones are highly biologically active with a number of pharmacological and medicinal applications (Saini &A.S.Choudhary, 2005). Chalcones and flavanones are widespread components in all parts of the plants and are important as flower pigments, growth regulators, phytoalexins, animal toxins (Conn, 1981; S. Ghosal & K. R. Chaudhuri, 1975). The growing interest of the synthesis of chalcones and flavanones for the last few years may be easily explained by their pharmacological activities Viz., Anti – bacterial (Delima, 1975), Antiulcer (Kyogoku, 1979), Antifungal (Bhakuni & R. Chatturvedi, 1984), Anticoagulating (Lafon, 1970), Vasodilatory (Pourrian, 1972), Antipepticulcer (Rene & D. Magnolato, 1986), Anti mitotic (Edwards & D. M. Stemerick, 1990), Narcosis Potentiation (Unicler, 1976) and Antileshmanial (Lin, C. Ming, 1999) activites. Anti – psychotics actions, Monoamine oxidize inhibition,Anti-tubercular. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoids (Laks and S. M. Pruner, 1989). Substitution of the flavonoid ring system with prenyl groups would increase their lipophilicity and consequently enhance their interaction withcellular membranes (Baron & K.I. Ragai, 1989).

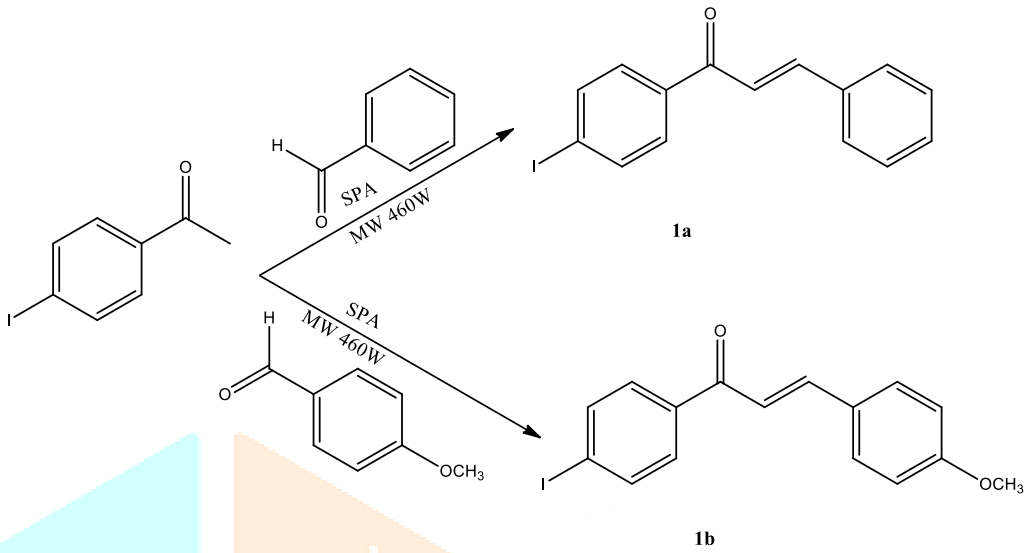
In the claisen-schemidt condensation of chalcone synthesis, (*E*)-1-(4-iodophenyl)-3-phenylprop-2-en-1-one and (*E*)-1-(4-iodophenyl)-3-p-tolylprop-2-en-1-one were prepared by microwave irradiation technique (Sathiyamoorthi & Thirunarayanan, 2013). It has been established on the basis of elemental (C, H, and O) analysis, IR, 1H NMR, MS spectral data and they were screened for antibacterial activities against *S. typhi, S. aureus, K. pneumonia, V. cholera, K. oxytoca, E. coli, S. paratyphi., P. mirabilis, V. parahaemolyticus, S. pyogenes* by the filter paper disc diffusion method.

