RESEARCH PAPER | Science | Volume : 4 | Issue : 10 | October 2014 | ISSN - 2249-555X

Reactionsof 2'-Subsituted-3-Aryl -2-Propen-1-one Derivatives Under Different Conditions

KEYWORDS: Dibromochalcone,Epoxyketone,2-amino-1,3-thiazine, 4-Quinolone ,Green techniques, Antimicrobial activities.

S.A. AL-Issa
Chemistry Department, Faculty of science,Princess Nora Bint Abdul Rahman University, Riyadh,KSA

A.A.Hattab
Chemistry Department, Faculty of Science,King Faisal University(AL-Hassa),KSA

ABSTRACT *Synthesis of some new dibromochalcones , flavones, 2-amino-1,3-thiazine, epoxy ketone and 4-quinolone derivatives using 2'-hydroxychalcones and 2'-amino chalcones as building block via different conditions by classical method or by using green techniques. In addition ,the antimicrobialactivity against different Gram -positive , Gram – negative bacteria and fungi of some isolated products was screened.*

Introduction
2'-Substituted chalcones are the most important intermediate in the synthesis of heterocyclic compounds such as flavones, azoles and quinoline derivatives. These compounds are well known for their significant biological activities [1-4].

α, β-Dibromo chalcones and epoxy ketones are prospect intermediates for synthesis various condensed and noncondensed heterocyclic systems [5-8]. Dibromo chalcones have been gained by bromination of chalcones using different organic reagents [9-11], but the main disadvantage of bromination of chalcones is quite often low yields of the desired products due to nuclear bromination occurs as a side reaction [8]. While α, β-epoxy ketones have been synthesized by oxidation of α, β-unsaturated ketones. This route of oxidation usually requires nucleophilic oxidation under basic conditions [12,13].

The challenge to minimized the amount of waste and by reactions requires increasing the use of new strategies methods for design organic synthesis. Such as using MWI, ultrasound and green solvents [14-16]. In continuation of our works aiming at development of easy and green technologies for the synthesis of heterocycles [17, 18], herein, we reported the reactions of 2'-substituted chalcones with different reagents using classical and echo friendly methods.

Experimental
All melting points were determined on Gallen Kamp apparatus. The ^{1}HNMR spectra were recorded in $CDCl_3$or in DMSO-d_6 on a Junmex-400 FT NMR AM 400 spectrophotometer using TMS as internal reference. IR spectra were recorded in KBr on Perkin-Elmer 380 Spectrometer. The elemental analyses were performed on a Heraus C,H,N analyzer. Mass spectra were record on micromass 7070 spectrophotometer operating at 70 eV. Microwave irradiation was carried out with microwave oven start SYNTH-Milestone-open vessel. Progress of the reactions was monitored by TLC.

Chalcones were prepared according to the procedures available in literature [8,9 ,19]. Heterogeneous catalyst I_2-Al_2O_3 was synthesized according to the procedures available in literature[20]. The structures of these starting materials were elucidated on the basis of reported m.p.s and spectroscopic measurements.

Synthesis of α-, β-dibromo-1,3-diarylpropanone derivatives (4a-c)
Method A :
A solution of (1a-c)(0.10 mol) in acetic acid (10 mL) was treated with bromine water (0.15 mol). The reaction mixture was allowed to stand at room temperature for 30 min and dilute with water. The solid product obtained was filtered, washed with water and re-crystallized.

Method B :
A solution of (1a-c)(0.10 mol), ammonium bromide (0.2 mol), ammonium persulphate (0.25 mol) and water (0.5 mL) was ground in a mortar at room temperature for 15 min. The reaction mixture was allowed to stand at for 30 min. The workup was carried out as described for method A.

Synthesis of α-bromo-β-hydroxy-1-(2'-hydroxy phenyl)-3-aryl-1-propanone derivatives (5a-c).
Asolution of(1a-c)(0.01 mol) bromine (0.01 mol) in water (5 mL) was added dropwise to a in DMSO (20 mL). The mixture was stirred for 1h. at room temperature. The solid product obtained was filtered off, dried and crystallized.

