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Invitro antimicrobial and antioxidant activity of substituted chalcones

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ABSTRSACT

Chalcones, precursors of open chain flavonoids and isoflavonoids present in edible plants, and their derivatives have attracted increasing attention due to numerous potential pharmacological applications. They have displayed a broad spectrum of pharmacological activities. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity. The present study highlights synthesized chalcones and their derivatives possessing important pharmacological activities. It involves synthesis of some novel chalcones and find out the potency against antimicrobial and antioxidant activity by DPPH method.

Key Words- Chalcones, Antimicrobial activity, Antioxidant activity, DPPH method

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INTRODUCTION

Chalcones are α,β-unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituent. Rings are interconnected by a highly electrophilic three carbon α, β-unsaturated carbonyl system that assumes linear or nearly planar structure [1, 4]. They contain the ketoethylenic group (–CO–CH=CH-) [9]. Chalcones possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings. Chalcones (*trans*-1, 3-diaryl-2-propen-1-ones), a biosynthetic product of the shikimate pathway, belonging to flavanoid family are precursors of open chain flavonoids and isoflavonoids, which are abundant in edible plants. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines, 1,4-diketones, and flavones. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. They have displayed a broad spectrum of pharmacological activities, among which antimalarial [1-4], anticancer [5-9], antiprotozoal (antileishmanial and antitrypanosomal) [10], anti-inflammatory [11, 12], antibacterial [13, 14], antifilarial [15], antifungal [16, 17], antimicrobial [18], larvicidal [19], anticonvulsant [20], antioxidant [21-23] activities have been reported. They have also shown inhibition of the enzymes, especially mammalian alpha-amylase [24], cyclo-oxygenase (COX) [25] and monoamine oxidase (MAO) [26]. They have shown antimitotic activity too [6]. Awasthi *et al* [2] synthesized several new chalcone analogues and evaluated as inhibitors of malaria parasite. Inhibitory activity was determined in *vitro* against a chloroquine-sensitive P. *falciparum strain* of parasites. Achanta *et al* [5] evaluated a series of boronic chalcones for their anticancer activity and mechanisms of action. Ten chalcones were synthesized and tested as leishmanicidal and trypanocidal agents by Lunardi *et al* [10] against *in vitro* growth of *Leishmania braziliensis and Trypanosoma cruzi*. The results showed that the positions of the substituents seem to be critical for their antiprotozoal activities Chalcone derivatives contain α,β-unsaturated

carbonyl moiety which is responsible for anti-inflammatory activity. Yadav *et al* [11] synthesized a series of five chalcone derivatives and were subjected to anti-inflammatory screening using the carrageenan-induced rat hind paw edema model. Chalcone derivatives at dose 25 mg/kg by oral route inhibited significantly the formation of edema.

MATERIALS AND METHODS

Melting points were measured in open capillary tubes and are uncorrected. IR (KBR) spectra were recorded in film or in potassium bromide disks on a FTIR-8400s, Fourier Transform, IR spectrophotometer (υ max in cm-1) and 1H NMR spectra on a Perkin Elmer spectrophotometer-300MHz spectrophotometer. The chemical shifts were reported as parts per million (d ppm) tetramethyl silane (TMS) as internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). The progress of the reaction was monitored on a readymade silica gel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Spectral data (IR, 1HNMR, Mass spectra and elemental analysis) confirmed the structure of the synthesized compounds.

Synthesized Of Some Novel Chalcone Derivative [27, 28]:-
Weighed 0.32 g of substituted benzaldehyde derivatives into a 10-mL round bottom flask added 0.36 g of acetophenone into the flask and stirr the mixture in ethanol and added sodium hydroxide solution, drop wise. Let the mixture stir at room temperature for about 45 minutes. If a reddish oil starts to separate from the reaction mixture, heat gently on a warm sand bath. That was served to redissolve the reagents to assure complete reaction. After 45 minutes, add 1 ml of cold water to the mixture and start scratching the inside walls of round bottom flask flask. At first there will be oil and a cloudy water layer, but keep scratching gently. Add another 3 ml of water, about a 0.5 ml at a time with a little scratching between additions. Remove the stir rod from the mixture and let the liquid for air-dry when the flask was placed in an ice bath. Added crushed of ice to the flask to crystallize the solid. Once some solid starts to form, scratching will help convert the oil to a tacky solid. Collected the product by suction filtration and recrystallized from mixture of hot ethanol and water.

