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SILICA H_2SO_4 AS AN EFFICIENT HETEROGENEOUS CATALYST FOR THE SYNTHESIS OF NEW COUMARIN DERIVATIVES AND EVALUATION OF ANTIBACTERIAL ACTIVITY

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Abstract:

The literature survey indicates that benzopyran derivatives possess different pharmacological and biological activities. Coumarin derivatives have been shown to have interesting pharmacological activities such as antibacterial, anti-inflammatory, and antifungal activities. When one biologically active molecule is linked to another, the resultant molecule generally has an increased potency. Therefore, in the present study, two systems of Coumarin and chalcone are fused to obtain highly potent, specifically anti-inflammatory and less toxic antibacterial agents. The objective of the present work is to synthesize chalcone-substituted Coumarin derivatives and in particular study their antibacterial properties. The paper makes a modest attempt in that direction. Coumarin derivatives were synthesized using SSA as a potent catalyst. All the synthesized derivatives were characterized by $1H^1$ NMR, Mass spectra, and I.R. spectra. The antibacterial activity of the compounds was carried out using the disc diffusion method on nutrient agar media. Ampicillin and Gentamycin were used as standard drugs for the comparison in the concentration of 50 µg/ml and 100 µg/ml against Gram-positive and Gram-negative bacteria used for the study. Compounds 3g,3i, and 3j were found to possess good activity while compounds 3a, 3b, 3c, 3d, 3e, and 3f, were found to exhibit moderate activity. Among these various compounds 3g, 3i, and 3j particularly exhibited good activities against gram-negative bacteria. Hence, these compounds appear to be promising anti-bacterial agents. Perhaps the presence of $N(CH_3)_2$ and OH as a substituent on the aromatic nucleus attached to the 4^{th} position attached to Coumarin nucleus at the 3rd may be responsible for the good anti-bacterial activity.

Key words: *Silica Sulphuric Acid Catalyst, Disc Diffusion Method, Antibacterial Activity, Coumarin, Chalcones*

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INTRODUCTION:

The development of resistance to current anti-bacterial therapy continues to stimulate the search for more effective agents. In addition, primary and opportunistic fungal infections continue to increase rapidly because of the increased number of immune compromised patients (AIDS, Cancer and Transplants). Several reviews have appeared illustrating the problems encountered by increasing contemporary clinicians dealing with infectious diseases. The increasing clinical importance of drug resistant bacterial and fungal pathogens has lent additional urgency to anti-microbiological research and development of new anti-bacterial compounds.

Benzopyran derivatives possess different pharmacological and biological activities of which the most potent activity are anti-inflammatory (Nohara et al. 1974) and antibacterial (Nakatani.k et al 1996). Coumarin derivatives have been shown to have interesting pharmacological activities, like antibacterial (Bose PK et al. 1958), anti-inflammatory (Dean FM et al. 1952), antifungal, antiviral (Hwu. Jr. et al. 2008, Virjsen R. et al. 1988) anti-inflammatory (Nohara et al. 1974), antiallergic (Toimil. MC et al. 2002, Wiley PF et al. 1952), antimutagenic (Cassady JM. et al 1988) (Kalkhambkar. RG et al. 2008) and anticarcinogenic activities (Bhat. AS et al. 1999, Moris J et al. 1994)

When one biologically active molecule is linked to another, the resultant molecule generally has an increased potency. Hence in the present study, the two systems such as Coumarin and chalcone are fused to obtain highly potent, more specific anti-inflammatory and less toxic antibacterial agents. The objective of the present work is to synthesize chalcone-substituted Coumarin derivatives and study their antibacterial activity. Thus an attempt has been made in this direction. The reaction sequences for the synthesis of title compounds (Schonberg A et al 1948, Schmutz J et al 1952,Torri S 1993Heli Bron IM et al 1923) are mentioned in scheme-1.

The above results establish the fact that Coumarin can be a rich source for exploitation. Therefore, in search of new generation of active compounds, it may be worthwhile to explore the possibility in this area by fusing and substituting different moieties and increase the potency.