Synthesis of 2-aryl-4H-benzopyran-4-one derivatives(8a-c).
Method A:
A solution of (5a-c) in acetic acid (15Ml) was heated under reflux for 1 h.. After cooling the reaction mixture was poured on ethanolic sodium hydroxide (4g NaOH in 30 mL EtOH). The mixture was stirred for 1h and allowed to stand at room temperature overnight.The solid that formed was filtered and washed with water and crystallized from the proper solvent.

Method B:
A mixture of (3a-c) (0.01 mol) and(0.25 g) of I_2-Al_2O_3 catalyst was subjected in Microwave (300) for 3-4 min. The mixture was cooled, diluted with ethyl acetate, filtered to separate insoluble Al_2O_3. The filtrate was washed with sodium thiosulphate (2%) and subsequently with water, evaporate the solvent under reduced pressure. The crude product was washed with water, dried and re-crystallized from the proper solvent.

Method C:
A mixture of (4a-c) (0.10 mol), anhydrous barium hydroxide (0.5 mol) and (0.5 mL) ethanol was ground in mortar at room temperature for 10 min. The workup was carried out

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as described for method A.

Synthesis of 2-amino-6H-4-(2′-hydroxy phenyl)-6-aryl-1,3-thiazinederivatives (12a-c)

Method A:

A mixture of (1a-c) (0.01 mol), thiourea (0.015 mol) in alcoholic KOH (15 mL) (3.0 g KOH in 20 mL EtOH) was refluxed for 3h. .The reaction mixture was cooled, poured into water, filtered and re-crystallized.

Method B:

A mixture of (1a-c) (0.01 mol), thiourea (0.012 mol) in alcoholic KOH (2 mL) was placed in a conical flask and subjected to MW (300 W) for 5-6 min, cooled to the room temperature and the workup was carried out as described for method A.

Synthesis of2–Aryl–3–hydroxy–4H–benzopyran–4–one derivatives(14a-c) and 2,3-epoxy-1-(2′-amino phenyl)-3-aryl-1-propanone derivatives (15a-c)

Method A :

To a solution of compound (1a-f)(0.02 mol) in methanol (15 mL), NaOH (10 mL, 20%) was added with stirring at 0°Cfor 10 min. Hydrogen peroxide(20 mL, 20%) was added to the mixture in a small portion over a period of 30 min. The reaction mixture was stirred for 3h. at 30°C and poured on 5N HCl. The resulting solid was filtered, washed, dried and re-crystallized.

Method B :

The same mixture was placed in conical flask and stirred for 5 min. The mixture covered with an inverted funnel and subjected to microwave irradiation (5W) for 4-5 min.The workup was carried out as described for method A.

Synthesis of1,2,3,4-tetra hydro-2-phenyl-3-hydroxy-1H-4-quinolone derivatives(16a-c)

Method A:

A solution of (15a-c)(0.01 mol.) in acetic acid (30 mL) was refluxed for 2 h. The mixture was cooled and poured into ice-cold water, filtered, washed with water and re-crystallized from the proper solvent.

Method B :

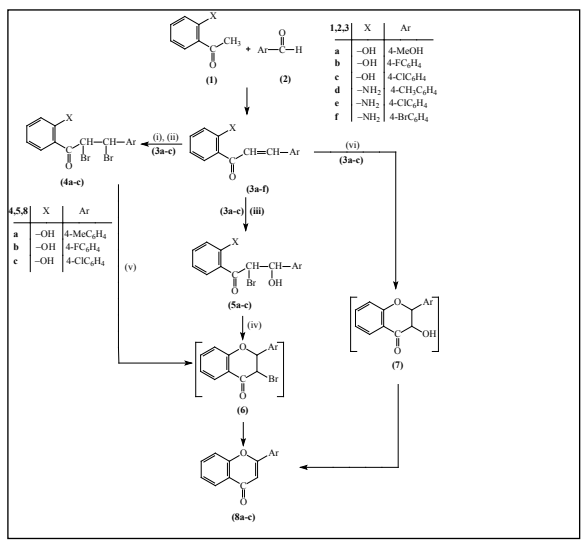
A mixture of compound (15a-c)(0.01 mol) in acetic acid (5 mL) was placed in conical flask, then subjected to microwave irradiation (80W)for 3 min, cooled to room temperature.The workup was carried out as described for method A.

