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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF DIBENZALKETONE DERIVATIVES

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ABSTRACT

The development of resistance to current Antimicrobial therapy continuous to stimulate the search for more effective agents, the increasing clinical importance of drug resistant and bacterial pathogens has lent additional urgency to microbiological research and development of biologically active compounds. Hence is to synthesize some Dibenzalketone constitute derivative and carry out Antimicrobial potentials with good activity and less toxic effects. Chalcone is an aromatic ketone that forms the central core for a variety of important biological compounds. Chalcone can be prepared by an aldol condensation between an aldehyde and a ketone in the presence of a catalyst. The conjugate base of an aldehyde or ketone adds to the carbonyl group of another aldehyde or ketone to give a β-hydroxyaldehyde or β-hydroxyketone product. The synthesized compounds were characterized by IR, ^{1}HNMR & Mass Spectra's, The presence of a reactive α, β-unsatutated keto function in chalcones was found to be responsible for their antimicrobial activity were screened by Disc Diffusion Method.

KEYWORDS: Chalcones, Dibenzalketone, Antimicrobial activity.

INTRODUCTION

Dibenzalacetone has a conjugated system and is expected to be easily oxidized. The more the double bond, the easier it will be oxidized. Therefore, it is assumed that Dibenzalacetone and its derivatives will show antimicrobial activity. Many important biochemical compounds and drugs of natural origin contain Heterocyclic ring structures. Among these e.g. Carbohydrates,

essential amino acids, Vitamins, alkaloids, glycosides etc. the presence of heterocyclic structures in such diverse Types of compounds is strongly indicative of the diverse types of the pharmacological Activity and recognition of this is reflected in efforts to find useful synthetic drugs. Bearing in mind that the biological activities of known moieties and attempting certain structural modification or adaptation in light of the recent trends in drug research incorporating newly emerged pharmacophores on existing moiety. Dibenzalketone revealed that it has diversified activities in which Chalcone is an aromatic ketone that forms the central core for a variety of important biological compounds. The presence of a reactive α, β-unsaturated keto function in chalcones was found to be responsible for their antimicrobial activity. Recently, more attention has been paid to the synthesis of α, α'- bis (substituted benzylidene) cycloalkanones are known as the dibenzalketone derivatives.

MATERIALS AND METHODS

All reagents and solvents used were of analytical grade have been purchased from sigma-Aldrich chemical company. The purity of the compounds was checked by TLC on silica gel G plates using Benzene, ethyl acetate (1:3) and methanol: chloroform (1:9) Solvent system and Ultraviolet lamp and iodine chambers used as a visualizing agent. The synthesized compounds were dried and kept in vacuum anhydrous condition. Melting points were determined by using Precision melting point apparatus in Open capillaries and are uncorrected. For drying of compounds calcium sulfate and silica gel of E. Merck was used. Watt man's filter paper was used for filtration. The conventional methodology was adopted to synthesize the titled compounds. These synthesized compounds were characterized by IR, ^{1}HNMR, Mass Spectra's, the title compounds were screened for Antimicrobial activity.

EXPERIMENTAL

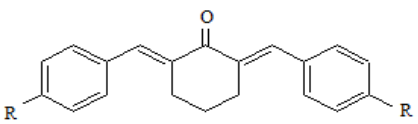
1. Preparation of Dibenzalketone Derivatives (SS1a-SS1d)

a. 1, 5-diphenylpenta-1, 4-dien-3-one (SS1a)

b. 1, 5-bis (4-chlorophenyl) penta-1, 4-dien-3-one (SS1b)

c. 1, 5-bis (4-nitrophenyl) penta-1, 4-dien-3-one (SS1c)

d. 1, 5-bis (4-methoxyphenyl) penta-1, 4-dien-3-one (SS1d)