II RESEARCH METHODOLOGY

All chemicals used were purchased from Sigma-Aldrich and E-Merck chemical companies. Melting points of all chalcones were determined in open glass capillaries on SUNTEX melting point apparatus and are uncorrected. The UV spectra of all synthesized chalcones were recorded in ELICO-BL222 SPECTROMETER (max/nm) in spectral grade methanol. Infrared spectra (KBr, 4000-400cm-1) were recorded on AVATAR-300 Fourier transform spectrophotometer. Bruker AV400 NMR spectrometer operating at 400 MHz has been utilized for recording 1H NMR spectra and 100 MHz for 13C spectra in CDCl3 solvent using TMS as internal standard. Mass spectra were recorded on a SIMADZU GC-MS2010 Spectrometer using Electron Impact (EI) techniques.

2.1 Synthesis of 4-iodophenyl chalcones

An appropriate mixture of aryl methyl ketone (2 mmol) and substituted benzaldehydes (2 mmol) and SiO_2-H_3PO_4 (Ahmed & Rmman, 2007) (0.5 g) taken in 50ml corning glass tube and tightly capped. The reaction mixture was subjected to microwave irradiation for 8-10 minutes in a microwave oven (**Scheme 1**) (LG Grill, Intellowave, Microwave Oven, 160-800W) and then cooled to room temperature. Added 10 mL of dichloromethane, the organic layer has been separated which on evaporation yields the solid product. The solid, on recrystallization with benzene-hexane mixture gives glittering pale yellow solid.



Scheme 1. Synthesis of aryl chalcones using silica-phosphoric acid catalyzed

2.2 Antibacterial Activity

An antimicrobial (Dorlands Medical Dictionary, 2010) is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi or protozoan. These include host defense mechanisms, the location of infection, and the pharmacokinetic and pharmacodynamics properties of the antibacterial (Pankey & Sabath, 2004), Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microstatic). Disinfectants (J. M. Swenson & Thornsberry, 1984) are antimicrobial substances used on non-living objects or outside the body. Antimicrobials include not just antibiotics but synthetically formed compounds as well. The discovery of antimicrobials like penicillin and tetracycline paved way for better health for millions around the world. Before penicillin became a viable medical treatment in early 1940's, no true cure for gonorrhea, strep throat or pneumonia existed. Patients with infected wounds often had to have a wounded limb removed or face death from infection. Now, most of these infections can be cured easily with a short course of antimicrobials. However, with the development of antimicrobials, microorganisms have adopted and become resistant to previous antimicrobial agents. The old antimicrobial technology was based either on poisons or heavy metals, which may not have killed the microbes survive, change and become resistant to the poisons and / or heavy metals. The antibacterial activity of the compound 1a and 1b shows the various zone of inhibition values for the following concentration 100µg/ml, 75 µg/ml, 50 µg/ml and 25 µg/ml. Tetracycline act as the positive control and DMSO (solvent of the compound) act as the negative control.

Inoculum preparation

Exactly 13 g of the nutrient broth was dissolved in 1000 mL of sterile distilled water. The pH of the medium was adjusted to 7.0. For 15 minutes, the conical flask was plugged with non-adsorbent cotton and sterilized at 121oC and 15 lbs/inc2 pressure. After cooling inside a laminar flow, a loopful of fresh bacterial sample was inoculated and incubated in an orbital shaker at 37oC for 24 h. Then the cultures were diluted 1:50 with sterile physiological saline and 0.5 mL of the inoculum (Barry & Creitz , 1984) was used for the preparation of the spread plate.

Preparation of test compound

Exactly 15 mg of the synthesized 4-iodochalcone was dissolved in 1mL of DMSO solvent. Using to find out the antimicrobial activity of the compound on each organism, using 100µmL solution, the discs were impregnated and placed on the Mueller Hinton solidified agar medium (Barry & Creitz , 1984). The antimicrobial activities of the five series of aryl styryl ketone compounds have been studied, by adopting the above procedure, on five microorganisms and the results have been discussed with the available data and clustered column chart in each case.

