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SYNTHESIS, CHEMICAL TRANSFORMATION AND ANTIMICROBIAL ACTIVITY OF A NOVEL CLASS OF NITROOLEFINS: 1,3-DIARYL-2-NITROPROP-1-ENES

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Abstract-The synthesis of novel, biologically active 1,3-diaryl-2-nitroprop-1-enes (**4**) is reported. The synthesis involves condensation between aromatic aldehydes (**1**) and β-aryl nitroethanes (**3**). The chemical transformation of the nitro group in diaryl nitropropenes to a carbonyl function has resulted in a new route to the synthesis of an α-hydroxy analog (**7c**) of a naturally occurring 3, 3′, 4, 4′ -tetramethoxy chalcone.The antimicrobial activity of the 1, 3-diaryl-2-nitroprop-1-enes (**4a-j**) was tested against three gram positive bacteria, two gram negative bacteria and two fungi. These compounds exhibited broad spectrum antimicrobial activity.

The past few years have witnessed an upsurge of interest in the chemistry of nitro compounds as starting materials for the synthesis of various natural products. Varma and Kabalka[1] have reviewed the synthetic utility of nitroalkenes. In continuation of our studies on nitroolefins[2-4], it was envisaged that the unique structural features of 1,3-diaryl-2-nitro-prop-1-enes (**4a-j**) make them potential synthons that would enable one to devise appropriate methods to synthesize various natural products ranging from chalcones through flavones to anthocyanins. The synthesis of these nitropropenes has not been reported earlier.A variety of preparations containing nitro compounds are of therapeutic importance in the treatment of

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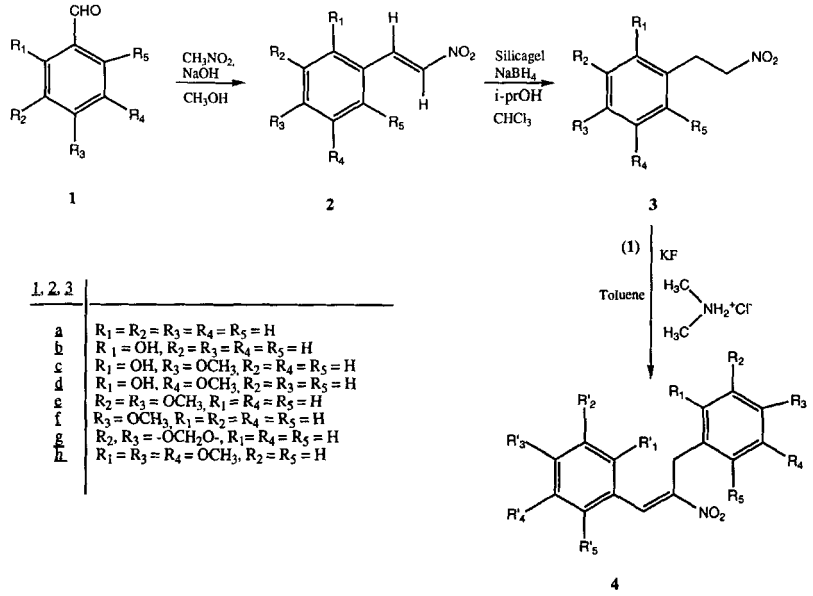
infectious diseases. Although the number of naturally occurring nitro compounds may be small, the group is still important as it ranges from antibiotics to carcinogens. Eckstein[5] has extensively reviewed the biological activity of nitro compounds both of natural and synthetic origin. The introduction of a nitro group into various aliphatic and aromatic hydrocarbons often results in substances with fungicidal activity[6]. A number of 2-nitro-3-propanediol derivatives are known to exhibit fungicidal activity including activity against plant pathogens[5]. β-Nitrostyrene is a fungicide used in medicine and agriculture[7], while the *m*- and *p*- fluoro derivatives are potent insecticides[8]. Also, β-nitrostyrene has been reported to inhibit bacterial growth and its effectiveness was slightly reduced when the culture medium contained protein. It was found that 1-(3,4-dichlorophenyl)-2-nitropropene was most effective against *Micrococcus pyrogenes var aureus* (*M. pyrogenes*) in protein free medium, while 2,6-dichloro-β-nitrostyrene was potent against the same organism in the presence of albumin[9]. β-Nitrostyrene in concentration of less than 1 mg/100 mL of culture medium inhibits the growth of *M. pyrogenes* and *Escherichia coli*. (*E. coli*). A β-nitrostyrene where the 2- or 3- position is substituted by a hydroxy group showed very little activity against *M. pyrogenes* while methoxy, ethoxy and nitro substituents increased the activity.