Result and Discussion

The route for synthesis ofα,β-dibromo derivatives (4a-c) andα-Bromo-β-hydroxy derivatives(5a-c)fromα, β-unsaturated ketones(3a-c) is illustrated in (Scheme1). Bromination of 2′-substituted chalcones(1a-f)were successfully synthesized using both classical method and grinding technique at R.T. [8, 10]. The bromination of (3a-c) with bromine water in DMSO gave α-bromo-β-hydroxy-1-(2′-hdroxyphenyl)-3-aryl-1-propanones(Scheme 1)(Tables 1&2).

Compounds 4 and 5 are the required intermediates for synthesis flavones (8a-c) [8, 20, 21]. When compounds 4 and 5 treatment with acetic acid underwent cyclization gave 3-bromo flavonone derivatives 6 as intermediate, which on treatment with aq. NaOH/EtOH solution yielded the corresponding flavones. Also, compounds (8a-c) could be synthesized by alternative, green method. Thus, compounds (4a-c) have been cyclodehydrobromination with barium hydroxide and ethanol using grinding technique. Moreover, oxidation of compounds (3a-c) by the heterogeneous catalysis I_2/Al_2O_3 under microwave irradiation for3- 4 min. afforded the corresponding products (8a-c) [20,21]. Among these three methods, microwave irradiation is the superior to that of three methods. Microwave method offers advantage in terms of easy procedures, mild conditions and excellent yields.

Both analytical and spectral data of all synthesized compounds were in full agreement with proposed structure(Tables 1&2).



Reagents and conditions:

(i) Br_2/AcOH, R.T., 30 min.
(ii) NH_4Br, $(NH_4)_2S_2O_8$, grinding, R.T., 15 min.
(iii) Br_2/DMSO, stirring, R.T., 1 h.
(iv) AcOH, refluxing 1 h./ aq NaOH/EtOH.
(v) $Ba(OH)_2$, EtOH, grinding, R.T., 10 min. (vi) I_2/Al_2O_3, MWI,3- 4 min.

Scheme 1: Synthesis of compounds 4, 5, 8.

Condensation of (1a-c) with thiourea under conventional heating and microwave irradiation gave 2- amino-6H-4,6- diaryl-1,3-thiazines(12a-c)(Scheme 2) [22, 23] which was characterized on the basis of IR,NMR,MS spectra.IR spectrum of (12b)showed an NH and OH peaks at 3310–3400 cm^{-1} respectively. The ^{1}HNMR displayed two doublet at δ5.24 and δ5.47 for protons at position 5 and 6 respectively, for NH abroad singlet at δ6.29, and singlet at d11.90for OH besides the aromatic protons. (Tables 1& 2). It was found that the microwave techniques required less time for competition the reaction as compared to conventional heating.

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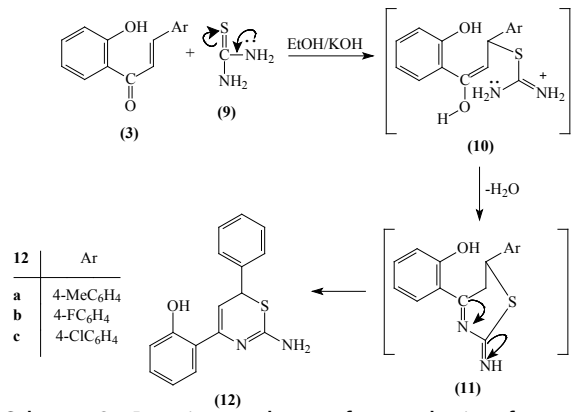
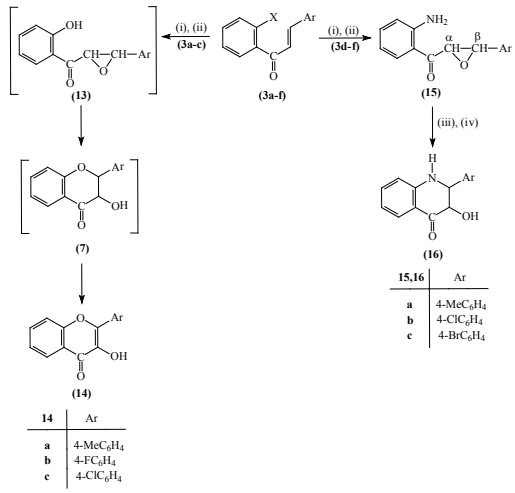


Scheme 2: Reaction pathways for synthesis of compounds12.

