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Ultrasound Promoted Synthesis and Characterization of Some Chalcones, Chromones and 1, 5 Benzothiazepines as Antibacterial and Antifungal Agents

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2-Hydroxy acetophenones on treatment with 6-methyl-2-(1*H*-pyrazol-1-yl) quinoline-3-carbaldehyde by conventional and ultrasonication methods gave the corresponding chalcones. These chalcones were transformed into chromones and 1, 5-benzothizepines by using DMSO/I_2 and 2-aminothiophenol respectively. Compounds **3b** and **3e** have shown better antibacterial activity against Gentamycin and Tetracycline. Similarly **2e** have also been shown moderate antifungal activity against Ketoconazole taken as reference drug.

Keywords: Ultrasonication, chalcones, chromones, antibacterial agents, 1, 5-benzothiazepines, antifungal agents

Ultrasound has increasingly been used in organic synthesis[1, 2]. This method is more convenient as they require shorter time for completion of reaction and higher yields are obtained as compared to conventional method.

Chalcones[3] constitute an important group of natural products and some of them possess wide range of biological activity such as antibacterial[4,5], antitummer[6], anticancer[7,8], antitubercular[9], antiviral[10,11], antifungal activities.

Chromones with aromatic substitutents at 2 positions have been reported to possess antifungal, antibacterial[12] and antitumor activities.

Benzothiazepines derivatives have diverse biological activities such as antimicrobial[13], antifungal[14], anticoagulant[15], antifeedent[16] and DPPH free radical scavengers[17].

Owing to the wide spread applications of chalcones, chromones and benzothiazepines and in continuation of our work, it was thought worthwhile to synthesis some chalcones by ultrasonication method and derivates it into corresponding chromones and thiazepine by conventional method.

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Results and discussion

Synthesis of (*E*)-1-(2-hydroxyphenyl)-3-(6-methyl-2-(1*H*-pyrazol-1-yl) quinoline-3-yl) prop-2-en-1-ones, **2**, 2-(6-methyl-2-(1*H*-pyrazol-1-yl) quinolin-3-yl)-4*H*-chromen-4-ones, **3**, 2-((*E*)-2, 3-dihydro-2-(6-methyl-2-(1*H*-pyrazol-1-yl) quinolin-3-yl) benzo[*b*][1,4]thiazepin-4-yl)phenols **4** are summarized in **scheme 1**. The starting compound **2** chalcones were prepared by conventional method i.e. Claisen-Schimdt condensation. Same chalcones were synthesized by ultrasonication method using various substituted acetophenones with 6-methyl-2-(1*H*-pyrazol-1-yl) quinoline-3-carbaldehyde in presence of ethanol/KOH.

In these two methods, ultrasonication method is environmentally clean technology that minimizes the production of waste at source. It also offers cleaner reactions by improving product yields, enhancing product recovery and quality through application to crystallization and other product recovery and purification processes. As we have used non activated and crude reagents as well as aqueous solvent system; therefore it is friendly and non toxic.

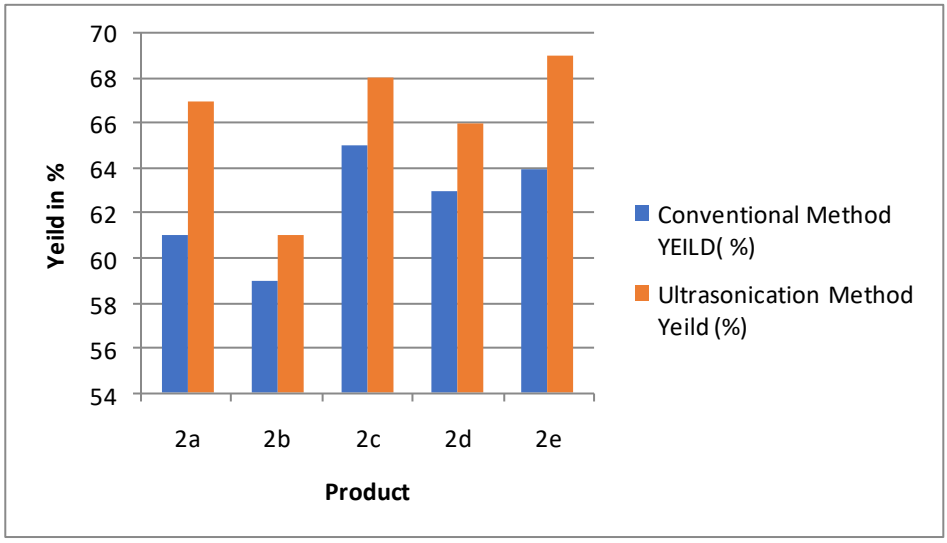

Fig-1: Graphs of yield for conventional and ultrasonication method.