In view of the significant biological activity of nitroolefins, we have prepared a novel class of 1,3-diaryl-2-nitroprop-1-enes which are structurally akin to b-nitrostyrenes. The synthesis of these compounds is shown in Scheme 1. The synthetic route involved condensation of aromatic aldehydes **1a-h** with nitromethane in the presence of sodium hydroxide. The nitrostyrenes **2a, e, f, g** obtained were reduced with sodium borohydride in a biphasic system consisting of silica gel, chloroform and isopropanol[10]. The saturated nitro compounds so formed (**3a, e, f, g**) were further condensed[11] with appropriate aromatic aldehydes to give the corresponding 1,3-diaryl-2-nitroprop-1-enes (**4a-j**) in good yields. The structures of compounds **4a-j** are listed in Figure 1. The products were purified by silica gel column chromatography using petroleum ether : ethyl acetate as the eluant. Table 1 lists the physical and spectral data of these compounds.



1, 2, 3	
a	$R_1 = R_2 = R_3 = R_4 = R_5 = H$
b	$R_1 = OH$, $R_2 = R_3 = R_4 = R_5 = H$
c	$R_1 = OH$, $R_3 = OCH_3$, $R_2 = R_4 = R_5 = H$
d	$R_1 = OH$, $R_4 = OCH_3$, $R_2 = R_3 = R_5 = H$
e	$R_2 = R_3 = OCH_3$, $R_1 = R_4 = R_5 = H$
f	$R_3 = OCH_3$, $R_1 = R_2 = R_4 = R_5 = H$
g	$R_2, R_3 = -OCH_2O-$, $R_1 = R_4 = R_5 = H$
h	$R_1 = R_3 = R_4 = OCH_3$, $R_2 = R_5 = H$

SCHEME 1

The conversion of a diaryl nitropropene **4(c)** to a dicarbonyl compound **7(c)** was successfully achieved in three steps as shown in Scheme 2. Sodium borohydride reduction of the 1,3-diaryl-2-nitroprop-1-enes (**4b-e**) gave the saturated nitro compounds **5(b-e)**. Chromium (II) chloride reduction of the nitro group in compounds **5(b-e)** resulted in the formation of the corresponding keto derivatives **6(b-e)**. The 1,3-bis(3,4-dimethoxyphenyl)-propan-2-one **6(c)** was oxidized using pyridinium chlorochromate[12] (PCC) to give the desired α-hydroxy chalcone **7(c)** in good yield. All the compounds thus synthesized were characterized by their spectral properties (Table 1). Thus, a novel class of biologically active nitroolefins has been synthesized and a convenient, alternative route has been developed for the synthesis of biodynamic α-hydroxy chalcones.

Antimicrobial Activity

The nitro group is strongly electron withdrawing and since the carbon-carbon double bond in nitroolefins is highly activated towards nucleophilic additions, it seems possible that the