Antibacterial sensitivity assay

Using well diffusion method Kirby-Bauer (Bauer & Kirby, 1966) disc diffusion technique, antibacterial sensitivity assay was performed. About 0.5 mL of the test bacterial sample was spread uniformly over the solidified Mueller Hinton agar, in each Petri plate using sterile glass spreader. Then the discs with 5mm diameter made up of Whatman No.1 filter paper were taken, impregnated with the solution of the compound and they were placed on the medium using sterile forceps. The plates were incubated for 24 hours at 37°C by keeping the plates upside down to prevent the collection of water droplets over the medium. The plates were visually examined and the diameter values of the zone of inhibition were measured, after 24 h. By repeating the above procedure, triplicate results were recorded and tabulated.

III. RESULTS AND DISCUSSION

3.1 Spectral characterization of (*E*)-1-(4-iodophenyl)-3-phenylprop-2-en-1-one (1a)

M.P. 86-87ºC (Choudhary &Vijay, 2011); Anal. Calcud for; C15H11IO,(334) C:55.19, H:3.76; UV(λmax/nm)=318, IR(KBr, v/cm -1) =1627.92(Cos-cis), 1597(COs-trans) 1122.57(C-Hip) 756.10(C-Hop), 1002.98(CH=CHop) 551.64(C=Cop); 1H NMR(400MHz, CDCl3, δ/ppm): =7.740(1Hα, d), 7.877(1Hβ, d), 7.263 – 7.867(9H,m, Ar-H); 13C NMR(100MHz CDCl3, δ /ppm): = 121.48(Cα), 145.47(Cβ), 189.750(CO), 137.50(C1), 129.96 (C2,C6)144.03(C3,C5)100.63 (C4), 134.60 (C1 '), 128.55 (C2 ',C6 '), 130.81 (C3 ', C5 ').121.48 (C4 ').; Mass spectrum: 334[M+], 256,230, 207, 203, 131, 77.

The compound **1a** has been characterized sing UV, IR & NMR data. The carbonyl group of this compound is confirmed by the presence of stretching frequencies at 1627.92 and 1597.92cm 1. Vinyl part is identified by the frequencies at 1002.98cm-1. The protons in this vinyl group is further confirmed by 1H NMR values i.e., chemical shift vale at 7.740 and 7.877ppm. Vinylic carbons are confirmed by chemical shift at 121.48 and 145.47ppm.

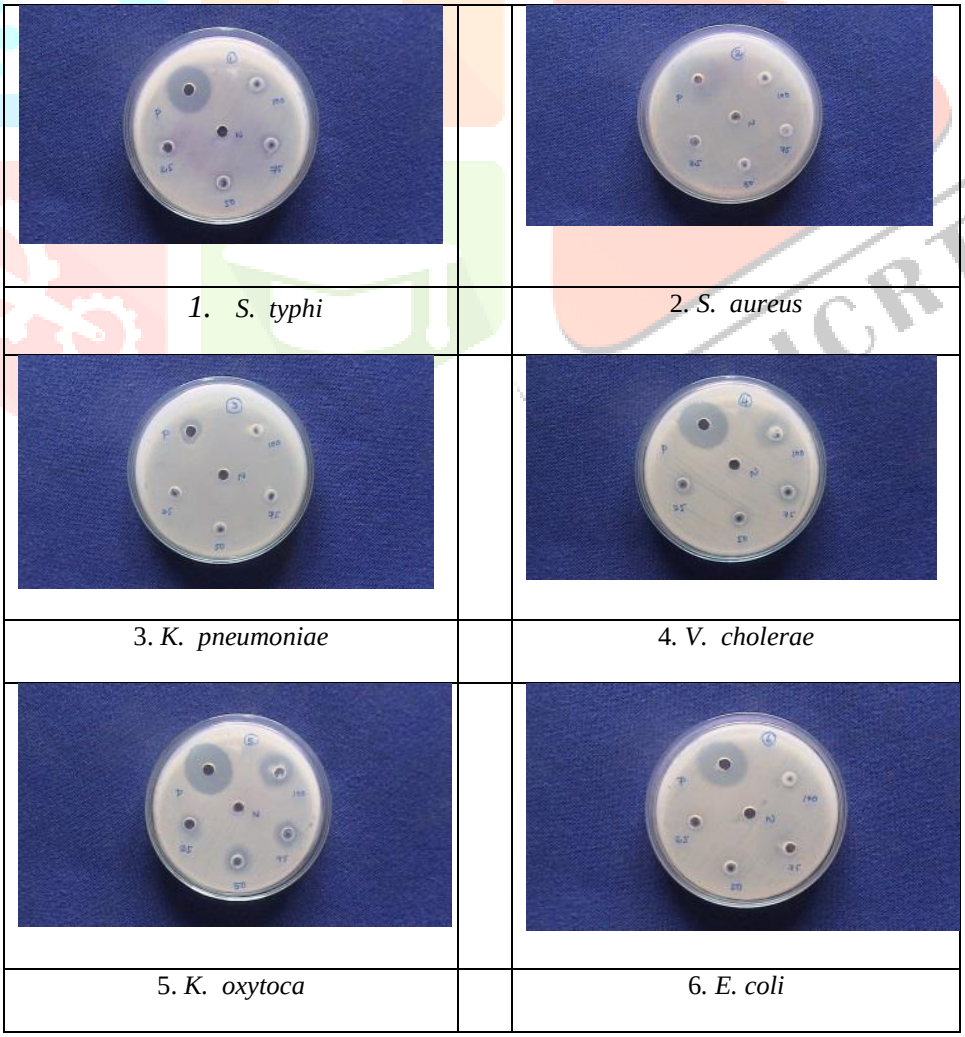
3.2 Spectral characterization of (E)-1-(4-iodophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (1b)