Oxidation of (3a-f) under AFO (Alger-Flynn-Oyamada) conditions was also investigated. Thus, when compounds (3a-c) were treated with hydrogen peroxide (20%) at R.T. yielded flavonol derivatives (14a-c). The formation of 14 may placed through the formation of the corresponding epoxy ketone(13) and flavonol derivatives(7) (Scheme 3).While oxidation of (1d-f) under AFO conditions gave the epoxide intermediate 15 which cyclized to tetrahydro-4-quinolone derivatives(16a-c) on treatment with acetic acid. The epoxide intermediate 15 was separated as yellow stable solid, the stability of 15 was noticed by Donnelly and Farell [12], contrast with that of 2′-hydroxy chalcones under AFO conditions,the amino group apparently has a significantly lower nucleophilicity than the corresponding OH^- (PhO^-) group under basic conditions [12,18,24].

The structure of (14a-c) and (15a-c) were established on the basis of their spectroscopic data (Tables 1&2). IR spectra of compound14a display appearance of peaks at 3400 cm^{-1} due to OH group. The ^1H NMR spectrum showed a singlet at δ 2.43 for methyl group, a singlet at d11.65for OH group, besides the signals of aryl protons. The MS spectrum of (14a) showed the molecular radical cation [M^+] at m/z = 252 (70%). The IR spectrum of compound 15c showed NH_2 and C=O peaks at 3320, 3380 cm^{-1} and 1675 cm^{-1} respectively. The ^1H NMR illustrated a two doublet for α-H and β-H at δ4.67 and δ4.90 respectively and a broad singlet at δ 6.22 ppm for NH beside other protons of the compounds.

The desired compounds 1,2,3,4-tetrahydro-3-hydroxy-2-aryl-4-quinolones (16a-c) were prepared from epoxy derivatives (15a-c) by refluxing in acetic acid or under MW irradiation (Scheme 3). The structure of (16a-c) were confirmed from the basis of their spectroscopic analysisIR, ^1H-NMR and MS spectral data(Tables 1& 2)



Reagents and conditions:

(i) CH_3OH, NaOH (20%), H_2O_2 stirring: 0°C, 3h.
(ii) CH_3OH, NaOH (20%), H_2O_2, MWI, 4-5 min,
(iii) AcOH, reflux, 2 h.
(iv) AcOH, MWI, 3 min.

Scheme 3: Synthesis of compounds 14-16.

CONCLUSION

A series of some new derivatives of 2′-substituted chalcones have been synthesized under different conditions and technique. From the study we can be conclude that using MWI in synthesis compounds (8, 12,14-16) was a rapid economic methodology and simplification of classical procedures. The results shown in (Table 3).

THE ANTIMICROBIAL ACTIVITY

The obtained compounds have been evaluated towards the following organisms :

1) *Aspergillus flavus.*
2) *Aspergillus fumigates.*
3) *Fusarium solani.*
4) *Myrothecium vorioti.*
5) *Salmonella typhi*
6) *Pseudomonas aerophacence*
7) *Penicillium ducloxi.*
8) *Bacillus cereus.*
9) *Staphylococcus aurous.*
10) *Macobacterium luteus.*
11) *Escherichia coli.*

The biological activity was evaluated according to the cup-plate method adopted with some modifications[25]. Whatman No. 2 filter paper disk (6.5 cm) were impregnated with 200 mg of the compound. The disk was placed on the surface of the cold solid medium Petridishes, inoculated with the considered organisms, and then incubated at 5°C for one hr, to permit good diffusion and then transferred to an incubator at 28°C for 24 hr and determine the effective diameter. A summary of the biological activity results is shown in (Table 4)

Table 1: Physical and analytical Data of compounds (4–16).