MATERIALS AND METHODS:

Experimental

All the melting points were recorded on the Cintex melting point apparatus and were uncorrected. IR spectra in KBr were recorded on the Shimadzu FTIR spectrophotometer in cm^{-1}. ^{1}HNMR spectra were recorded in $CDCl_3$ or DMSO on a Bruker DRX-300 MHZ NMR instrument. Chemical shifts were reported in ppm using TMS as an internal standard on the δ scale. Mass spectra of compounds were recorded on a mass spectrometer (Agilent 1100 series). Elemental analysis was carried out on Carlo Erba 106 and PerkinElmer model 240 analyzers. Completion of the reactions was monitored from time to time by TLC using E-Merck 0.25 mm silica gel plates and chloroform: methanol (9:1) as solvent system.

General Procedure for the synthesis of title compounds

PREPARATION OF 3-ACETYL COUMARIN (II):

- Into a clean dry round-bottomed flask salicylaldehyde (**I**) (0.1 mole, 12.2gm) and ethyl acetoacetate (0.1 moles, 13.1gm), and 25 ml of dry alcohol were introduced. Then 0.5 ml of piperidine was added with constant stirring. The reaction mixture was refluxed for 6 hrs at refluxing temperature and cooled. The separated yellow-colored product was collected by filtration, washed with 10 ml of alcohol, and dried. The product obtained was then recrystallized from ethanol with a melting point of 123° C and a yield of 85%.

PREPARATION OF SSA AS A CATALYST (SILICA-H_2SO_4):

The sulphuric acid was added to a stirred silica gel suspension in diethyl oxide. After stirring for 1 hr, the solvent was evaporated under reduced pressure. The resulting SSA was placed in an oven at 120° C for 3hr, which afforded SSA (Ayesha Sultan et al 2013) as a white solid.

GENERAL METHOD FOR THE PREPARATION OF COUMARINCHALCONES (IIIa-j):

The SSA(0.2 g) was added to a well stirred suspension of 3-acetyl coumarin (II) (1ml,0.90 g,7.53 mmol,1eq.) and different aldehydes (0.84g,7.91mmol,1.05 eq.) and the resulting mixture was heated at 65^0 C for 1.5hr.

The reaction mixture was cooled to room temperature and partitioned between brine (25ml) and CH_2Cl_2(3* 15 ml) and solid SSA was filtered off. The SSA was washed with acetone (25ml) to ensure desorption of product on SSA surface. The combined organic extract was washed with brine (3 * 25 ml) and the organic extract dried over anhydrous Na_2SO_4,filtered and concentrated under reduced pressure to afford the chalcone as colourless solid (1.48 g,91%).

The scheme & characterization of the compounds mentioned in **Scheme-1 and Table -1**.

Compound2: 3-Acetyl-2H-Chromen-one

Molecular formula:$C_{11}H_8O_3$, molecular Weight:188,Melting Point:118-121,Solvent for recrystallisation: Ethanol.^{1}HNMR (DMSO-d_6)δ8.653(s, H of coumarin),δ7.3-7.7(m,4H of aromatic protons),δ2.582(s,3H of $CH_3$of OCH_3).

Compounds 3a-3j

3a.3-[(*E*)-3-phenyl-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{18}H_{12}O_3$, Molecular Weight:276.2, Melting Point:221, Solvent for recrystallisation: Ethanol.
IR(KBr)cm^{-1}2922,2852(CH(s)),1722,1658(C=O(s)),1606(C=S(s)),1255,1041(C-O-C(s)),867,758(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.3-7.7(m,10H (8H aromatic&2Hof CH=CH)),mass: m/z277.3(M+1) anal, calculated from M.F is 276.2.