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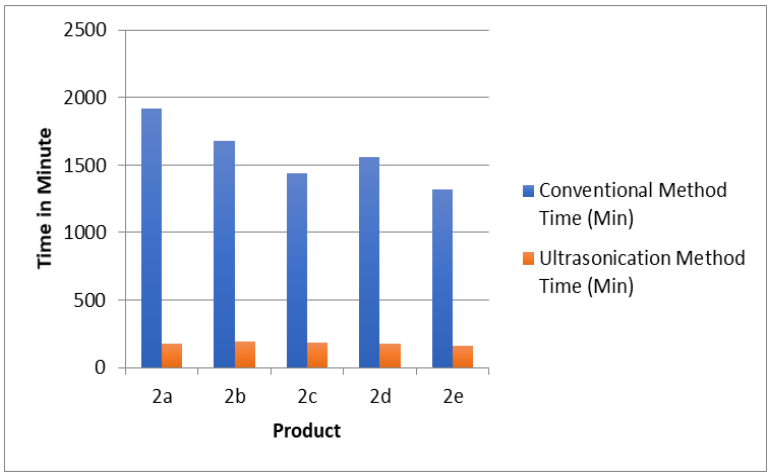

Fig 2: Graphs of time required for completion of reaction by conventional and ultrasonication method.

Statistical data for different synthesized compounds **2a-e**, its % yield and time required for completion of reaction was studied by graphical method. The bar graphs and line graphs are shown in fig-**1** and fig-**2**. It shows that the reactions carried out by ultrasonication method have significant difference in yields as compared to conventional method. The reactions which were carried out by ultrasonication method have higher yields as compared to conventional method fig-**1**.

It has been observed that there is large difference in time requirement for completion of reaction between conventional and ultrasonication method. Ultrasonication method proceeds 15-20 times faster than conventional method fig **2**.

The oxidative cyclisation of chalcones **2a-e** by using DMSO/I_2 gave compounds **3a-e** in good yield. These compounds **3a-e** were characterized by NMR and Mass spectrometry. The ^{1}H NMR spectra of chromones **3 e** shows characteristic doublet of doublet at δ 7.73-7.84 (J = 7.2Hz and 2Hz).

The chalcones **2a-e** were treated with 2-aminothiophenol at reflux condition in ethanol under the influence of glacial acetic acid for 6 hr. The reaction smoothly afforded the desired products **4a-e** in good yield. These compounds were characterized by combined application of mass, ^{1}H NMR and IR spectroscopy. ^{1}H NMR spectra of benzothiazepines displayed four characteristic signals; singlet at δ 2.36, triplet at δ 3.01, J = ~ 12 Hz, doublet of doublet at 3.26, J = 4.2 Hz and 12.2 Hz and δ 5.01 as a doublet of doublet with J = 11.5 Hz and 4.3 Hz.

Antimicrobial activities

All the newly synthesized compounds were screened for their *in vitro* antimicrobial activity against *Pseuodomonas aeruginosa*, *Staphylococcus aureus* and *E. coli* using Gentamycin and Tetracycline as reference standard by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using Ketoconazole as a standard drug. All the test compounds were evaluated at 50-100 µg/ml

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concentration. The zone of inhibition was measured in mm. The compounds **2e**, **3b, 3e,** and **3h** showed good to moderate antibacterial activity against *Staphylococcus aureus* and compound **2e** showed moderate antifungal activity against *Candida sp.*

Experimental Section

All the reactions under ultrasonication were carried out in bath type digital ultrasonicator model VGT-1200H manufactured by PCI company having maximum power output 60W and 40KHz operating frequency. Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. IR Spectra were recorded on Shimadzu FTIR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on Bruker Avance–II, 400MHz spectrophotometer in $CDCl_3$ and DMSO-d_6 as solvent and TMS as an internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on Pep-Sciux-APIQ pulsar (electron pre ionization) mass spectrometer. The progress of reactions and purity of the products were checked by TLC on silica gel 'G' coated aluminum plates. Further, the antimicrobial activity of synthesized compounds was tested by disc diffusion method. The source of microbial activity culture was obtained from NCL Pune.