Biological Evaluation Of Synthesized Compounds:-
A) Antimicrobial activity:-
Determination of Zone of Inhibition:

The Zone of Inhibition was determined by the disk diffusion [29] method. The method is as follows-

Preparation of nutrient agar media (500ml):- Peptone 5gm, Sodium chloride 2.5gm, Beef extract 5gm, Agar 10gm, Distilled water q.s., Adjusted p^H 7.2-7.4. Sodium chloride, peptone, beef extract , agar were weighed out and dissolved in required amount of distilled water by keeping the media in the steam bath, agar was melted out and the indicator was added and the volume was made upto distilled water , ph was adjusted at 7.2-7.4 . Then the flask was plugged and wrapped in paper then autoclave at 15 PSI pressure at 121 c at 15 min.

Preparation of Liquid broth media:- Peptone 5gm, Sodium chloride 2.5gm, Yeast extract 2.5gm, Distilled water q.s., P^H 7.2-7.4. Sodium chloride, peptone, yeast extract were weighed out the dissolve in required amount of distilled water by keeping the media in the steam bath, and the volume was made with the distilled water, ph was adjusted at 7.2-7.4 .Then the flask was plugged and wrapped in paper and then autoclave at 15 PSI pressure at 121^0 c for 15 min.

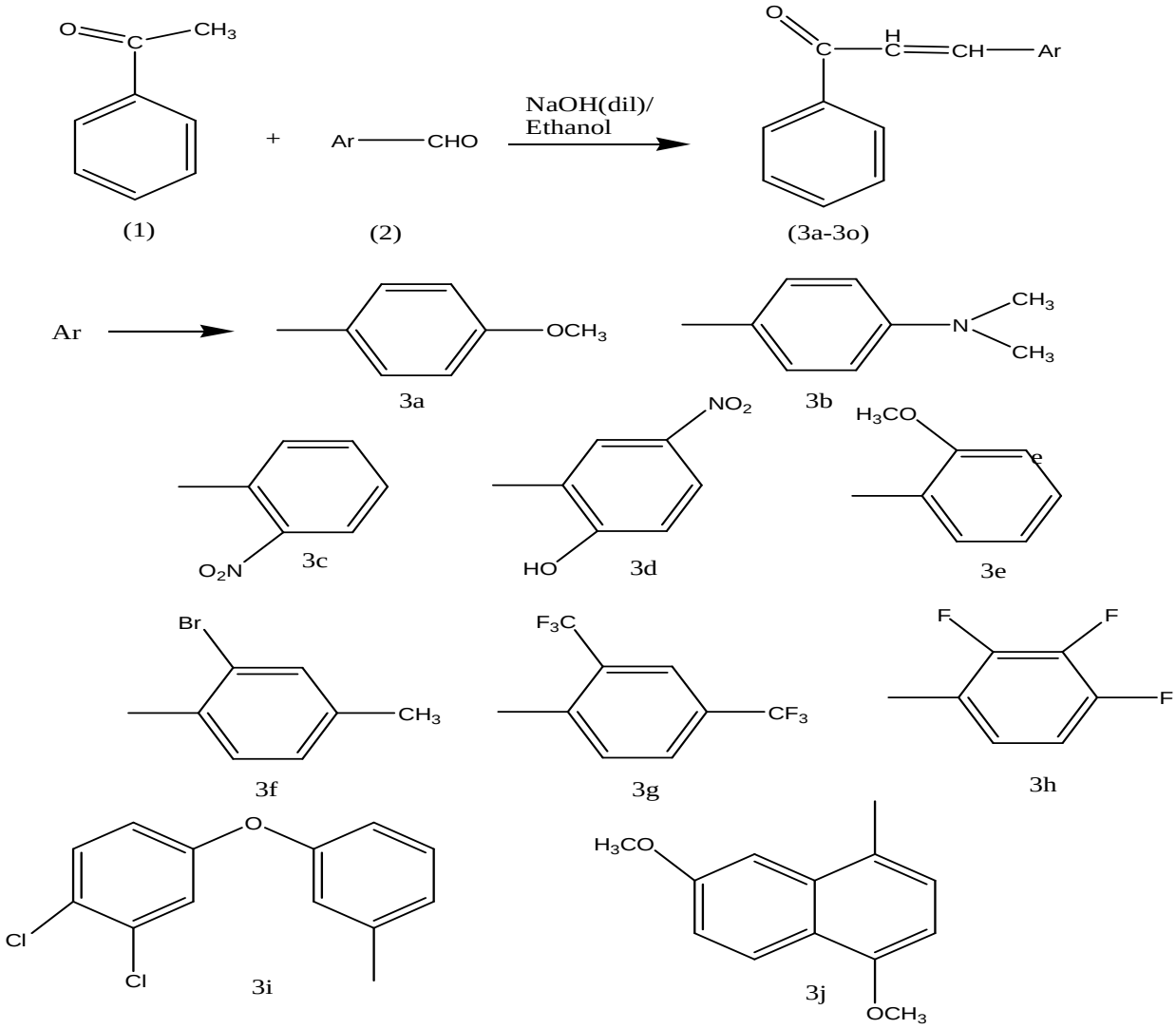
Procedure:-
The test was performed according to the disk diffusion method [29] adopted with some modification for the prepared compound using streptomycin as reference. The prepared compounds were tested against one strain of Gram +ve bacteria, Gram –ve bactria, fungi. Whatman filter paper disk of 5mm diameter were sterilized by autoclaving for 15 min at 121^0 c. The sterile disk were impregnated with different compounds (600gm/disk). Agar plates were surface inoculated uniformly from the both culture of the tested microorganism. The disk were placed on the medium suitably spaced apart on the plate were incubated at 5^0 c for 1 hr to permit good diffusion and then transferred to an incubator at 37 c. for 24hr for bacteria and 28^0 c for 72hrs for fungi. The inhibition zones caused by the various compounds on the microorganism were explained. The antimicrobial data shown in the **Table-2.**