3b.3-[(*E*)-3-(4-chlorophenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{18}H_{11}ClO_3$, Molecular Weight:310.7, Melting Point:221, Solvent for recrystallisation: Ethanol
IR(KBr)cm^{-1}2919,2855(CH(s)),1725,1650(C=O(s)),1612(C=S(s)),1250,1046(C-O-C(s)),865,752(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.0-7.5(m,10H (8H aromatic&2Hof CH=CH)),mass:m/z311.9(M+1)anal, calculated from M.F is 310.7.

3c.3-[(*E*)-3-(2-chlorophenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{18}H_{11}ClO_3$, Molecular Weight:310.7, Melting Point:229Solvent for recrystallisation: Ethanol.
IR(KBr)cm^{-1}2921,2853(CH(s)),1723,1655(C=O(s)),1615(C=S(s)),1250,1048(C-O-C(s)),862,750(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.0-7.5(m,10H (8H aromatic&2Hof CH=CH)),mass:m/z311.8(M+1)anal, calculated from M.F is 310.7.

3d.3-[(*E*)-3-(4-nitrophenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{18}H_{11}NO_5$, Molecular Weight:321.2, Melting Point:209, Solvent for recrystallisation: Ethanol.
IR(KBr)cm^{-1}2919,2848(CH(s)),1720,1653(C=O(s)),1611(C=S(s)),1252,1046(C-O-C(s)),858,755(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.3-7.8(m,10H (8H aromatic&2Hof CH=CH)),mass:m/z322.8(M+1)anal, calculated from M.F is 321.2.

3e.3-[(*E*)-3-(2-nitrophenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{18}H_{11}NO_5$, Molecular Weight:321.2, Melting Point:231, Solvent for recrystallisation: Ethanol.
IR(KBr)cm^{-1}2919,2848(CH(s)),1720,1653(C=O(s)),1611(C=S(s)),1252,1046(C-O-C(s)),858,755(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.3-7.8(m,10H (8H aromatic&2Hof CH=CH)),mass:m/z322.6(M+1)anal, calculated from M.F is 321.2.

3f.3-[(*E*)-3-(4-methoxyphenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{19}H_{14}O_4$, Molecular Weight:306.3,Melting Point:222,Solvent for recrystallisation: Ethanol IR(KBr)cm^{-1}2917,2846(CH(s)),1719,1655(C=O(s)),1607(C=S(s)),1250,1048(C-O-C(s)),855,757(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.5-7.9(m,13H(8Haromatic&2HofCH=CH&3HofOCH_3)),mass:m/z307.6(M+1)anal, calculated from M.F is 306.6.

3g.3-(*E*)-3-[4-(dimethylamino)phenyl]-2-propenoyl-2*H*-2-chromenone

Molecular formula:$C_{20}H_{17}NO_3$, Molecular Weight:319.3, Melting Point:241, Solvent for recrystallisation: Ethanol
IR(KBr)cm^{-1}2916,2845(CH(s)),1718,1657(C=O(s)),1609(C=S(s)),1253,1050(C-O-C(s)),852,753(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.2-7.5(m,10H(8Haromatic&2HofCH=CH))δ2.3(6HofN(CH_3)$_2$),mass:m/z320.6(M+1)anal, calculated from M.F is 319.3.

3h.3-[(*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula: $C_{19}H_{14}O_5$, Molecular Weight:322.3,Melting Point:211,Solvent for recrystallisation: Ethanol

IR(KBr)cm^{1}3063(OH(s)),2917,2846(CH(s)),1719,1655(C=O(s)),1607(C=S(s)),1250,1048(C-O-C(s)),855,757(sub.benzenering)^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.5-

7.9(m,13H(8Haromatic&2HofCH=CH&3HofOCH$_3$)),δ10.5(s,broadHof OH)mass:m/z323.6(M+1)anal, calculated from M.F is 322.3.