Synthesis of (*E*)-1-(2-hydroxyphenyl)-3-(6-methyl-2-(1*H*-pyrazol-1-yl) quinoline-3-yl) prop-2-en-1-one, 2a

A) Conventional method

The compound **1**(0.001mol) and 6 methyl-2-(1*H* pyrazol-1-yl) quinoline-3-carbaldehyde (0.001 mol) were dissolved in 95% ethanol. To this reaction mixture 40% KOH (10 ml) was added. The reaction mixture was stirred at room temperature for 24-32 hr. The reaction mixture was quenched into crushed ice and neutralized by conc. HCl. The yellow solid product thus obtained was filtered and purified by recrystallization from ethanol to afford compounds **2a-e**. The physical data of compounds synthesized by above procedure are shown in **Table 1**.

B) By ultrasound method

In 100 ml beaker the compound **1** (o.oo1mol) and 6 methyl-2-(1*H* pyrazol-1-yl) quinoline -3-carbaldehyde (0.001 mol) were dissolved in 50% 7ml ethanol. To this reaction mixture 40% KOH (5 ml) was added. Reaction mixture was subjected to ultrasonication for 72–180 min. The temperature of the reaction was maintained 60 ℃. The progress of reaction was monitored with the help of TLC. After the completion of the reaction, the reaction mixture was quenched into crushed ice and neutralized by conc. HCl. The product obtained was separated by filtration and purified by recrystallization from ethanol to afford compounds **2a-e**. The compounds synthesized by the above procedure are shown in **Table 1**.

2e: IR (KBr,cm^{-1}) 3180 (-OH), 1666 (C=O), 1654 (C=C), 1527 and 1577 (Aromatic C=C), 2831 and 3014 (C-H); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.46 (s, 3H), 7.47 (d, 1H, *J* = 14.8 Hz, trans olefinic H), 7.87 (d, *J* = 14.8 Hz), 6.31 (t, *J* = 2.7 Hz, 1H, Ar-H), 6.56-8.67 (m, 8H, Ar-H), 12.60 (s, 1H, -OH); MS (M^+): m/z 424.

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2a: IR (KBr, $cm^{-1)}$ 3200 (-OH), 1637 (C=O), 1047 (Ar-Cl), 1523 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 6.31 (t, *J* = 2.7 Hz, 1H, Ar-H), 7.47 (d, 1H, *J* = 14.8 Hz, trans olefinic H), 7.87 (d, *J* = 14.8 Hz), , 6.92-7.67 (m, 8H, Ar-H), 8.00 (s, *J* = 2 Hz, 2H, Ar-H), 12.60 (s, 1H, -OH); MS (M^+): m/z 356.

Synthesis of 2-(6-methyl-2-(1*H*-pyrazol-1-yl) quinolin-3-yl)-4*H*-chromen-4-one, 3a

The compound **2** (0.001mol) in 100ml RBF was dissolved in 5-7ml DMSO. To this reaction mixture 2-3 crystals of I_2 were added. Contents were heated at 140^{o}C for 3hr and left overnight. Then the reaction mixture was poured onto crushed ice containing 2-3 g of sodium thiosulphate .The solid thus obtained was washed with the cold water. The product obtained was recrystallized from ethanol to afford pure compound **3a-e.** The compounds synthesized by the above procedure are shown in **Table 2**.

3e: IR (KBr,cm^{-1}):1658 (C=O), 1568 (Aromatic C=C), 1045 (Ar-Cl), 1651 (C=C), 1226 (C-O), 2850, 2908 and 3028 (C-H); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H), 6.37 (t, 1H, *J* = 2 Hz, Ar-H), 6.71 (s, 1H, Ar-H), 7.41 (d, *J* = 2.76 Hz,1H, Ar-H), 7.56 (d, *J* = 2.76 Hz,1H, Ar-H), 7.6 (s, 1H), 7.58- 8.07 (m, 5H, Ar-H); MS(M^+): m/z 422.

3a: IR (KBr,cm^{-1}):1643 (C=O),1562 (Aromatic C=C), 1093 (Ar-Cl), 1602 (C=C),1236 (C-O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H), 6.37 (t, 1H, *J* = 2 Hz, Ar-H), 6.71 (s, 1H, Ar-H), 7.41 (d, *J* = 2.76 Hz,1H, Ar-H), 7.56 (d, *J* = 2.76 Hz, 1H, Ar-H), 7.6 (s, 1H), 7.58- 8.07 (m, 6H, Ar-H); MS(M^+): m/z 353.