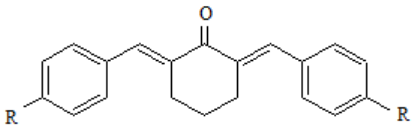
R= -CHO, -Cl, -NO_2 & -OCH_3

Procedure

Prepare an ice-water bath in a 250ml beaker, place 15ml of ethanol and 20ml of aqueous 10% NaOH into a 100 ml beaker & add a stir bar. Place the 100ml beaker into the ice-water bath. Set then the entire assembly on to a magnetic stirrer. While stirring, cool the solution to 20°c. After the solution reaches to 20°c, remove the ice-water bath, continue to stir the solution. Prepare the mixture of 2.1 ml (2 m mol) of fresh Benzaldehyde and 758 µl (1 m mol) of Acetone in a test tube over a period of 5-10 mins, add the Benzaldehyde-acetone mixture to the ethanol-NaOH solution in a small portions, then stir the reaction for another 30 mins. Cool the mixture using the ice water bath for one hour. Collect the crystals by vaccum filtration. Wash the crystals by suspending them in 50ml of distil water. Again collect the crystals by vaccum filtration. Finally recrystalised with ethyl acetate. Check the filtrate by testing the last few drops of water using red-litmus paper. If the litmus changes to blue wash the crystals again until red-litmus do not changes colour. Keep a small sample aside to dry for a crude melting point measurement**.**

2. Preparation of Dibenzalketone Derivatives (SS2a-SS2d)

a. 1, 5-diphenylpenta-1, 4-dien-3-one (SS2a)
b. 1, 5-bis (4-chlorophenyl) penta-1, 4-dien-3-one (SS2b)
c. 1, 5-bis (4-nitrophenyl) penta-1, 4-dien-3-one (SS2c)
d. 1, 5-bis (4-methoxyphenyl) penta-1, 4-dien-3-one (SS2d)



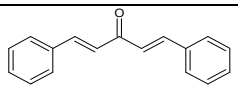
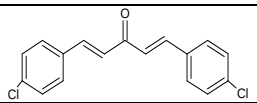
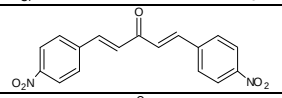
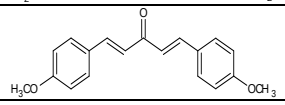
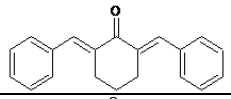
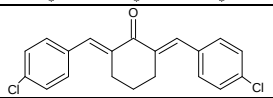
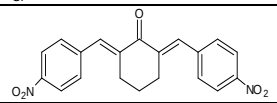
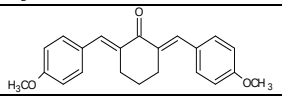
R= -CHO, -Cl, -NO_2 & -OCH_3

Procedure

Prepare an ice-water bath in a 250ml beaker, place 15ml of ethanol and 20ml of aqueous 10% NaOH into a 100 ml beaker & add a stirbar. Place the 100ml beaker into the ice-water bath. Set then the entire assembly on to a magnetic stirrer. While stirring, cool the solution to 20°c. After the solution reaches to 20°c, remove the ice-water bath, continue to stir the solute. Prepare the mixture of 2.1 ml (2 m mol) of fresh Benzaldehyde and 1263.3µl (1 m mol) of Cyclohexanone in a test tube over a period of 5-10 mins, add the Benzaldehyde-Cyclohexanone mixture to the ethanol-NaOH solution in a small portions, then stir the

reaction for another 30 mins. Cool the mixture using the ice water bath for one hour. Collect the crystals by vaccum filtration. Wash the crystals by suspending them in 50ml of distil water. Again collect the crystals by vaccum filtration. Finally recrystalised with ethyl acetate. Check the filtrate by testing the last few drops of water using red-litmus paper. If the litmus changes to blue wash the crystals again until red-litmus does not changes colour. Keep a small sample aside to dry for a crude melting point measurement**.**

Table No 1: Physical Parameters of synthesized Dibenzalketone Derivatives.

S.No	Compound Results						
	Compound Code	Molecular formula	Molecular Structure	Molecular weight	Percentage yield	R_f value	Melting point
1	SS1a	$C_{17}H_{14}O$		234	82%	0.91	110^0c
2	SS1b	$C_{17}H_{12}Cl_2O$		303	99%	0.92	132^0c
3	SS1c	$C_{17}H_{12}N_2O_5$		324	66%	0.94	147^0c
4	SS1d	$C_{19}H_{18}O_3$		294	59%	0.92	188^0c
5	SS2a	$C_{20}H_{18}O$		274	70%	0.92	117^0c
6	SS2b	$C_{20}H_{16}Cl_2O$		343	70.1%	0.94	148^0c
7	SS2c	$C_{20}H_{16}N_2O_5$		364	72%	0.96	159^0c
8	SS2d	$C_{22}H_{22}O_3$		334	60%	0.93	204^0c