M.P.78-79°C (Fleming, 1980) Anal. Calud for; C16H13IO2(364), C:55.19, H:3.7;UV(λmax/nm)=327.5, IR(KBr, v/cm-1)=1640.37(CO s-cis), 1593(CO s-trans), 1134(C-Hip), 812(C-Hop), 1006.8(CH=CHop), 524(C=Cop) 1H NMR(CDCl3):δ= 7.425(d 1Hα), 7.799(d 1Hβ), 7.224-7.815(m 8H Ar-H), 3.864(3H s, -OCH3) 13C NMR(100MHz CDCl3 δ/ppm)=120.45(Cα), 145.59(Cβ), 189.33(CO), 137.65(C1), 129.94 (C2,C6)131.98(C3,C5)100.48 (C4), 128.60 (C1 '), 128.60 (C2 ',C6 '), 137.88 (C3 ', C5 ').145.59 (C4 '). Mass spectrum: 364[M+], 257, 237, 231, 203, 161, 133, 129,107

The compound **1b** has been characterized sing UV, IR & NMR data. The carbonyl group of this compound is confirmed by the presence of stretching frequencies at 1640.37 and 1593cm 1. Vinyl part is identified by the frequencies at 1006.8cm-1. Methoxy group in aldehyde group is confirmed by 3.864ppm. The protons in this vinyl group is further confirmed by 1H NMR values i.e., chemical shift vale at 7.425 and 7.799ppm. Vinylic carbons are confirmed by chemical shift at 120.45 and 145.59ppm.

3.3 Antibacterial activity of present compounds 1a & 1b

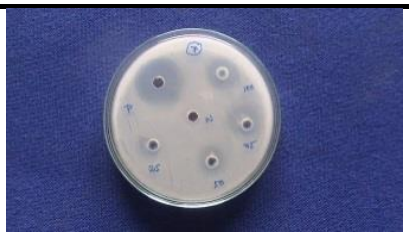
The antibacterial activity of present study is performed at different concentrations and is displayed in **Fig. 1 & 2**. The zone of inhibition values are given in **Table 1 & 2**. The compound 1a has remarkably good activity against bacterial species namely S. *typhi, V. cholera, K. oxytoca, E. coli and S. paratyphi*. The compound 1b has remarkably good activity against bacterial species namely *S. typhi, V. cholera, K. oxytoca, E. coli and S. paratyphi* in addition with *S. paratyphi and P. mirabilis.*