B) Antioxidant activity:-

Antioxidant potential: It is well-known that free radicals cause autoxidation of unsaturated lipids in food. In addition, antioxidants are known to interrupt the free-radical chain of oxidation and to donate hydrogen from phenolic hydroxy groups, thereby, forming stable free radicals, which do not initiate or propagate further oxidation of lipids[30] .The antioxidant potential of any compound can be determined on the basis of its scavenging activity of the stable 1,1-diphenyl-2-picryl hydrazyl (DPPH) free radical as described by Sadhu et al.[31] DPPH is a stable free radical containing an odd electron in its structure and usually utilized for detection of the radical scavenging activity in chemical analysis. The aliquot of the different concentrations (5-500 µg/mL) of the test sample is added to 3 ml of a 0.004% ethanolic solution of DPPH. Absorbance at 517 nm is determined after 30 min, and IC (Inhibitory concentration 50%) is also determined. IC50 value denotes the concentration of sample required to scavenge 50% of the DPPH free radicals.

The formula used for %inhibition is as follows:

$$\% \text{ inhibition} = (\text{Blank OD} - \text{Sample OD/Blank OD}) \times 100$$



Scheme1

Sampling, screening and IC calculation: At first 5 test tubes were taken to make aliquots of 5 different concentrations level (5, 10, 50, 100 and 500µg/mL). Tested sample and ascorbic acid were weighed 3 times and dissolved in ethanol to make the required concentrations by dilution technique. DPPH was weighed and dissolved in ethanol to make 0.004% (w/v) solution. To make homogeneous solutions of the tested samples, magnetic stirrer was used. After making the desired concentrations, 2 ml of 0.004% DPPH solution was applied on each test tube by using pipette. The room temperature was recorded and kept the test tubes for 30 minutes in light exposure to complete the reactions. DPPH was also applied on the blank test tubes at the same time where only ethanol was taken as blank. After 30 min, absorbance of each test tube was determined by UV spectrophotometer. Then %inhibitions were plotted against log concentration of each of the test sample. Then IC was calculated from the graph. The experiment was performed in duplicate and average absorption was noted for each concentration. Ascorbic acid was used as a positive control. Calculated antioxidant data of all the test samples were summarized in **Table 3.**