Compd. No.	M.P. °C Solvent	Ar	Molecular Formula (M.Wt.)	%Analysis: Calculated/Found		
				C	H	N
4a	105-107 MeOH	4-$CH_3C_6H_4$	$C_{16}H_{14}Br_2O_2$ 397.8	48.26 48.50	3.51 3.34	–
4b	186-170 C_6H_6	4-FC_6H_4	$C_{15}H_{11}FBr_2O_2$ 401.8	44.79 44.70	2.73 2.61	–

4c	210-213 C_6H_6	4-ClC_6H_4	$C_{15}H_{11}ClBr_2O_2$ 418.3	43.03 43.50	2.62 2.24	–
5a	90-92 MeOH+H_2O	4-$CH_3C_6H_4$	$C_{16}H_{15}BrO_3$ 334.93	57.38 57.40	4.47 4.50	-
5b	160-162 C_6H_6	4-FC_6H_4	$C_{15}H_{12}FBrO_3$ 338.9	53.11 53.40	3.54 3.60	–
5c	220-223 C_6H_6	4-ClC_6H_4	$C_{15}H_{12}ClBrO_3$ 355.4	50.64 50.70	3.37 4.50	–
8a	90-93 EtOH	4-$CH_3C_6H_4$	$C_{16}H_{12}O_2$ 236	81.35 81.40	5.08 4.80	–
8b	143-145 EtOH	4-FC_6H_4	$C_{15}H_9FO_2$ 239.9	75.00 75.40	3.75 3.90	–
8c	196-197 EtOH	4-ClC_6H_4	$C_{15}H_9ClO_2$ 256.5	70.17 70.35	3.50 3.70	–
12a	80-83 AcOH	4-$CH_3C_6H_4$	$C_{17}H_{16}N_2SO$ 296	68.91 68.15	5.40 5.01	9.45 9.30
12b	90-92 EtOAc	4-FC_6H_4	$C_{16}H_{13}N_2FSO$ 300.0	64.00 64.20	4.33 4.00	9.33 9.40
12c	100-103 EtOAc	4-ClC_6H_4	$C_{16}H_{13}N_2ClOS$ 316.5	60.66 60.80	4.10 4.40	8.84 8.60
14a	170-174 EtOH	4-$CH_3C_6H_4$	$C_{16}H_{12}O_3$ 252	76.19 76.20	4.76 4.60	–
14b	150-153 EtOH	4-FC_6H_4	$C_{15}H_9FO_3$ 256.0	70.31 70.42	3.51 3.80	–
14c	132-134 EtOH	4-ClC_6H_4	$C_{15}H_9ClO_3$ 272.5	66.05 66.52	3.30 3.41	–
15a	104-106 AcOH	4-$CH_3C_6H_4$	$C_{16}H_{15}NO_2$ 253	75.88 78.90	5.92 5.60	5.53 5.51
15b	150-152 AcOH	4-ClC_6H_4	$C_{15}H_{12}NClO_2$ 273.5	65.81 65.85	4.38 4.40	5.11 5.50
15c	177-179 AcOH	4-BrC_6H_4	$C_{15}H_{12}NBrO_2$ 317.9	56.62 56.70	3.77 3.80	4.40 4.61
16a	270-273 AcOH	4-$CH_3C_6H_4$	$C_{16}H_{14}NO_2$ 252	76.19 76.20	5.55 5.60	5.55 5.40
16b	270-272 EtOH	4-ClC_6H_4	$C_{15}H_{11}NClO_2$ 272.5	66.05 65.40	4.03 3.80	5.13 5.12
16c	260-262 EtOH	4-BrC_6H_4	$C_{15}H_{11}NBrO_2$ 316.9	56.80 56.85	3.47 3.50	4.41 4.50

Table 2 : IR, ^{1}HNMR and Mass data of compounds (4–16).

