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RAPID AND GREENER ULTRASOUND ASSISTED SYNTHESIS OF SERIES (2-((SUBSTITUTED 2-CHLOROQUINOLIN-3-YL) METHYLENE)-3,4-DIHYDRONAPHTHALEN-1(2H)-ONE) DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

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ABSTRACT

In the current research framework, an efficient and greener synthesis has been developed. A new series of α, β unsaturated carbonyl compounds have been designed by the reaction between 3,4-dihydronaphthalen-1(2H)-one with various substituted quinolines in presence of NaOH as a base, EtOH:Water (1:1) act as a greener solvent under conventional and ultrasound irradiation methods. From the comparison between conventional and ultrasound-assisted synthesis, it was observed that the ultrasound assisted method provided 63-83% yield in 30-45 min against 75-90 min required getting 46-57% yield by conventional method. The newly synthesized derivatives were characterized by the most acceptable analytical techniques *i.e.* IR, ^{1}H NMR, ^{13}CNMR and Mass spectral analysis, also were evaluated for their *in-vitro* anti-microbial activity against two gram positive, two gram negative and three fungal strains.

Keywords: Ultra sound irradiation, quinoline, 3,4-dihydronaphthalen-1(2H)-one, α, β unsaturated carbonyl compounds, Antimicrobial activity

1. INTRODUCTION

Antimicrobial chemotherapy has begun from 1940s; it was found that thousands of people were killed in the world every year because of infection caused by multidrug-resistant bacteria and that was due to the enhancement in the properties of the micro-organisms that showing unusual resistance towards the drug moiety day by day. However human being is losing the battle against never ending resistance due to the efficiency micro-organisms, so there is an urgent need to develop a huge and effective spectrum of anti microbial agents [1-4]. In the search of potent and effective scaffold having sufficient activity against gram positive and gram negative microbes, the quinolines have established much-well deserved enthusiasm [5]. Quinoline is a fused heterocyclic ring containing nitrogen atom and in presence of different functional groups, it resulted as variety of therapeutic agents [6]. As a unique scaffold, quinoline possess broad spectrum of biological activities as anti bacterial [7-9], anti microbial [10-12], anti malarial [13, 14], anti oxidant [15], anti cancer [16, 17] activities. On other hand, as a vision of effective research work, green chemistry approaches can be helpful. In order to minimize or eliminate the use of hazardous chemicals or to decrease the ratio of side product, green solvents (water, ethanol etc) or green methods (ultrasound irradiation, microwave assistance) can be used [18,19]. Green chemistry approaches are not only useful to prevent the environmental pollution but also helpful to develop more resource-efficient and inherently safer design of molecular materials which enhance the properties of the functionalized derivatives with low consumption of energy source and high amount of yield [20, 21]. 3,4-dihydronaphthalen-1(2H)-one is also used as a highly potent and efficient moiety in medicinal chemistry which also possess various of biological activities like anti cancer [22], anti microbial [23, 24] activities.