Synthesis of 2-((*E*)-2, 3-dihydro-2-(6-methyl-2-(1*H*-pyrazol-1-yl) quinolin-3-yl) benzo[*b*][1, 4] thiazepin-4-yl) phenol, 4a

Compound **2** (00.00069 mol) in 100 ml RBF was dissolved in 5-10 ml of ethanol. To this 4-6 drops of 2-aminothiophenol was added and resulting reaction mixture was refluxed for three hour. Then the reaction mixture was acidified by using 5-6 drops of acetic acid and the heating was continued for next 3 hr. Then the contents were transferred in a clean and dry beaker. After the cooling, pale yellow colored crystals were obtained. It was filtered and recrystallized by using ethanol to afford compound **4a-e**. The compounds synthesized by the above procedure are listed in **Table-2**.

4e: IR (KBr,cm^{-1}):3142 (-OH), 1604 and 1653 (Aromatic C=C),1592(C=N),1035 (Ar-Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 3.01 (apparent triplet, *J* = ~ 12Hz, 1H), 3.26 (dd, *J* = 12.2 Hz and 4.2 Hz, 1H), 5.01 (dd, *J* = 11.5 and 4.3 Hz, 1H), 6.31 (t, *J* = 2.2 Hz, 1H, Ar-H), 7.00 - 8.01 (m, 12H, Ar-H), 12.1 9 (s, 1H, -OH, D_2O exchangeable); MS(M^+): m/z 531.

4a: IR (KBr, $cm^{-1)}$:3400 (-OH), 1600 (Aromatic C=C), 1533 (C=N) , 2800 (C-H); ^{1}H NMR ($CDCl_3$, 400MHz): δ 2.36 (s, 3H), 3.01 (apparent triplet, *J* = ~ 12Hz, 1H), 3.26 (dd, *J* = 12.2 Hz and 4.2 Hz, 1H), 5.01 (dd, *J* = 11.5 and 4.3 Hz, 1H), 6.31 (t, *J* = 2.2 Hz, 1H, Ar-H), 7.00 - 8.01 (m, 14H, Ar-H), 12.1 9 (s, 1H, -OH, D_2O exchangeable)MS(M^+): m/z 466.

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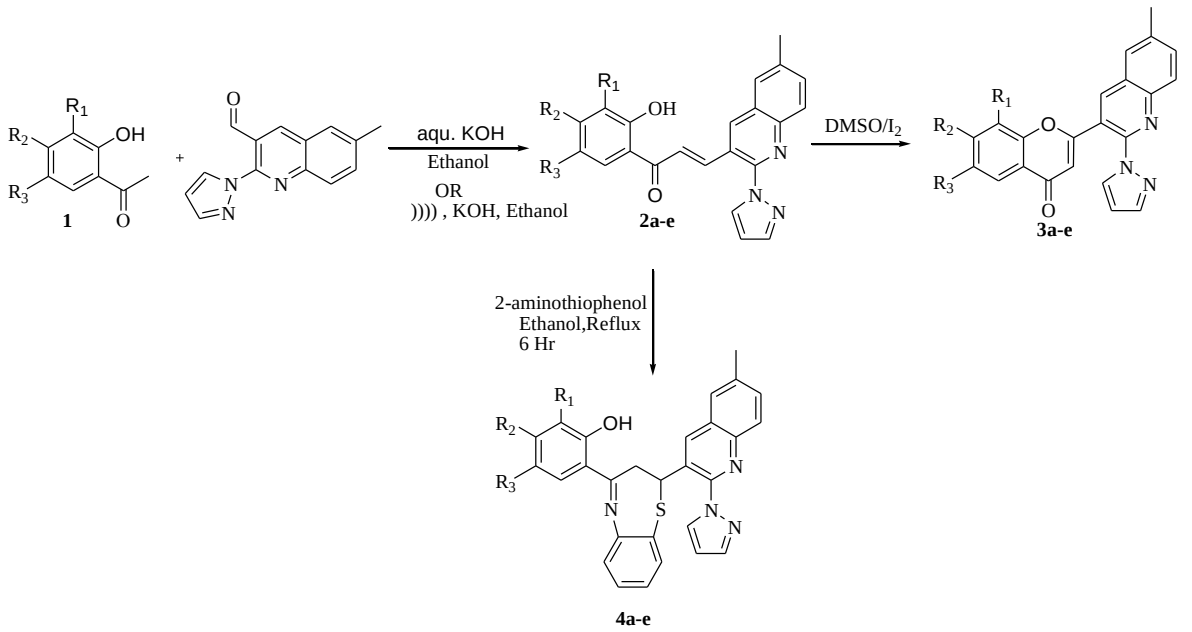