Table 1: Physical and Spectral Data of Compounds 4, 5, 6 and 7

Entry	Compound	Yield (%)	M.P.(°C)	IR (υ_{max}, $CHCl_3$)	^{1}H-NMR (δ,$CDCl_3$)	m/z	Elemental Analysis*		
							C	H	N
1	4a	70	112	3360,1640,1600 1500,1320	4.21(s,2H,-CH_2), 5.49(s,1H,OH), 6.8-7.3(m,9H,Ar-H), 8.4(s,1H,olefinic)	256(M+),237 220,165,91,65	70.56 (70.58)	5.09 (5.09)	5.38 (5.49)
2	4b	65	Liq**	1520,1460,1310 1260	4.21(s,2H,-CH_2), 3.77,3.82(s,6H, OCH_3), 5.49(s,1H,OH), 6.8-6.9(m,8H,Ar-H), 8.2(s,1H,olefinic)	300(M+),238, 209,165,91,77	68.20 (68.23)	5.59 (5.68)	4.62 (4.68)
3	4c	80	121	1630,1580,1460, 1310,1280	4.21(s,2H,-CH_2), 3.7-3.9(4s,12H,OCH_3), 6.7-7.2(m,6H,Ar-H), 8.3(s,1H,olefinic)	360(M+),313 298,175,107,77	63.23 (63.50)	5.73 (5.84)	3.80 (3.89)
4	4d	70	137	1640,1610,1520 1480,1270	4.2(s,2H,-CH_2), 3.4-3.9((5s,15H,OCH_3), 6.5-7.2(m,5H,Ar-H), 8.6(s,1H,olefinic)	390(M+),372, 312,197,107,77	61.62 (61.69)	5.84 (5.91)	3.62 (3.59)
5	4e	65	142	1650,1610,1500 1480,1240	4.18(s,2H,-CH_2), 5.9-6.0(2s,4H,OCH_2O), 6.6-7.2(m,6H,Ar-H), 8.6(s,1H,olefinic)	328(M+),281, 165,111,77	62.35 (62.38)	3.89 (3.97)	4.23 (4.28)
6	4f	65	124	1620,1600,1570 1470,1280	4.16(s,2H,-CH_2), 3.4-3.9(6s,18H,OCH_3), 6.5-7.2(4s,4H,Ar-H), 8.6(s,1H,olefinic)	420(M+),402 341,206,91,69	60.04 (60.14)	5.93 (5.96)	3.25 (3.34)

Table 1 (Contd.)

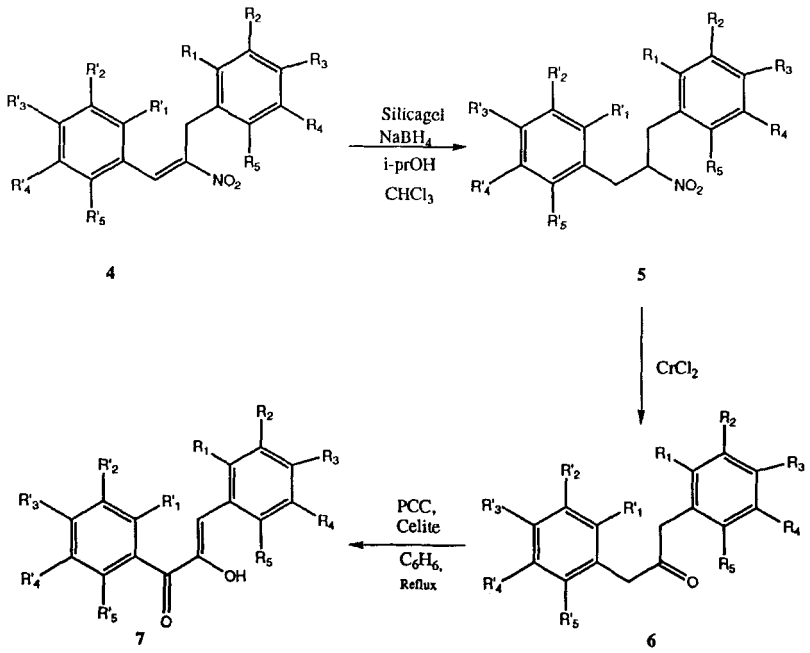
7	4g	70	136	3340,1610,1600 1520,1490,1260	4.25(s,2H,-CH_2), 3.7(s,3H,OCH_3),5.7 (s,1H,OH),6.4-7.4 (m,8H,Ar-H)	286(M+),239 165,91,77,65	67.28 (67.36)	5.32 (5.26)	4.72 (4.91)
8	4h	60	113	3400,1640,1600 1510,1460,1280	4.25(s,2H,-CH_2), 3.5(s,3H,OCH_3), 5.2(s,1H,OH),6.7-7.3 (m,8H,Ar-H),8.4 (s,1H,olefinic)	286(M+),240 207,165,91,77 65	67.23 (67.36)	5.25 (5.26)	4.89 (4.91)
9	4i	65	177	3380,1630,1600 1500,1450,1280	4.15(s,2H,-CH_2), 3.83(s,3H,OCH_3), 5.4(s,1H,OH),6.7-7.3 (m,7H,Ar-H),8.4(s,1H, olefinic)	316(M+),298, 238,165,91,77 65	64.72 (64.76)	5.41 (5.39)	4.32 (4.44)
10	4j	70	174	3360,1630,1600 1510,1460,1280	4.19(s,2H,-CH_2), 3.79,3.84,3.85 (3s,9H,OCH_3),5.6 (s,1H,OH),6.4-7.2 (m,6H,Ar-H),8.5(s,1H, olefinic)	345(M+),298, 161,107,91,77, 65	62.53 (62.66)	5.49 (5.51)	4.04 (4.05)
11	5b	70	134	1600,1550,1440 1350	2.9-3.2(2dd,4H,2-CH_2), 3.7(s,3H,OCH3),4.8 (m,1H,H-CNO_2),6.8-7.0 (2dt,8H,Ar-H)	301(M+),255, 223,121,91	67.64 (67.77)	6.2 (6.3)	4.59 (4.65)
12	5c	76	117	1600,1540,1440 1350	3.0-3.2(2dd,4H,2-CH_2), 3.8(s,12H,OCH_3),4.8 (m,1H,H-CNO_2),6.6-7.2 (m,6H,Ar-H)	362(M+),315 283,151,107, 91	63.20 (63.16)	6.41 (6.37)	3.85 (3.88)