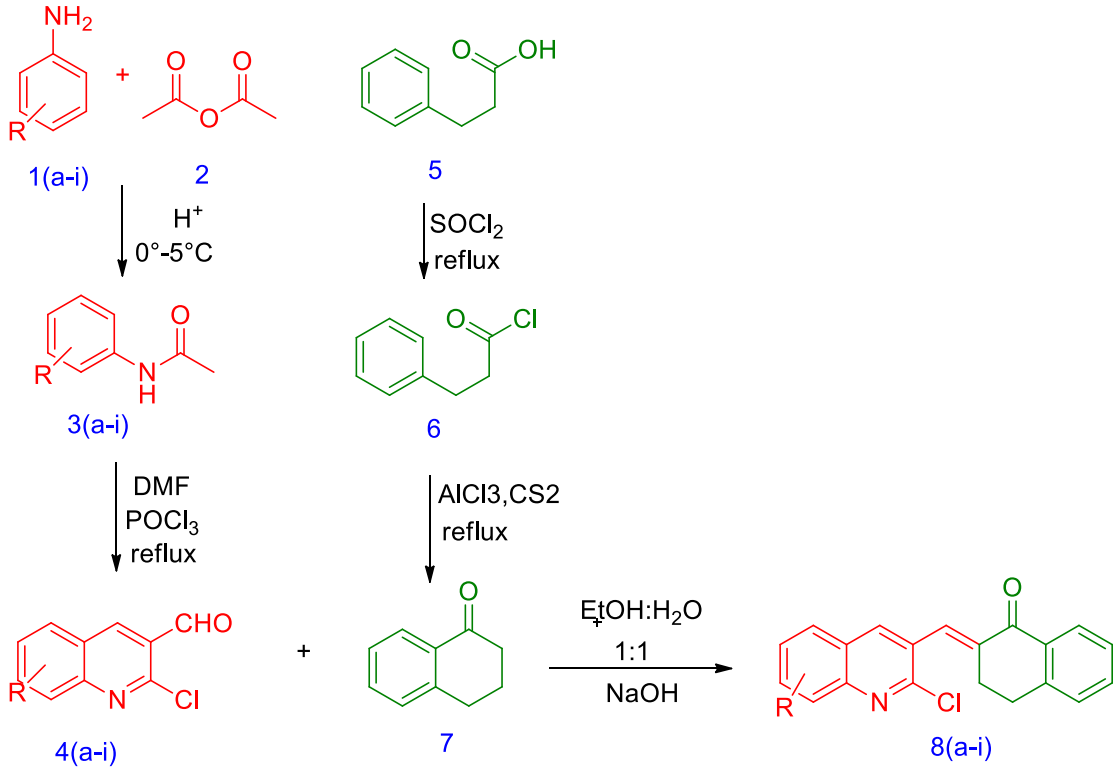
The ultrasound assisted synthesis of organic molecule technique becomes extremely effective and attractive. Ultrasound irradiation is used to increase the rate of the reaction and synthesis of various classes of organic compounds [25, 26]. This method is considered in terms of energy conservation and waste minimization compared to conventional heating method [27]. All the reactions and conditions were taken place via mild condition and short reaction time [28]. In the present

framework, we have synthesized a series of α, β unsaturated carbonyl compounds via ultrasound irradiation in presence of EtOH:water (1:1) solvent system to minimize the drawbacks. All the compounds were characterized by using the most significant analytical methods like ^{1}HNMR, ^{13}CNMR Mass, IR spectroscopy. All the derivatives were screened for their microbial activity.

2. EXPERIMENTAL

2.1. General information

All chemicals and solvents were purchased from, Spectrochem, Sigma-Aldrich, Lobachemie and Merck, Thin layer chromatography (TLC) was conducted by using aluminum plates 20x20 cm coated by silica gel 60 F254 purchased from Merck. Melting points were determined by melting point apparatus. Solvents were evaporated by the help of a BUCHI rotary evaporator. IR spectra were recorded on FTIR-8400 spectrometer using DRS prob. Mass spectra of the products were recorded by Shimadzu GCMS-QP-2010 model. Nuclear magnetic resonance spectra ^{1}HNMR and ^{13}C-NMR spectra were determined in CDCl3/DMSO-*d6* (in 3/1 ratio) or DMSO-*d6* and were recorded on a Bruker AVANCE II, 400 MHz Chemical shifts (δ scale) were reported in ppm (parts per million) downfield from tetramethylsilane (TMS) used as internal standard. Splitting patterns are designated as followings: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; brs, broad singlet; dd, double doublet.



Reaction scheme

2.2. Synthesis of various substituted 2-chloroquinoline-3-carbaldehyde (4a-i)

Substituted Aniline (1) (1 mol) was taken in round bottom flask (RBF) in cooling conditions at 0 °C-5 °C, Acetic anhydride (1.5 mol) was added drop wise into RBF with continuous stirring. After addition, sulfuric acid (H_2SO_4) was added in catalytic amount to produce acidic medium. Reaction progress was reported by TLC. After the completion of that reaction, mixture was poured into ice cooled water and produced solid (4) was filtered, washed with cold water and dried (white solid product yield: 80.02%). In the next step, phosphorus oxychloride ($POCl_3$) (9 mol) was taken in RBF at 0 °C-5 °C, DMF (3 mol) was added drop wise into $POCl_3$ very slowly by maintaining the temperature with continuous stirring. Yellow colored salt was observed after completion of addition and at that stage calculated amount of N-phenylacetamide (3) (1mol) was added in to it & reaction mass was refluxed in oil bath for 16-24 hours. By observing the completion of reaction on TLC, reaction mass was poured into

crushed ice to get solid precipitate (Yellow solid product; yield 83.76%).