CHARACTERISATION

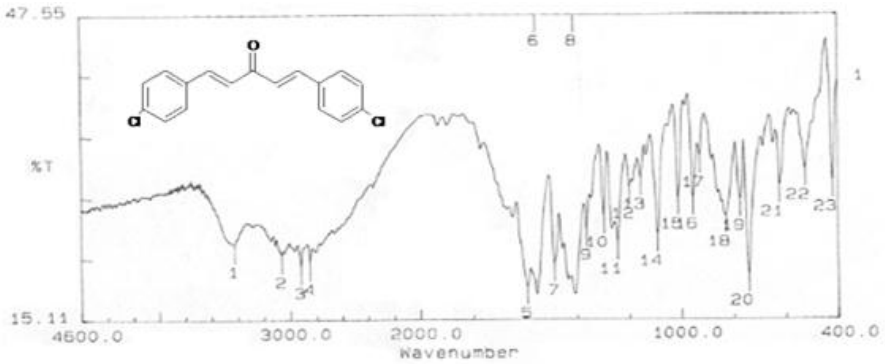


Figure No 1:- IR Spectra of 1, 5-bis (4-chlorophenyl) penta-1, 4-diyn-3-one (SS1b).

Table No 2:-IR Spectral data of 1, 5-bis (4-chlorophenyl) penta-1, 4-diyn-3-one (SS1b)

Functional Group assaigned	Group Frequency in Wave Number (cm^{-1})
C-C Aromatic Stretch	1410 (17.9)
Conjugated C=O Stretch	1770 (19.9)
C=C Aromaic Stretch	1363 (24.8)
C-C bending	422 (29.9)
C=C bending	742 (20.0)
Cl Stretch	1591(18.7)
C-H Aromatic Stretch	2918 (20.8)

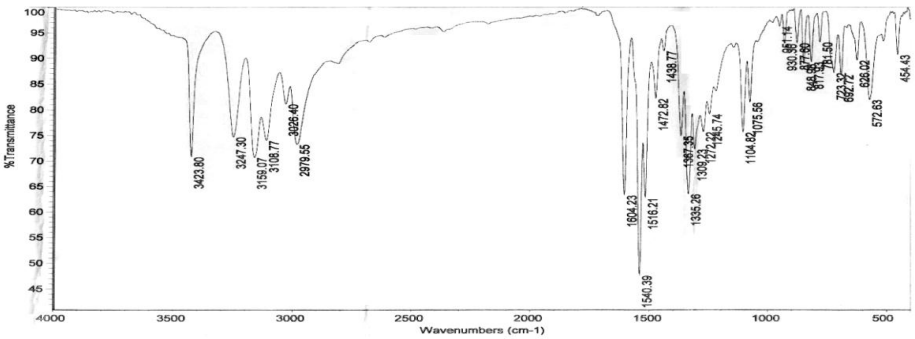


Figure No 2: IR Spectra of 2, 6-bis (4-nitrobenzylidene) cyclohexanone (SS2c)

Table No 3: IR Spectral data of 2, 6-bis (4-nitrobenzylidene) cyclohexanone (SS2c)

Functional Group assaigned	Group Frequency in Wave Number (cm^{-1})
Ar C=C Str.	1604.23
Ar C-C Str.	1516.24
Ar N-N Str.	817.93
Ar C=N Str.	1472.82
Ar N-H Str.	3423.80
Ar C=O Str.	1690.
Ar C-H Str.	3026.40-2979.55
Ar C=C bend	454.43
Ar NO_2 Str.	1540.39