Free radical scavenging mechanism of antioxidants: The 1,1-diphenyl-2-picrylhydrazyl radical has been widely used to evaluate the free radical scavenging capacity of different antioxidants **[**32-34] . With this method it is possible to determine the antiradical power of an antioxidant activity by measurement of the decrease in the absorbance of DPPH at 517 nm. Resulting from a color change from purple to yellow the absorbance decreased when the DPPH is scavenged by an antioxidant, through donation of hydrogen to form a stable DPPH molecule. In the radical form this molecule had an absorbance at 517 nm, which disappeared after acceptance of an electron or hydrogen radical from an antioxidant compound to become a stable diamagnetic spin paired molecule [35]. The odd electron in the DPPH free radical gives a strong absorption maximum at 517 nm and is purple in color. The color turns from purple to yellow as the molar absorptivity (optical density) of the DPPH radical at 517 nm reduces from 9660 to 1640 when the odd electron of DPPH radical becomes paired with hydrogen radical from a free radical scavenging antioxidant to form the reduced DPPH-H. The resulting decolorization is stoichiometric with respect to the number of electrons captured.

RESULTS

Table-1 Physical Data Of Compounds

Compoud no	Molecular formula	Melting point	Colour	$R_f$value	Percentage yield(%)	Solubility
3a	$C_{16}H_{14}O_2$	98	*Reddish brown*	0.91	60.90%	chloroform
3b	$C_{17}H_{17}NO$	60	*Cream*	0.95	80.34%	chloroform
3c	$C_{15}H_{11}NO_3$	105	*yellow*	0.91	74.58%	chloroform
3d	$C_{15}H_{11}NO_4$	55	*Reddish yellow*	0.95	63.34%	chloroform
3e	$C_{16}H_{14}O_2$	59	*Reddish brown*	0.86	83.34%	chloroform
3f	$C_{16}H_{13}BrO$	89	*Cream*	0.97	94.38%	chloroform
3g	$C_{17}H_{10}F_6O$	103	Brown	0.98	53.34%	chloroform
3h	$C_{15}H_9F_3O$	88	White	0.94	87.34%	chloroform
3i	$C_{21}H_{14}C_{l2}O_2$	108	White creamy	0.921	79.28%	chloroform
3j	$C_{21}H_{18}O_3$	104	orange	0.87	80.14%	chloroform

Spectral analysis of the compounds

The structure of the compounds were done by spectral analysis (ir,nmr,mass) and the results are shown below

Compound 3a :- NMR($CDCl_3$,δ PPM):2.09(s ,3H, -OCH_3) ; 2.29-2.27(d, 1H,J=6Hz,-CH=CH-) ; 2.33-2.31(d, 1H,J=6Hz,- CH=CH-) ; 6.08-6.06(d,2H,J=6Hz,Ar-H) ; 6.39-6.37 (d,2H,J=6Hz, Ar-H) ; 7.22-7.20(d,1H,J=6Hz,Ar-H) ;7.27-7.25(d,2H,J=6Hz,Ar-H) ; 7.39-7.37(d,2H,J=6Hz,Ar-H) . FTIR (KBr,cm^{-1}): 1658.55 (C=O ,str,s) ; 3300.1(CH=CH,b ,w) ; 2955.29(O-CH_3,str,w) .EI-MS (m/e) : 238.10 (100.0%), 239.10 (17.4%), 240.11 (1.4%) .