(continued)

Table 1 (Contd.)

13	5d	75	105	1600,1540,1450 1370	2.9-3.2(2dd,4H,2-CH_2), 3.7-3.8(5s,15H,OCH_3), 5.0(m,1H,H-CNO_2), 6.4-6.8(m,5H,Ar-H)	392(M+),345 181,151,107, 91	61.35 (61.38)	6.37 (6.39)	3.25 (3.58)
14	5e	50	103	1600,1520,1480 1360	2.9-3.2(2dd,4H,2-CH_2), 4.8(m,1H,H-CNO_2), 5.9(S,4H,-OCH_2O), 6.5-6.8(m,6H,Ar-H)	329(M+),283, 161,105,77	62.00 (62.00)	4.50 (4.56)	4.18 (4.25)
15	6B	60	172	1700,1600	3.6(s,4H,2-CH_2),3.8 (s,6H,OCH_3),6.8-7.0 (2dt,8H,Ar-H)	270(M+),121, 91,77	75.50 (75.55)	6.67 (6.67)	
16	6c	60	102	1710,1600,1590	3.6(s,4H,2-CH_2), 3.3.83,3.87(2s,12H, OCH_3),6.6-6.8(m,6H, Ar-H)	331(M+),196, 151,107	69.03 (69.09)	6.62 (6.67)	
17	6d	76	91	1700,1600,1580	3.6(s,4H,2-CH_2), 3.7-3.8(5s,15H,OCH_3), 6.5-6.8(m,5H.Ar-H)	361(M+),182 152,107,91	66.67 (66.67)	6.67 (6.67)	
18	6e	40	79	1690,1600	3.6(s,4H,2-CH_2), 5.9(s,4H,-OCH_2O), 6.5-6.7(m,6H,Ar-H)	299(M+),162, 135,79,51	68.42	4.50	
19	7c	60	98	3440,1710,1650, 1600	3.8-4.2(2s,12H,OCH_3), 5.9(s,1H,OH),7.48(s,1H, olefinic),6.9-7.8(m,6H,Ar-H)	344(M+),178, 151,107,65	62.28 (66.28)	5.81 (5.81)	

*-Calculated values are indicated in parentheses; **-boiling points not recorded



SCHEME 2

biological activity may involve reactions with a variety of biologically important nucleophiles such as sulfhydryl groups[13]. It also seemed possible that the saturated nitro compounds first undergo a reaction to form the unsaturated derivatives prior to exhibiting biological activity. If the biological activity of ß-nitrostyrenes is due to the electrophilicity of the double bond, then many properly substituted nitroolefins would be expected to be potent antimicrobial agents.