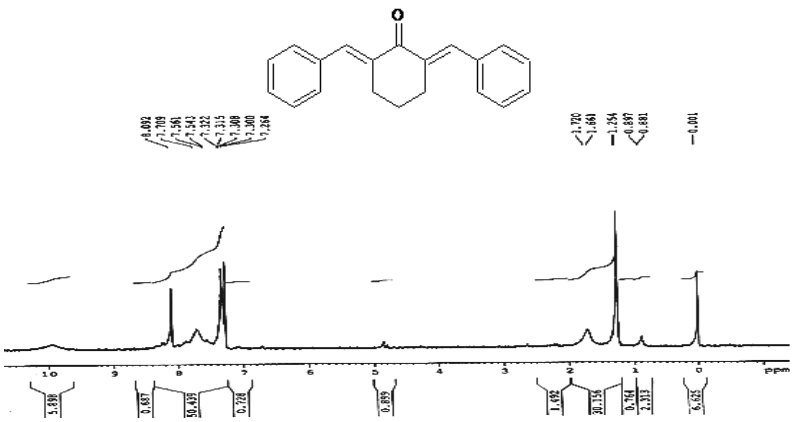


Figure No 3: ^{1} H NMR spectra of Compound 2, 6-Dibenzylidene cyclohexanone (SS2a)

^{1} H NMR spectral Report

The compound 2, 6-Dibenzylidene cyclohexanone is subjected for ^{1} H NMR spectrum in $CDCl_3$ using TMS as solvent internal reference standard. The extra peaks are seen between 0.9 to 1.8 δ may be give to the impurities of the molecule. Aromatic protons of the molecule have gives rise to multiplet from 7.4 δ to 8.1 δ, all these in agreement with the tentative structure of the molecule assign.

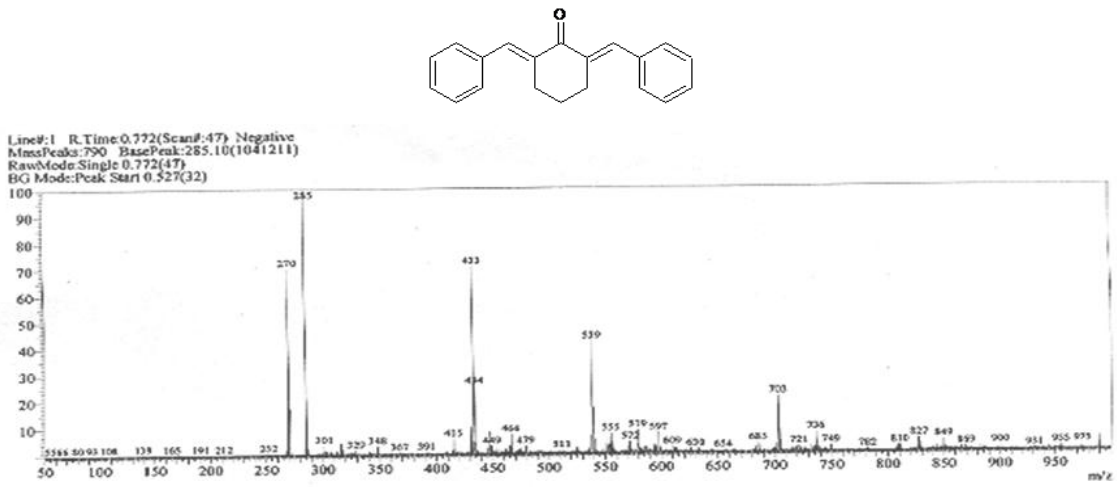


Figure No 4:- MASS Spectra of Compound 2, 6-dibenzylidene cyclohexanone (SS2a)

Mass Spectral data

The molecular weight of the compound is 274 and mass spectral data matching the same as 271 m/z it shows that the m+1 peak.

BIOLOGICAL ACTIVITIES

ANTIMICROBIAL ASSAY

Apparatus and Microorganism

The list of apparatus which were used in the antibacterial assay, were as follows: incubation bottle (500 mL), sample bottles, tips and micropipette (10 µL and 500 µL), Whatman paper disc (6 mm), disposable Petri dishes (8 mm), disposable micro-titer well U shape, needles, glass rod, cotton and test tubes (13 mm diameter,140 mm length). The apparatus were sterilized by autoclave for 15 minutes at 121°C. Two bacteria namely Escherichia coli, Staphylococcus aureus and aeruginosa were used in the antibacterial assay.

Preparation of Nutrient Agar and Broth

Antimicrobial assay was performed using nutrient agar and nutrient broth for bacteria. Nutrient agar (28g) and nutrient broth (30g) each was suspended in one liter of distilled

water. All solutions were sterilized by autoclave for 15 minutes at 121°C.each compound (1mg) was dissolved in DMSO (1ml).