Compound 3b :- NMR($CDCl_3$,δ PPM): 2.08(s,6H,-CH_3) ; 2.99-2.97(d,1H,-CH=CH-) ; 3.53-3.51(d,1H,J=6Hz,-CH=CH-) ; 6.74-6.72(d,2H,J=6Hz,Ar-H) ; 7.53-7.50(d,2H,J=6Hz,Ar-H) ; 7.61-7.59(d,2H,J=6Hz,Ar-H) ; 7.67-7.65(d,2H,J=6Hz,Ar-H) ; 8.09-8.07(d,1H,J=6Hz). FTIR (KBr,cm^{-1}): 2891.55 (C=O ,str,s) ; 3311.1(CH=CH,b ,w) ; 3370.02(H_3C-N-CH_3 ,str , s).EI-MS (m/e) : 251.13 (98.0%) .

Compound 3c :- NMR($CDCl_3$,δ PPM) : 2.38-2.36(d,1H,J=6Hz,-CH=CH-) ; 2.43-2.41 (d,1H, J=6Hz,-CH=CH-) ; 6.08- 6.06(d,2H,J=6Hz,Ar-H) ; 6.36-6.34(d,1H,J=6Hz,Ar-H) ; 6.39-6.37 (d, 1H,J=6Hz,Ar-H) ; 7.1-6.99(d,2H,J=6Hz,Ar-H) ; 7.09-7.07(d,1H,J=6Hz,Ar-H) ; 7.37-7.35 (d,2H, J=6Hz,Ar-H) . FTIR (KBr,cm^{-1}):

1163.99(C-O ,str , s) ;1570.75(C-NO_2 ,str , s) ;1642.12(C=O, str , w) ;3336.01(HC=CH,str,m) ..EI-MS (m/e) : 253.07 (99.1%).

Compound 3d :- NMR($CDCl_3$,δ PPM): 2.5-2.48(d,1H,J=6Hz,-CH=CH-) ; 2.48-2.46(d,1H, J=6Hz,-CH=CH-) ;4.3(S,1H,-OH) ; 6.74-6.72(d,2H,J=6,Ar-H) ; 7.3-7.29(d,2H,J=6,Ar-H) ; 7.28- 7.26 (d,2H,J=6,Ar-H) ; 8.30-8.29 (d,2H, J=6,Ar-H) . FTIR (KBr,cm^{-1}): 1162.99(C – O ,str , s) ;1573.75(C – NO_2,str , s) ;1649.12(C=O ,str , w); 3338.04(HC=CH,str , m); 3855.91(H – O, def , w) .EI-MS (m/e) : 269.07 (99.3%).

Compound 3e :- NMR($CDCl_3$,δ PPM) :2.09(s ,3H, -OCH_3) ; 2.29-2.27(d, 1H,J=6Hz,-CH=CH-) ; 2.3-2.29(d, 1H,J=6Hz,- CH=CH-) ; 6.18-6.16(d,2H,J=6Hz,Ar-H) ; 6.39-6.37 (d,2H,J=6Hz, Ar-H) ; 7.22-7.20(d,1H,J=6Hz,Ar-H) ;7.17-7.15(d,2H,J=6Hz,Ar-H) ; 7.29-7.27(d,2H,J=6Hz,Ar-H) . FTIR (KBr,cm^{-1}): 1656.55 (C=O ,str,s) ; 3301.1(CH=CH,b ,w) ; 2954.29(O-CH_3,str,w) .EI-MS (m/e) : 238.10 (100.0%), 239.10 (17.4%), 240.11 (1.4%) .

Compound 3f :- NMR($CDCl_3$,δ PPM):2.25(s ,3H, -CH_3) ; 2.29-2.27(d, 1H,J=6Hz,-CH=CH-) ; 2.3-2.29(d, 1H,J=6Hz,- CH=CH-) ; 6.18-6.16(d,2H,J=6Hz,Ar-H) ; 6.39-6.37 (d,2H,J=6Hz, Ar-H) ;6.95-6.93(d,1H,6Hz,Ar-H)) 7.22-7.20(d,1H,J=6Hz,Ar-H) ;) 7.18(s,1H, Ar-H) ; 7.29- 7.27(d, 2H,J=6Hz,Ar-H),8.07-8.05(d,1H,J=6Hz , Ar-H) . FTIR (KBr,cm^{-1}) :728(C-Br,str); 1656.55 (C=O ,str,s) ;2972.21(C-H,sta),3301.1 (CH=CH,b ,w) ;.EI-MS (m/e) : 300.01.