Compd. No.	IR υ (KBr, cm^{-1})	^{1}H NMR δ (ppm) (A,B)	m/z (%)
4a	3449 (OH); 1690 (C=O)	(A) :2.41 (s, 3H, CH_3); 5.30 (d, 1H, J =12 Hz, β-H); 5.64 (d, 1H, J =12 Hz, α-H); 7.30-8.21 (m, 8H, ArH's); 11.2 (s, 1H, OH) .	397.8 [M^+] (80)
4b	3440 (OH); 1685 (C=O)	(A) :5.20 (d, 1H, J =12 Hz, β-H); 5.60 (d, 1H, J =12Hz, α-H); 7.23-8.38 (m, 8H, ArH's); 11.25 (s, 1H, OH) .	401.8 [M+] (100)
4c	br. 3450 (OH); 1690 (C=O)	(A) :5.30 (d, 1H, J =11.4 Hz; β-H); 5.68 (d, 1H, J =11.5 Hz, α–H); 7.20-8.34 (m, 8H, ArH's); 11.25 (s, 1H, OH) .	418 [M^+](75)
5a	3400 (OH); 1670 (C=O)	(A) :2.34 (s, 3H, CH_3); 5.30 (d, 1H, J =11.5 Hz, α-H); 5. 82 (d, 1H, J =11.5 Hz, β-H); 7.21-8.07 (m, 8H, ArH's); 11.60 (s, 1H, β-OH); 11.87 (s, 1H, Ar-OH).	334.9 [M^+] (75)
5b	3400 (OH); 1680 (C=O)	(A) :5.40 (d, 1H, J =11.5 Hz, β-H); 5.62 (d, 1H, J =11.5 Hz, α-H); 7.20-8.30 (m, 8H, ArH's); 11.47 (s, 1H, β-OH); 11.70 (s, 1H, Ar-OH).	338.9 [M^+] (90)
5c	3410 (OH); 1680 (C=O)	(A) :5.60 (d, 1H, J =11.7 Hz, β-H); 5.70 (d, 1H, J =11.5 Hz, α-H); 7.26-8.03 (m, 8H, ArH's); 11.52 (s, 1H, β-OH); 11.80 (s, 1H, Ar-OH).	355 [M^+](80)

8a	1690 (C=O)	(A) :2.42 (s, 3H, CH_3); 6.40 (s, 1H, CHpyrane); 6.91-8 .00(m, 8H, ArH's).	336 [M^+] (100)
8b	1665 (C=O)	(A) :6.43 (s, 1H, CHpyrane); 6.90.-7.88 (m, 8H, ArH's).	239.9[M^{+1}] (93)
8c	1660 (C=O)	(B) :6.61 (s, 1H, CHpyrane); 7.01-7.98 (m, 8H, ArH's).	256.5 [M^+] (85)
12a	br.3400 (OH & NH_2)	(A) :2.10 (s, 3H, CH_3); 5.12 (d, 1H, J =5.3,CH-Ar); 5.40 (d, 1H, J = 5.3 Hz, CH-OH); 6.85 (br. s, 2H, NH_2); 7.12-8.29 (m, 8H, ArH's); 11.19 (s, 1H, OH).	296 [M^+](90)
12b	3310, 3400 (NH_2& OH)	(A) :5.24 (d, 1H, J = 4.5 Hz, CH-Ar); 5.47 (d, 1H, J = 4.5 Hz, CH-OH); 6.29 (br. s, 2H, NH_2); 7.11-8.20 (m, 8H, ArH's); 11.90 (s, 1H, OH).	300[M+] (98)
12c	3200 , 3340 (OH & NH_2)	(A) :5.22 (d, 1H, J = 5.4 Hz, CH-Ar); 5.90 (d, 1H, J =5.4 Hz, CH-OH); 6.71(br. s, 2H, NH_2); 7.00-8.13 (m, 8H, ArH's);11.24 (s, 1H, OH).	316.5[M^+] (100)
14a	3400 (OH); 1680 (C=O)	(B) : 2.43 (s, 3H, CH_3); 6.91-8.10 (m, 8H, ArH's); 11.65 (s, 1H, OH).	252 [M^+](70)
14b	3410 (OH); 1680 (C=O)	(A) :7.13-8.47 (m, 8H, ArH's); 11.80 (s, 1H, OH).	256 [M^+] (95)
14c	3460 (OH); 1685 (C=O)	(A) :7.04-8.22 (m, 8H, ArH's); 10.92 (s, 1H, OH).	272.5[M^+] (90)
15a	3320,3390 (NH2); 1675 (C=O)	(A) :2.33 (s, 3H, CH_3); 4.63 (d, 1H, J = 2.5 Hz, β-H); 4.95 (d, 1H, J =2.5 Hz , α-H); 6.24 (br. H, 2H, NH_2); 6.90-8.00 (m, 8H, ArH's); 8.70 (s, 1H, OH).	253 [M+] (100)
15b	br.3400 (NH2); 1675 (C=O)	(B) :4.52 (d, 1H, J =2.5 Hz, Hz , β-H);4.76 (d, 1H, J =2.0 Hz, α-H);6.40(br. H, 2H, NH2); 7.03-8.15 (m, 8H, ArH's); 11.10 (s, 1H, OH).	273.5[M^{+1}] (90)