Culturing Microbe

Each of the selected microbes was impregnated in nutrient broth (20 ml) in sterilized conical flask (250 ml). The flasks were sealed and kept in an incubator for24 hours at 37±1°C.

Preparation of Agar Plate

Sterilized agar (17 mL) was pipetted into Petri dishes immediately. The agar was let to cool before the dishes were kept in a refrigerator. The Petri dishes were kept upside down in the refrigerator.

Disc Diffusion Method

The disc diffusion method was carried out on the cultures of microbes. The discs were prepared by impregnating them in DMSO solution of each sample. The paper disc containing 1 mg of compound was placed on the agar surface previously inoculated with suspension of each microbe to be tested. All determinations were made in duplicate. Streptomycin sulphate (30µg/disc) was used as the positive control. Inhibition diameter was determined after incubation at 37^{o}C ± 1 for 24hours. The antimicrobial activity was indicated by the presence of clear inhibition zones around each disc**.**

Table No 4: Antimicrobial Activity Results.

S.NO	SAMPLE	Mean zone of inhibition(mm/mg)							
		Staphylococcus aureus				Echerichia coli			
		50µg	100µg	150µg	200µg	50µg	100µg	150µg	200 µg
1	Control(DMF)	-	-	-	-	-	-	-	-
2	Benzyl penicillin	20	24	28	33	11	16	21	28
3	Streptomycin	18	21	24	27	23	25	30	35
4	SS1a	09	11	20	22	05	07	12	21
5	SS1b	02	06	03	13	04	11	07	18
6	SS1c	08	04	09	13	04	09	11	09
7	SS1d	05	09	09	11	-	05	16	11
9	SS2a	08	13	11	19	05	06	09	09
10	SS2b	-	02	08	11	01	07	15	17
11	SS2c	12	13	16	18	06	09	11	21
12	SS2d	-	10	07	14	-	-	17	19

RESULTS AND DISCUSSION

literature survey it also reveals that chalconated Dibenzalketone have been reported for number of pharmacological activities and some molecules have shown significant activities and some compounds shows moderate and good activities. Here the synthesized all Dibenzalketone derivatives were screened for antimicrobial activity using DMSO as a solvent against the organisms, *S.aureus* and *E.coli.* The preliminary screening test for antimicrobial activity was performed by disc diffusion assay, Determination of Mean zone of inhibition (mm/mg) the procedures were repeated on the test organisms using standard antibiotics such as Benzyl penicillin & Streptomycin & Control by DMF. The antimicrobial screening results presented on above table reveals that the Mean zone of inhibition (MZI) of Dibenzalketone derivatives using bacterial strains, the compounds (at 200 µg/ml) SS1a & SS2a have exhibited good activity against *Staphylococcus aureus*, and SS1b,SS1c,SS1d, SS2b, SS2c and SS2d have moderate activity. Activities against *E. coli* SS1a, SS1d, SS2a & SS2d have exhibited good.

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CONCLUSION

From the data of the Table No 4 of antimicrobial activity it is clearly concluded that the synthesized compounds are promisingly significant, good anti-microbial agents. The substituted Dibenzalketone moieties are already known for different biological activities. Here we have synthesized some Dibenzalketone analogues combining with different substituted aromatic and hetero cyclic aldehydes ring system with view to get a good antimicrobial agent with less toxic and side effects. As per the results of screening it is clearly indicated that the compounds of the scheme have shown good antimicrobial activity equipotent with the standard drugs. This is because of the presence of groups like -OCH_3, -NO_2, -Cl etc. at the different positions of phenyl nucleus and heterocyclic system attached to Dibenzalketone nucleus, from the above results one can establish that the synthesized substituted Dibenzalketone can be rich source for the exploitation. Therefore in search of new

generation of the active compounds, it may be worthwhile to explore the possibility in this area or by making or introducing different functional groups or secondary amines or by cyclization as substitutions. Which may results into better pharmacological agents. The major of finding of this study is that the Synthesized compound have been confirmed to possess a highly significant activity by antimicrobial screening techniques and proves to be a better drug with respect to the inhibitory concentration of the pathogen when compared to the standard marketed miraculous drug.

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