Compound 3g :- NMR($CDCl_3$,δ PPM): 2.31-2.29(d,1H,J=6Hz,-CH=CH-);2.3-2.29(d, 1H, J=6Hz,- CH=CH-) ; 6.16-6.14(d,2H,J=6Hz,Ar-H) ; 6.39-6.37 (d,2H,J=6Hz, Ar-H) ;6.95-6.93 (d,1H,6Hz,Ar-H)) 7.20-7.18(d,1H,J=6Hz,Ar-H) ;7.14(s,1H, Ar-H);7.11-7.09(d, 2H, J=6Hz, Ar-H),8.07-8.05(d,1H,J=6Hz , Ar-H) .FTIR (KBr,cm^{-1}): 903(C-F,str); 1659.55 (C=O ,str,s) ;2974.21(C-H,str),3301.1 (CH=CH,b ,w). EI-MS (m/e): 344.06 (100.0%), 345.07 (18.5%), 346.07 (1.8%).

Compound 3h :- NMR($CDCl_3$,δ PPM): 2.31-2.29(d,1H,J=6Hz,-CH=CH-);2.3-2.29(d, 1H, J=6Hz,- CH=CH-) ; 6.16-6.14(d,2H,J=6Hz,Ar-H) ; 6.39-6.37 (d,2H,J=6Hz, Ar-H) ;6.95-6.93 (d,1H,6Hz,Ar-H)) 7.20-7.18(d,1H,J=6Hz,Ar-H) ;7.14(s,1H, Ar-H); .FTIR (KBr,cm^{-1}) :903(C-F,str); 1659.55 (C=O ,str,s) ;2974.21(C-H,sta),3301.1 (CH=CH,b ,w) ;.EI-MS (m/e) : 262.06

Compound 3i :- NMR($CDCl_3$,δ PPM): NMR($CDCl_3$,δ PPM)- 2.09(s ,3H, -OCH_3) ; 2.29-2.27(d, 1H,J=6Hz,-CH=CH-) ; 2.33-2.31(d, 1H,J=6Hz,- CH=CH-); 3.09(s ,3H, -OCH_3); 6.08-6.06(d,2H,J=6Hz,Ar-H) ; 6.39-6.37 (d,2H,J=6Hz, Ar-H) ;6.44(S,1H);6.99-6.97(d.1H,6Hz) ; 7.22-7.20(d,1H,J=6Hz,Ar-H) ;7.27-7.25(d,1H,J=6Hz,Ar-H) ; 8.01-7.39(d,2H,J=6Hz,Ar-H) . FTIR (KBr,cm^{-1})- FTIR (KBr,cm^{-1}) :1658.55 (C=O ,str,s) ; 3300.1(CH=CH,b ,w) ; 2955.29(O-CH_3,str,w) ..EI-MS (m/e):318.13 (100.0%), 319.13 (23.0%), 320.13 (3.1%).