We report herein the antimicrobial activity of 1,3-diaryl-2-nitroprop-1-enes (**4a-j**) against two gram positive and two gram negative bacteria and two species of fungi. Special attention was paid to study the influence of positional variation of methoxy and hydroxy groups in the aromatic rings on the antimicrobial potency of compounds **4a-j**. The zone inhibition values for these compounds are presented in Table 2. The minimum inhibitory concentrations of these molecules were evaluated against each of the microorganisms using broth dilution technique[14] and are

Table 2: Inhibition Zone Measurements (mm)*

Compound	Gram Positive Bacteria			Gram Negative Bacteria		Yeasts	
	Sa	Bs	Sl	Ec	St	Sc	Ca
4a	-	12	-	-	18	20	17
4b	14	-	-	25	21	21	21
4c	-	-	-	20	12	-	13
4d	12	16	10	20	16	-	22
4e	11	20	-	24	22	20	24
4f	-	21	-	17	10	18	20
4g	-	18	-	-	14	12	11
4h	-	20	-	22	20	24	18
4i	12	17	-	16	15	18	20
4j	-	17	11	20	22	14	18

*- Only inhibition zones greater than 10 mm in diameter are reported.

Sa: Streptomyces aureus, Bs: Bacillus subtilis, Sl: Sarcina lutea, Ec: Escherichia coli, St: Salmonella typhosa, Sc: Saccharomyces cerevesciae, Ca: Candida albicans

reported in Table 3. Most of these compounds were very active against the two gram negative bacteria *E.coli* and *Salmonella typhosa* (*S. typhosa*) (MIC: 50-100 μg/mL). Except for **4c** and **4j** which showed a slight activity (200 and 100 μg/mL respectively), the other compounds were inactive against *Sarcina lutea.* (*S. lutea.*). Therefore, the presence of a methoxy group at 4 or 4′ position seems to be essential in addition to a hydroxy or a methoxy group at 2′ position. This was confirmed by the lack of activity of compound **4a** (no methoxy substitutions at positions 4 or 4′) against *S. lutea.* All the 1,3-diaryl-2-nitroprop-1-enes were moderately active against *Bacillus subtilis* (*B. subtilis*), *S. typhosa*, *E. coli*, *Saccharomyces cerevesciae* (*S. cerevesciae*) and *Candida albicans* (*C. albicans*). These compounds were not found to be superior to the antibiotics used as the standards for the test systems.

Table 3: Minimum Inhibitory Concentration (μg/mL) of Diaryl Nitropropanes (4a-j) against Bacteria and Yeasts

Compound	Gram Positive Bacteria			Gram Negative Bacteria		Yeasts	
	Sa	Bs	Sl	Ec	St	Sc	Ca
4a	200	70	x	x	100	50	70
4b	50	100	x	50	50	50	70
4c	x	x	x	70	200	x	200
4d	50	50	200	70	100	x	70
4e	70	50	x	50	50	50	50
4f	x	50	x	100	200	75	70
4g	x	70	x	x	70	100	100
4h	x	70	x	50	50	50	50
4i	100	50	x	50	100	50	50
4j	x	50	100	100	50	100	100
S*	5	-	-	3	-	-	-
A	2	1	-	-	-	-	-
N	-	-	-	-	-	-	3

x- indicates growth
Sa: Streptomyces aureus, Bs: Bacillus subtilis, Sl: Sarcina lutea, Ec: Escherichia coli, St: Salmonella typhosa, Sc: Saccharomyces cerevesciae, Ca: Candida albicans, S: Streptomycin, A: Ampicllin, and N: Nystatin.