2.3. Synthesis of 3,4-dihydronaphthalen-1(2H) -one(7)

4-phenybutanoic acid (5)(0.2 mol) was taken in RBF. Sulphonyl chloride (0.3 mol) was added drop wise at 0 °C-5 °C. The prepared mixture was placed on heating bath with continuous stirring until the acid was melted. Reaction mass was then allowed to proceed at 25 °C for 1.5 to 2 hour and progress of reaction was reported by TLC plate. After completion of the reaction, mixture was allowed to be warm on hot plate until the excess $SOCl_2$ and moisture got evacuated and then heated for ten minutes on the steam bath and thus the 4-phenylbutanyl chloride(6) was prepared. The obtained acid chloride was nearly colorless and immediately cooled in ice bath to prevent the decomposition of acid chloride and about 200 ml of carbon disulfide and aluminum chloride (0.25 mol) was added in to it. The reaction mixture was immediately transferred in steam bath for reflux, after some time as the evaluation of hydrogen chloride has stopped the reaction was completed. Further normal phase column chromatography was used to separate out the pure product and excess of solvent was evaporated and yellowish colored liquid substance 3,4-dihydronaphthalen-1(2H)-one(7) was obtained (yield 60%).

2.4. General procedure for synthesis of substituted 8(a-i)

As a solvent, 2.5 ml ethanol and 2.5ml water (1:1) were taken in the RBF and NaOH (0.15 mol) was added as a base and mixed properly to get dissolved, after that 3,4-dihydronaphthalen-1(2H)-one(7) (0.25 mol) was added, substituted quinoline (4) (0.2 mol) was added and, the mixture was introduced to ultrasonic irradiation for 10 to 15 minutes on power 100W. Reaction progress was recorded by TLC plate. Solid product was separated by filtration, washed by cold water, dried and re-crystallized from ethanol.

2.5. Biological evaluation

Newly synthesized chalcones were screened for their anti-bacterial activity against the gram positive bacteria *S. aureus* (MTCC-96), *B.cereus* (MTCC-430) and gram negative bacteria *E.Coli* (MTCC-443) and *P. Aeruginosa* (MTCC-1688). Ampicillin was used as standard drugs in minimum bacterial inhibitory concentration (MIC). The same compounds were also screened for their anti-fungal activity against *Candida albicans* (MTCC-227), *Aspergillus Niger* (MTCC-282) and *Alternaria alternate* (MTCC-8123). Nystain was used as standard drugs in MIC. The strains were inoculated in nutrient broth, and kept for overnight culture at 35 °C. Antimicrobial activity was determined by broth micro dilution method [29] performed in 63 well micro titer plates. As an indicator, 2,3,5-triphenyl tetrazolium chloride (TTC) was used for detection of bacterial growth, samples have prepared by dissolving 3 mg of antimicrobial agents in 1 mL dimethylsulfoxide solvent.

3. RESULTS AND DISCUSSION

Novel series of α, β unsaturated carbonyl derivatives (8a-i) were prepared via ultrasound assisted and conventional procedure using various substituted quinoline as core moieties shown in table 2. All the reactions were performed in closed vessels and the ultrasounds program was composed of appropriate steps. All the derivatives were identified by analytical spectral data i.e. ^{1}HNMR, ^{13}CNMR, Mass and IR Spectroscopy.

3.1. Spectral data of synthesized compounds

3.1.1. (E)-2-((2-chloroquinolin-3-yl)methylene)-3,4-dihydronaphthalen-1(2H)-one (8a)

White solid, Chemical Formula: $C_{20}H_{14}ClNO$ melting point: 167; IR (KBr, cm^{-1}): 3579, 3430, 3389, 3323, 2930, 2850, 1695, 1625, 1613, 1540, 1418, 1329, 1238, 1147, 1067, 962, 834, 785, 711; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm): 8.320 - 8.279 (m, 1H), 7.981 - 7.954 (m, 1H), 7.546-7.542 (d, J=16.0Hz, 1H), 7.527 - 7.506(m, 1H), 7.831-7.611(m, 5H) 7.281(s, 1H), 3.052-3.043(t, J=18Hz, 2H)3.037-3.006 (t, J=18Hz,2H); ^{13}CNMR (100 MHz) δ 189.63 (s),172(s).162(s), 158(s), 146.75 (dd, J = 489.1, 228.3 Hz), 138(s) 135.62 (s), 145.25 - 134.96 (m),127.03(s),126.4(s) 28.86 (d, J = 17.1 Hz), 21.79 (s); Mass m/z: 319.07.