Table No-2 Antimicrobial Data

Comound no	*Gram Positive bacterias*						*Gram negative bacterias*						*Fungus*					
Conc (mcg/ml)	*Staph aureus*			*Bacillus substilis*			*Escherichia coli*			*Enterobacter cloacae*			*Aspergillus niger*			*Candida albicans*		
	Zone of inhibitions(mm)																	
	100	150	250	100	150	250	100	150	250	100	150	250	100	150	250	100	150	250
3a	10	13	15	11	13	15	18	20	20.5	10.6	13	15	9	10.5	13	10	12	15
3b	11	16	18	11	13.5	16	17	19	21	11.5	16	18	11	13	15	11	14	15
3c	16	19	21	17	16.1	18	19.8	22	23.2	16.1	19	21	16	17	18	16	18	19
3d	15	18	20	18	15	19	21	22	24	15	18	20	15	17	18.3	15	17	19
3e	17	21	22	17	17	19.5	22	23.6	25	17.4	21	22	17	17.5	19	17	21	22
3f	14	18	20	14	13	15	17	19	21	17	18	20	14	16	18	14	16	17
3g	12	17	19	12	12	17	19	21	22	15	17	19	12	14	16.5	12	13	15
3h	19	23	25	19	18	19	21	22	23	20	23	25	19	21	23	19	21	22
3i	13	15	19	13	13	14	18	20	23	13	15	19	13	19	21	21	22	23
3j	11	18	19	11	11.2	17	19	21	22.7	15	18	19	11	14	17	11	14	18
Amoxycillin	12	14	17.1	12	14	17.1	18	20	22.1	12	14	17.1	_	_	_	_	_	_
Streptomycin	11	13	16	11	13	16	19	21	22	11	13	16	_	_	_	_	_	_
Nystatin	_	_	_	_	_	_	_	_	_	_	_	_	10	13.5	16	10	13.5	16

Table No.3Observation for antioxidant activity in terms of DPPH method

Compound code	% Scavenging [mean ± SEM]					IC_{50} ug/ml
	25ug/ml	50ug/ml	75ug/ml	100ug/ml	125ug/ml	
3a	15.61 ±06	21.31±0.026	23.41±0.098	36.97±0.15	47.32±0.026	137.67
3b	18.06±0.01	28.56±0.06	31.91±0.05	52.75±0.12	60.20±0.14	96.38
3c	21.21±0.12	31.37±0.09	38.22±0.24	43.44±0.15	56.53±0.16	107
3d	12.39±0.05	25.60±0.025	37.24±0.16	56.52±0.052	63.70±0.01	88.41
3e	8.83±0.098	14.95±0.026	45.00±0.023	56.24±0.05	65.01±0.11	86.70
3f	17.26±0.25	29.56±0.13	40.40±0.16	51.50±0.09	57.47±0.12	96.24
3g	14.10±0.13	32.12±0.25	41.51±0.12	52.97±0.01	62.29±0.11	98.30
3h	35.00±0.12	58.23±0.01	65.31±0.18	75.00±.0.08	82.13±0.14	44.31
3i	25.00±0.17	50.11±0.05	62.03±0.2	75.80±0.03	85.00±0.08	49.75
3j	28.44±0.03	37.09±0.12	48.89±0.14	55.60±0.21	72.48±0.12	83.41
STD (Ascorbic acid)	22.28±0.12 5ug/ml	41.03±0.19 10ug/ml	52.06±0.2 15ug/ml	75.02±0.09 20ug/ml	96.10±0.18 25ug/ml	14.66

DISCUSSION

Chalcones generally used as anti-microbial, anti-cancer, analgesic, anti-inflammatory agents. In the proposed scheme the substituted chalcones were prepared by aldol condensation reaction. From the extensive Literature survey this is found that no such compounds have been reported before. The compounds are prepared by the reaction between acetophenone and substituted aromatic aldehydes and recrystallization were done by hot ethanol. After purification the physical data was recorded and the melting point, percentage yield, RF values were determined. The formation of the compounds were confirmed by spectral studies the proton NMR spectra from spectral data the peaks at δ value 2.2-2.4 doublet indicates the aliphatic alkene proton which indicate the formation of the compound. The peak at 1655.55-1658 cm^{-1} (str.) indicates the presence of ketonic group. The presence of alkenes also confirmed by peaks in the range 3300.10 cm^{-1}(str.). From the mass spectra it was found that the entire compounds were formed. The invitro antimicrobial activity against different strains of bacterias and fungus and antioxidant activity by DPPH method was determined. It was observed that all the compounds exhibited activity against all the organisms employed. The compound 3c,3d,3e,3h shows maximum inhibitory concentration and others shows moderate activity. As we consider all results obtained from antibacterial and antifungal tests together we can say that entire compounds tested are active towards bacterias and fungus. From the invitro antioxidant activity it was found that all the compound shows potent antioxidant activity and compound 3h shows maximum potency.

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