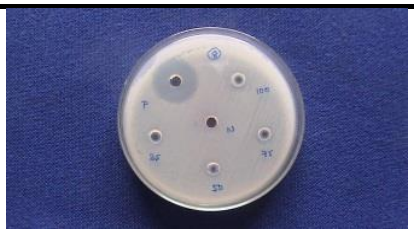
1. *S. typhi* 2. *S. aureus*

3. *K. pneumoniae* 4. *V. cholerae*

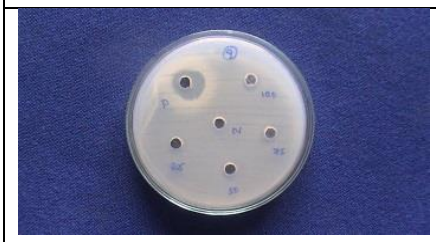
5. *K. oxytoca* 6. *E. coli*



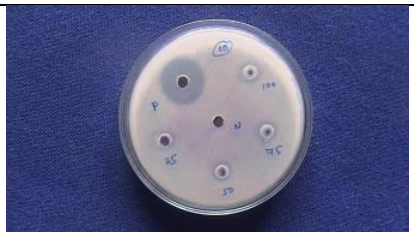
7. *S. paratyphi.*



8. *P. mirabilis*



9. *V. parahaemolyticus*



10. *S. pyogenes*

Fig: 1 Antibacterial activity of (*E*)-1-(4-iodophenyl)-3-phenylprop-2-en-1-one

Table.1 Zone of inhibition values of (E)-1-(4-iodophenyl)-3-phenylprop-2-en-1-one

S. No	Name of the strains	Zone of inhibition (mm)					
		25µg/ ml	50µg/ ml	75µg/ ml	100µg/ ml	Tetracycline	DMSO
1	*S. typhi*	11	12	14	17	29	Nil
2	*S. aureus*	8	9	10	11	28	Nil
3	*K. pneumoniae*	10	12	14	16	29	Nil
4	*V. cholerae*	12	14	16	18	29	Nil
5	*K. oxytoca*	13	16	18	19	29	Nil
6	*E. coli*	10	12	14	18	28	Nil
7	*S. paratyphi.*	15	16	17	19	29	Nil
8	*P. mirabilis*	09	11	13	14	28	Nil
9	*V. parahaemolyticus*	08	09	10	11	22	Nil
10	*S. pyogenes*	07	08	10	11	22	Nil