Scheme 1

Table I - Characterization data of synthesized compounds **2 (a-j)**

Compd	R_1	R_2	R_3	Conventional Method		Ultrasonication Method		M.P.
				Yield (%)	Time (Hr)	Yield (%)	Time(Min.)	(°c)
2a	H	H	H	61	32	67	180	118
2b	H	H	CH_3	59	28	61	190	92
2c	H	CH_3	Cl	65	24	68	186	103-105
2d	H	H	Cl	63	26	66	180	87
2e	Cl	H	Cl	64	22	69	160	82-84

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Table II - Characterization data of synthesized compounds **3 (a-j) and 4 (a-j)**

Compd	R_1	R_2	R_3	M.P. (^oC)	Yield (%)
3a	H	H	H	260	56
3b	H	H	CH_3	276-278	54
3c	H`	CH_3	Cl	264	59
3d	H	H	Cl	220	57
3e	Cl	H	Cl	239	63
4a	H	H	H	257	61
4b	H	H	CH_3	269-271	59
4c	H	CH_3	Cl	262	64
4d	H	H	Cl	274	62
4e	Cl	H	Cl	252	61

Table III -Antimicrobial analysis data

Sample	*E.coli* ATCC25922	*P. aeruginosa* ATCC27853	*S. aureus* ATCC25923	*Candida*
2c	No zone	No zone	No zone	No zone
2e	No zone	No zone	No zone	1omm
3b	No zone	No zone	8mm	No zone
3a	No zone	No zone	12mm	No zone
4b	No zone	No zone	No zone	No zone
4e	No zone	No zone	No zone	No zone
Gentamicin	20mm	20mm	25mm	--------
Tetracycline	20mm	-------	25mm	--------
Ketoconazole	-------	-------	--------	23mm

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Graphical abstract:

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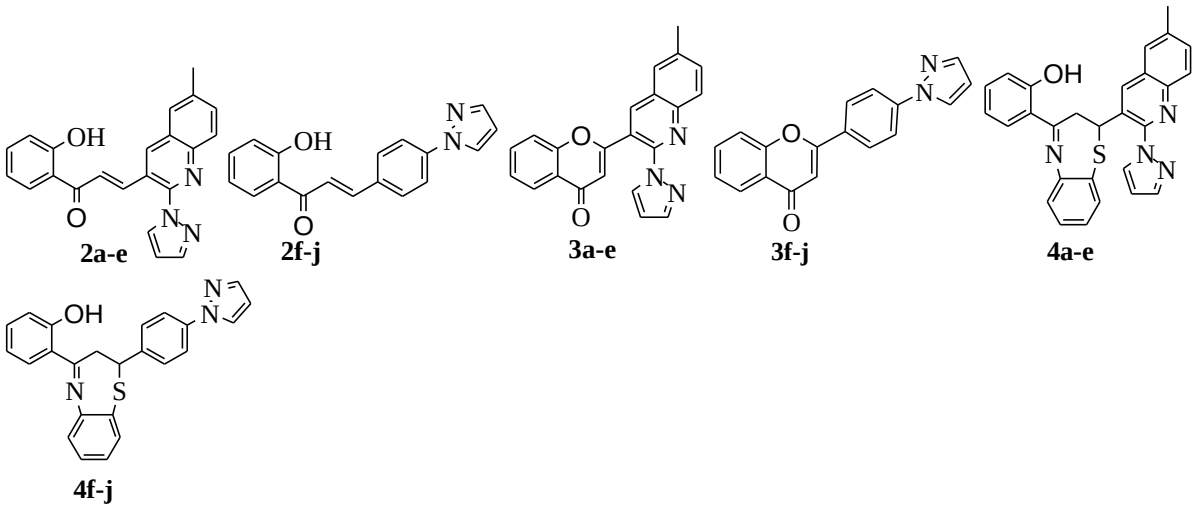

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