Experimental Section.

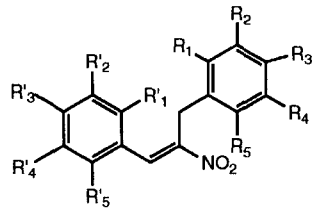
All melting points are uncorrected. Infrared spectra were scanned on a Perkin-Elmer Model 681 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were recorded on a Varian VXR-300 FT NMR spectrometer ($CDCl_3$, TMS as internal standard). Mass spectra were recorded on a Shimadzu QP-1000 mass spectrometer.

General Procedure:

β-Nitrostyrenes (2 a, e, f, g): A mixture of nitromethane (0.2 mol) and the appropriately substituted benzaldehyde (**1a-h**, 0.2 mol) in methanol (50 mL) was stirred at 0 °C. An aqueous solution of sodium hydroxide (0.225 mol) was added over a period of 30 minutes. The stirring was continued for another half hour in the temperature range of 0-5 °C. The mixture was diluted with water (100 mL) and poured over crushed ice containing 32 mL conc. HCl. The yellow solid which precipitated out was filtered, dried in a vacuum dessicator and recrystallized from ethanol. The nitrostyrenes were characterized by their physical and spectral data (Table 1).

2-Aryl-1-Nitroethanes (3a, e, f, g): To an efficiently stirred mixture of β-nitrostyrene (1 mmol), silica gel (2 g), 2-propanol (3 mL) and chloroform (16 mL), was added sodium borohydride (4.1 mmol) over a period of 15 minutes at 25 °C. The mixture was stirred for an additional 15 minutes (disappearance of yellow color). The excess borohydride was decomposed with dilute HCl followed by the washing of the silica gel cake with methylene chloride. The resultant solution was washed with brine, water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the 2-aryl-1-nitroethanes in good yields.

1,3-Diaryl-2-Nitroprop-1-enes (4a-j): 2-Aryl-1-nitroethane (0.021 mol), dimethyl amine hydrochloride (0.04 mol), benzaldehyde (0.021 mol), toluene (15 mL) and potassium fluoride (0.0016 mol) were taken in a 100 mL round bottomed flask fitted with a Dean-Stark water separator. The mixture was refluxed with stirring for 6-10 hrs. The solvent was removed from the reaction vessel to give a crude product. Chloroform (10 mL) and 0.2N HCl (20 mL) were added to the crude material and the solution was heated on a water bath at 60 °C for 2 minutes



(a) $R_1' = OH$, $R_1 = R_2 = R_3 = R_4 = R_5 = R_2' = R_3' = R_4' = R_5' = H$
(b) $R_3 = R_3' = OCH_3$, $R_1 = R_2 = R_4 = R_5 = R_1' = R_2' = R_4' = R_5' = H$
(c) $R_2 = R_3 = R_2' = R_3' = OCH_3$, $R_1 = R_4 = R_5 = R_1' = R_4' = R_5' = H$
(d) $R_1' = R_2 = R_3 = R_2' = R_3' = OCH_3$, $R_1 = R_4 = R_5 = R_2' = R_5' = H$
(e) $R_2, R_3 = R_2', R_3' = -OCH_2O-$, $R_1 = R_4 = R_5 = R_1' = R_4' = R_5' = H$
(f) $R_1 = R_3 = R_4 = R_1' = R_3' = R_4' = OCH_3$, $R_2 = R_5 = R_2' = R_5' = H$
(g) $R_1' = OH$, $R_3' = OCH_3$, $R_2' = R_4' = R_5' = R_1 = R_2 = R_3 = R_4 = R_5 = H$
(h) $R_1' = OH$, $R_4' = OCH_3$, $R_2' = R_3' = R_5' = R_1 = R_2 = R_3 = R_4 = R_5 = H$
(i) $R_1' = OH$, $R_2 = R_3 = OCH_3$, $R_2' = R_3' = R_4' = R_5' = R_1 = R_4 = R_5 = H$
(j) $R_1' = OH$, $R_3' = R_2 = R_3 = OCH_3$, $R_2' = R_4' = R_5' = R_1 = R_4 = R_5 = H$