3i.3-[(*E*)-3-(4-hydroxyphenyl)-2-propenoyl]-2*H*-2-chromenone

Molecular formula:$C_{18}H_{12}O_4$,Molecular Weight:282.2,Melting Point:201Solvent for recrystallisation: EthanolIR(KBr)cm^{1}3068(OH(s)),2917,2846(CH(s)),1719,1655(C=O(s)),1607(C=S(s)),1250,1048(C-O-C(s)),855,757(sub.benzenering),^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.1-7.5(m,10H(8Haromatic&2HofCH=CH)),δ10.5(s,broadHofOH)mass:m/z283.6(M+1)anal, calculated from M.F is 282.2.

3j.3-[(*E*)-3-(2-hydroxyphenyl)-2-propenoyl]-2*H*-2-chromenone

Molecularformula:$C_{18}H_{12}O_4$, Molecular Weight:282.2, Melting Point:236, Solvent for recrystallisation: Ethanol

IR(KBr)cm^{1}3072(OH(s)),2917,2846(CH(s)),1719,1655(C=O(s)),1607(C=S(s)),1250,1048(C-O-C(s)),858,755(sub.benzenering),^{1}HNMR(DMSO-d_6),δ8.6(s,Hofcoumarin),δ7.5-7.9(m,10H(8Haromatic&2HofCH=CH)),δ10.8(s,broadHofOH)mass:m/z283.4(M+1)anal, calculated from M.F is 282.2.**Biological Activity**

ANTI-BACTERIAL ACTIVITY: (Gammill RB 1971)

All the compounds synthesized in the present investigation were screened for their anti-bacterial activity by subjecting the compounds to standard procedures. Antibacterial activities were tested in a nutrient medium against Bacillus pumilus, Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa which are representative types of gram-positive and gram-negative organisms respectively. The antibacterial activity of the compounds was assessed by disc-diffusion method.[25-26]

PREPARATION OF NUTRIENT AGAR MEDIA

The weighed quantities of peptone and beef extract were dissolved in distilled water through gentle warming and then specified amount of agar was dissolved by heating on water bath. The P^h of the solution was adjusted to 7.2 to7.4 by adding sodium chloride and the volume of the final solution made up to 1000 ml with distilled water. Then it was transferred into a suitable container, plugged with non-adsorbent cotton and the media sterilized in autoclave at 121^{0}C for 20 minutes at 15 lbs pressure.**PREPARATION OF TEST SOLUTIONS:**

10 mg of the compound was dissolved in 10 ml of DMF. From this 1 ml of solution was taken and diluted up to 10 ml with DMF. Now the concentration of the test solution was 100 µg/ml.

PREPARATION OF STANDARD ANTIBIOTIC SOLUTION:

Gentamycin and Ampicillin were used as standard antibiotics for comparison and solutions were prepared using sterile water, as they were water-soluble. The solutions were diluted using sterile water so that the concentrations of the solutions were 100 µg/ml.

PREPARATION OF DISCS:

Discs of 6-7 mm in diameter were punched from NO:1 Whattmann filter paper with sterile cork borer of the same size. These discs were sterilized by keeping in oven at 140^{0}c for 60 minutes. Then standard and test solutions were added to each disc and discs air-dried.

METHOD OF TESTING:

The sterilized media was cooled to 45^{0}c with gentle shaking to bring about uniform cooling and then inoculated with 18-24 hrs old culture under aseptic conditions gently mixed well. This was poured in to sterile Petri dishes (properly labeled) and allowed the medium to set. After solidification all the Petri dishes were transferred to laminar flow unit. Then the discs previously prepared were carefully kept on the solidified media using sterilized forceps. These Petri dishes were kept as it is for one-hour diffusion at room temperature and then for incubation at 37^{0}c for 24 hours in an incubator. The extent diameter of inhibition after 24 hours was measured as the zone of inhibition in millimeters and the results are shown in **Table-II.**

RESULTS AND DISCUSSION:

Chemistry

The synthetic methodology followed to obtain the target compounds is outlined in Scheme 1. The synthesis of compound-2, 3 Acetyl Coumarin through the reaction between salicylaldehyde (**I**) (0.1 mole, 12.2gm) and ethyl acetoacetate (0.1 mole, 13.1gm) and 25 ml of dry alcohol. Then 0.5 ml of piperidine was added along with constant stirring. The reaction mixture was refluxed for 6 hrs at refluxing temperature and then cooled. The separated yellow coloured product was collected by filtration, washed with 10 ml of alcohol and dried. The obtained product was recrystallized from ethanol at melting point 123 ^{o}C and the yield was 85%. The Coumarin

chalcones (3 a-j) were synthesized by reacting SSA ,3 Aetyl Coumarin, Different aldehydes & brine solution. All the obtained compounds were characterized by IR,[1]HNMR, Mass Spectroscopy.

ANTI-BACTERIAL SCREENING

The resulted 10 compounds were screened for antibacterial activity studies at a concentration of 50µg/ml and 100µg/ml using DMF as control against *Staphylococcus aureus, Bacillus pumilus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa* by disk-diffusion method on nutrient agar media. Ampicillin and Gentamycin were used as standard drugs for the comparison in the concentration 50 µg/ml and 100 µg/ml against Gram positive and Gram negative bacteria used for the study.

The data in the Table 3 indicate that compounds 3g, 3i and 3j were found to possess good activity. The compounds 3a, 3b, 3c, 3 d, 3 e, and 3f, were found to exhibit moderate activities. Among these various compounds 3g, 3i and 3j showed good activities in particular against gram-negative bacteria and the results were shown in TABLE-II. Hence these compounds appear to be promising anti-bacterial agents. Perhaps the presence of N $(CH_3)_2$ and OH as a substituent on aromatic nucleus is attached to 4th position which in turn is attached to Coumarin nucleus at 3 rd and could be responsible for good anti-bacterial activity.

CONCLUSION:

The two moieties, i.e. Coumarin and chalcone moieties that are independently antibacterial agents and screened for antibacterial studies showed a broad spectrum of antibacterial activity. The Coumarin molecule is responsible for antibacterial activity, but it is interesting to note that chalcone moiety when fused with other moieties showed a good antibacterial activity. The above results establish the fact that Coumarin can be a rich source for exploitation. Therefore, in searching for a new generation of active compounds, exploring the possibility in this area by fusing and substituting different moieties and increasing the potency may be worthwhile. Hence in the present study, the two systems Coumarin and chalcones are linked to each other and show highly potent and less toxic antibacterial agent. In this combination, a significant increase in activity is expected as a result.