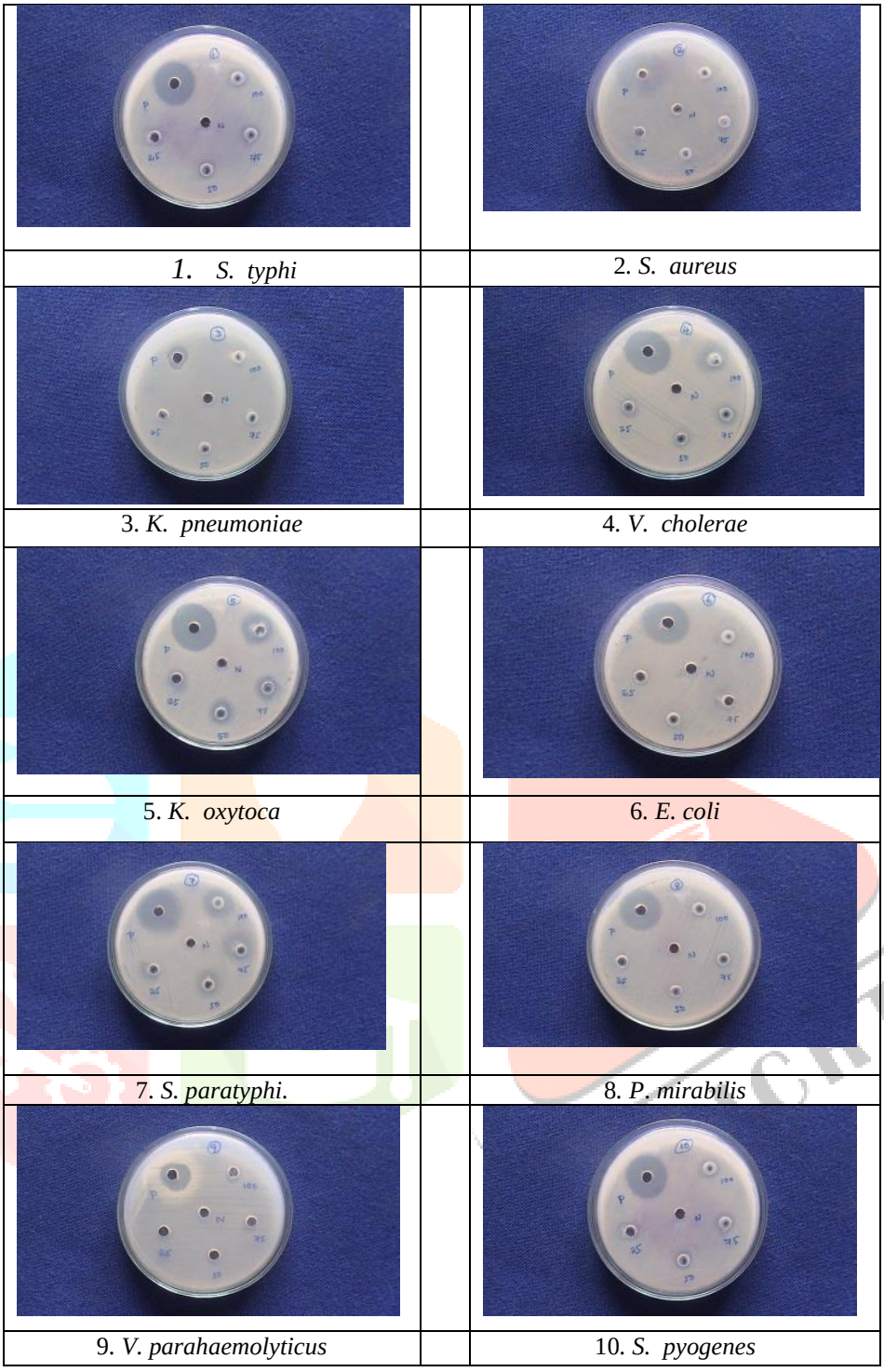


Fig: 2 Antibacterial activity of (*E*)-1-(4-iodophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one

Table.2 Zone of inhibition values of (*E*)-1-(4-iodophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one

S. No	Name of the strains	Zone of inhibition (mm)					
		25 µg/ml	50 µg/ml	75 µg/ml	100µg/ml	+ve	-ve
1	*S. typhi*	9	11	13	16	26	Nil
2	*S. aureus*	15	17	18	20	28	Nil
3	*K. pneumoniae*	9	10	13	16	27	Nil
4	*V. cholerae*	12	14	16	18	29	Nil
5	*K. oxytoca*	11	13	15	18	29	Nil
6	*E. coli*	10	12	13	14	28	Nil
7	*S. paratyphi.*	12	14	14	16	29	Nil
8	*P. mirabilis*	10	12	14	17	28	Nil
9	*V. parahaemolyticus*	10	11	13	15	27	Nil
10	*S. pyogenes*	-	-	-	-	27	Nil

IV CONCLUSION

The authors have synthesized two specific chalcones from 4-iodoacetophenone with benzaldehyde and 4-methoxy benzaldehyde. In this present work, authors have taken effort in synthetic method i.e., greener approach. For this greener synthetic method, we have to utilized Flyash mixed Silica-Phospharic Acid (SPA) as catalyst which easily available waste material. The yields of these two chalcones are more than 90% and are formed with very short duration. Their formation was confirmed by spectral analysis. Furthermore, their anti-bacterial activity is performed at different concentrations. The two chalcones are effectively acted against pathogens used in this study. On comparing these two compounds, 4-methoxy substituted compound has displayed good activity against most of pathogens than another one.

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