under reduced pressure. The crystalline solid obtained after cooling the mixture at 0 °C overnight was filtered and dried. The chloroform layer was separated and the aqueous layer was extracted with methylene chloride. Both the organic extracts were dried over anhydrous $MgSO_4$. The residue which was obtained after removal of methylene chloride and the previously filtered solid were chromatographed on silica gel (pet ether:ethyl acetate, 90:10). The product was further recrystallized from pet ether-ethyl acetate to yield 1,3-diaryl-2-nitroprop-1-enes (**4a-j**). The compounds were characterized by their physical and spectral data.

1,3-Diaryl-2-Nitropropanes (5b-e): To an efficiently stirred mixture of β-nitrostyrene (1 mmol), silica gel (2 g), 2-propanol (3 mL) and chloroform (16 mL), was added sodium borohydride (4.1 mmol) over a period of 15 minutes at 25 °C. After stirring for an additional 15 minutes (disappearance of yellow color), the excess borohydride was decomposed with dilute HCl and the silica gel cake was washed with methylene chloride. The resultant solution was treated with brine, water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the 1,3-diaryl-2-nitropropanes in good yields.

1,3-Diaryl Propan-2-ones (6b-e): To a solution of diaryl nitropropane (**5b-e**, 2 mmol) in tetrahydrofuran (15 mL), aqueous chromous chloride solution (40 mL) was added under nitrogen atmosphere at ambient temperature. After 10 minutes, the reaction mixture was diluted with water and extracted with methylene chloride. The organic extract was washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent gave a crude product which was recrystallized from pet ether-ethyl acetate.

Chalcone (7c): To a solution of diaryl propanone (**6c**, 2 mmol) in benzene (20 mL), a finely powdered and homogenized mixture of pyridinium chlorochromate (5 mmol) and celite (5 g) was added. The reaction mixture was stirred and refluxed for 10 hrs and then diluted with ether (60 mL). The solution was filtered and the cake was washed with ether. Flash chromatography of the filtrate after concentration using pet ether-ethyl acetate (90:10) as the eluant gave the pure compound (**7c**).

Experimental Antimicrobial Tests

S. aureus, B. subtilis, S. lutea, E. coli, S. typhosa, S. cerevesciae and C. albicans were all obtained as lyophilized preparations from the National Chemical Laboratories, Pune, India. The bacteria were subcultured on nutrient agar and nutrient broth, while the fungi were grown on Sabauraud agar.

Inhibition Zone Measurements

The compounds (**4a-j**) were dissolved in propylene glycol at a concentration of 1mg/ml. The bacterial species were inoculated on nutrient agar and the fungal species were inoculated on Sabauraud's agar. One hundred micrograms of the solution of each of the test compound was placed separately in cups of 8 mm diameter and 5 mm height cut in agar. The plates were incubated for 16 - 18 hrs for bacteria and 48 hrs for fungi and the resulting inhibition zones were measured and these are recorded in Table 2. Propylene glycol was used as a negative control since it did not exhibit any antimicrobial activity against the test organisms.

Minimum Inhibitory Concentration (MIC) Measurements

MIC is defined as the lowest concentration of the visible growth of the microorganism. The minimum inhibitory concentration of each of the compounds (**4a-j**) was determined on nutrient agar for bacteria and Sabauraud agar for fungi and presented in Table 3. Inocula of the microbial species were prepared by picking colonies of each after overnight growth on a nutrient agar or a Sabauraud agar slant and resuspending the cells in a sterile nutrient broth or Sabauraud broth medium to give a concentration of 10^8 colony forming units (cfu/ml). The inocula were applied to plates containing compounds (1 mg dissolved in 1 ml propylene glycol) in a serial two-fold dilution in the range of 25 μg/ml - 250 μg/ml in broth and the plates were incubated overnight. Ampicillin, Streptomycin and Nystatin were used as reference standards for the above tests.

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