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SCHEME 1

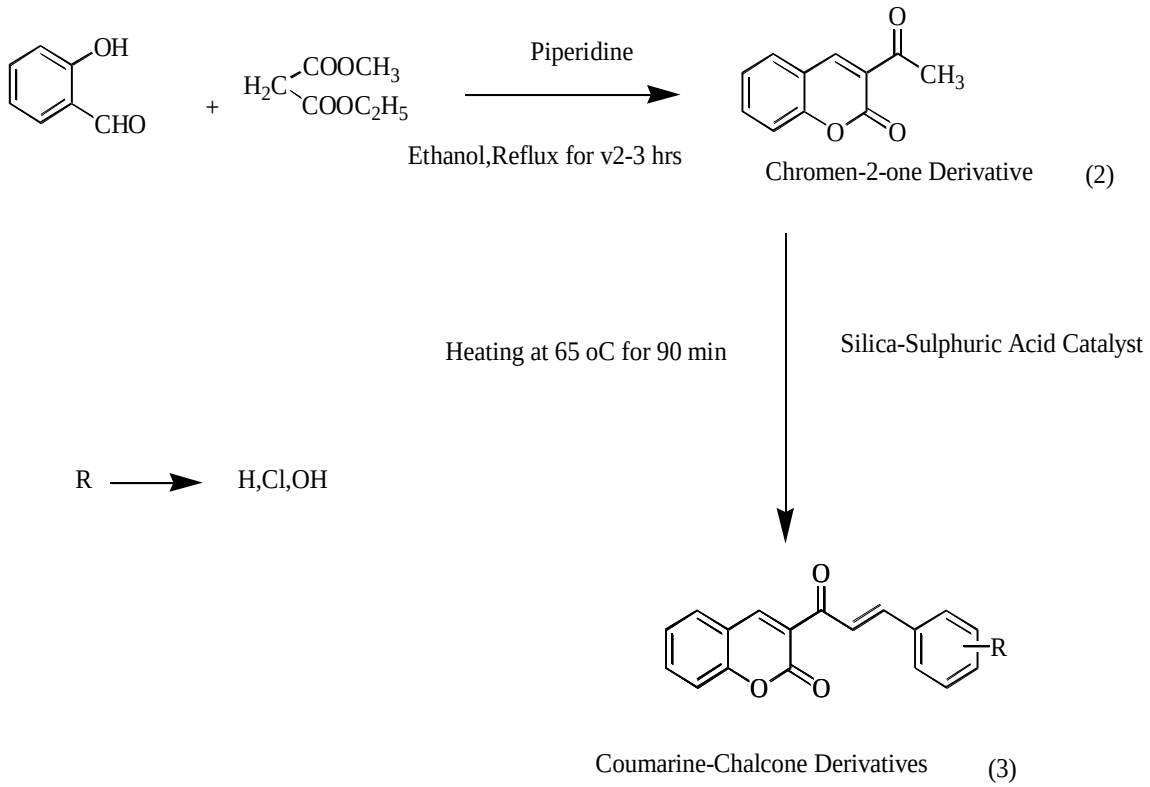

TABLE-1

Characterization of Compounds 3(a-j)

S.No	Product code	R	Mol.Formula (Mol.Weight)	Solvent recrystallisation	M.P(Yield %)
1	3a	H	$C_{18}H_{12}O_3$(276.2)	Ethanol	221(70)
2	3b	p-Cl	$C_{18}H_{11}ClO_3$(310.7)	Ethanol	221(70)
3	3c	o-Cl	$C_{18}H_{11}ClO_3$(310.7)	Ethanol	229(70)
4	3d	p-NO_2	$C_{18}H_{11}NO_5$(321.2)	Ethanol	202(70
5	3e	o-NO_2	$C_{18}H_{11}NO_5$(321.2)	Ethanol	231(70
6	3f	p-OCH_3	$C_{19}H_{14}O_4$(306.3)	Ethanol	222 (70
7	3g	$N(CH3)_2$	$C_{20}H_{17}NO_3$(319.3)	Ethanol	241(70
8	3h	p-$OCH_{3,}$),o-OH	$C_{19}H_{14}O_5$(322.3)	Ethanol	211(70
9	3i	p-OH	$C_{18}H_{12}lO_4$(292.2)	Ethanol	201(70
10	3j	o-OH	$C_{18}H_{12}lO_4$(292.2)	Ethanol	236(70

TABLE :2

Antibacterial activity of newly synthesized Coumarin derivatives:

Sample Code	*Inhibition zone diameter in mm									
	S.aureus		B.subtilis		B.pumilis		E.coli		P.aureginosa	
	50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
3a	3	7	4	8	5	9	4	9	6	10
3b	7	11	8	14	6	13	12	14	8	12
3c	5	7	4	9	4	8	7	10	5	8
3d	7	16	7	17	7	15	11	17	7	15
3e	3	10	5	12	3	9	6	12	6	11
3f	8	19	8	18	9	18	12	20	8	18
3g	7	18	8	19	8	18	8	19	11	22
3h	8	17	7	17	8	16	8	17	9	18
3i	6	15	6	16	7	13	10	16	10	21
3j	2	8	5	11	4	9	-	8	9	20
Gentamycin	13	19	12	17	15	20	13	24	15	25
Ampicillin	15	23	14	24	13	23	14	22	14	23
DMF	-	-	-	-		-	-	-	-	-

*Average of triplicate ± Standard deviation

Note: '-'denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 above good.