Table 2 : Cont'd

Compd. No.	IR u (KBr, cm^{-1})	^{1}H NMR δ (ppm) (A,B)	m/z (%)
15c	3320, 3380(NH2); 1675 (C=O)	(A) :4.67 (d, 1H, J =2.6 Hz , β-H); 4.90 (d, 1H, 2.6 Hz , α-H); 6.22 (br. H, 2H, NH_2); 6.91-8.12 (m, 8H, ArH's); 11.60 (s, 1H, OH).	317 [M^+](95)
16a	3420 (OH), 1660 (C=O)	(A) :2.30 (s, 3H, CH_3); 5.61 (d, 1H, J =6.7 Hz ,CH-Ar); 6.40 (d, 1H, J =2.6 Hz, CH-OH);7.00-8.20 (m, 8H, ArH's); 10.40 (s, 1H, OH).	252 [M^+](90)
16b	3360 (OH), 1670 (C=O)	(A) :5.6 3(d, 1H, J = 6.7 Hz, CH-Ar);6.21 (d, 1H, J =2.6 Hz, CH-OH); 6.97 (br. s, 2H, NH);7.20-8.31 (m, 8H, ArH's); 11.2 (s, 1H, OH).	272.5 [M^+](95)
16c	3330 (OH) , 1670 (C=O)	(A) :5.60 (d, 1H, J = 6.7 Hz CH-Ar); 6.21 (d, 1H, J = 2.6 Hz, CH-OH); 6.43(br.s, 2H, NH);7.20-8.51 (m, 8H, ArH's); 11.55 (s, 1H, OH).	316.9 [M^+](85)

A: $CDCl_3$
B: DMSO-d_6.

Table 3: Comparisons between classical and microwave procedures forpreparation of compounds (4-16).

Compd. No.	Classical technique		Grinding technique		MW technique	
	Reaction time (h.)	Yield %	Reaction time (min.)	Yield %	Reaction time (min.)	Yield %
4a	0.30	65	15	75	–	–
4b	0.30	70	15	72	–	–
4c	0.30	70	15	70	–	–
5_a	1	52	–	-	-	-

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5_b	1	56	–	-	-	-
5_c	1	53	–	-	-	-
8a	1	63	10	74	3	88
8b	1	78	10	80	4	91
8c	1	77	10	79	4	93
12_a	3	68	–	–	6	90
12_b	3	58	–	–	5	95
12_c	3	58	–	–	5	90
14_a	3	60	–	–	5	85
14_b	3	72	–	–	4	84
14_c	3	70	–	–	4	80
15_a	3	60	–	–	5	90
15_b	3	55	–	–	4	92
15_c	3	60	–	–	4	92
16_a	2	37	–	–	3	95
16_b	2	36	–	–	3	92
16_c	2	34	–	–	3	90

Table 4 : Antimicrobial Activity of Some Selected Compounds(4-16)

Type of organism	Test organisms	Inhibition zone (m.m.) of the different compounds								
		4_a	8_a	12_a	14_a	14_b	15_a	15_b	16_a	16_b
Fungi	***Aspergillus flavus***	-	-	-	-	-	8	-	8	-
	Aspergillus fumigates	–	8	–	–	–	–	–	10	8
	Fusarium solani	–	–	–	9	10	–	–	11	–
	Myrothecium vorioti	8	–	–	12	–	–	–	–	10
	Penicillium ducloxi	15	–	–	–	–	–	–	–	–
Gram positive Bacteria	***Bacillus cereus***	-	-	-	10	8	10	8	-	-
	Staphylococcus aurous	-	8	8	-	-	-	-	8	-
	Macobacterium luteus	10	15	-	-	-	-	-	10	12
Gram negative Bacteria	***Escherichia coli***	–	–	12	8	–	–	–	–	–
	Pseudomonas aeropha-cence	8	–	10	–	10	–	11	8	15
	Salmonella typhi	–	–	–	–	–	8	–	16	8

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