3.1.2. (E)-2-((2-chloro-6-methylquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2H)-one (8b)

White solid, Chemical formula: C21H16ClNO melting point:172°C; IR (KBr, cm^{-1}): 3597, 3429, 3392, 3327, 2926, 2850, 1693, 1635, 1602, 1539, 1508, 1413, 1309, 1230, 1157, 1039, 972, 835, 781, 713, 594 cm^{-1}; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm):8.20 - 8.179 (m, 1H), 7.98-7.954 (m, 1H), 7.9321 (d, J = 18.0 Hz,

2H), 7.611-7.588 (m, 2H), 7.548-7.544 (d, J=16.0Hz, 1H), 7.529-7.507(m, 1H), 7.283(s, 1H), 3.052-3.043(t, J=18Hz, 2H)3.037-3.006 (t, J=18Hz,2H) ,2.991(s,3H); ^{13}CNMR (100 MHz) δ 191.68 (s), 144.72 (dd, J = 489.1, 228.3 Hz), 137.62 (s), 135.25 - 124.96 (m), 29.86 (d, J = 17.1 Hz), 21.69 (s); MS (m/z):333.

3.1.3. (E)-2-((6-bromo-2-chloroquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2H)-one(8c)

Pale yellow solid, Chemical formula: $C_{20}H_{13}BrClNO$; melting point:174°C; IR (KBr, cm^{-1}): 3344, 3316, 2940, 2860, 1632, 1540, 1480, 1435, 1324, 1187, 1092, 830, 765, 744; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm): 8.197-8.179(d, J = 15.5 Hz, 1H), 8.027-7.982(m, 2H), 7.931-7.910(m, 2H), 7.844-7.822(m, 1H), 7.556- 7.522(m, 1H), 7.426-7.391(m, 1H), 7.291-7.266(m, 1H), 3.022-3.014(s, 4H).^{13}CNMR (100 MHz) δ 191.68 (s), 144.99 (dd, J = 363.4, 281.8 Hz), 137.62 (s), 135.25 - 125.22 (m), 117.75 (s), 29.86 (d, J = 17.1 Hz); MS (m/z): 396.78.

3.1.4. (E)-2-((2,6-dichloroquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2H)-one (8d)

White solid, Chemical Formula: $C_{20}H_{13}Cl_2NO$ melting point: 170; IR (KBr, cm^{-1}): 3349, 3315, 3245, 2945, 2868, 1641, 1539, 1481, 1460, 1435, 1321, 1167, 1072, 832, 761, 742; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm): 8.197-8.179(d, J = 15.5 Hz, 1H), 8.027-7.982(m, 2H), 7.931- 7.910(m, 2H), 7.844- 7.822(m, 1H), 7.556- 7.522(m, 1H), 7.426-7.391(m, 1H), 7.291-7.266(m, 1H), 3.022-3.014(s, 4H); ^{13}CNMR (100 MHz) δ 191.78 (s), 149.99 (dd, J = 363.4, 281.8 Hz), 149(s), 144.3(s), 136.62 (s), 134.25 - 124.22 (m), 123(s), 117.75 (s), 29.86 (d, J = 17.1 Hz). 23.3(s) Mass m/z: 353.57.

3.1.5. (E)-2-((2-chloro-6-fluoroquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2H)-one(8e)

White solid, Chemical Formula: $C_{20}H_{13}ClFNO$ melting point: 168; IR (KBr, cm^{-1}): 3342, 3159, 3022, 2924, 2857, 1624, 1541, 1450, 1418, 1243, 1196, 893, 843, 730, 683, 594, 510; ^{1}HNMR(400MHz,$CDCl_3$) (δ ppm): 8.197-8.179(d, J = 15.5 Hz, 1H), 8.027-7.982(m, 2H), 7.931- 7.910(m, 2H), 7.844- 7.822(m, 1H), 7.556- 7.522(m, 1H), 7.426-7.391(m, 1H), 7.291-7.266(m, 1H), 3.022-3.014(s, 4H); ^{13}CNMR (100 MHz) δ 191.68 (s), 143.03 (dd, J = 489.1, 228.3 Hz),139.02(s), 137.62 (s), 135.25 - 124.96 (m), 29.86 (d, J = 17.1 Hz), 23.3 (s).;Mass m/z: 337.07

3.1.6. (E)-2-((2-chloro-6,7-dimethylquinolin-3-yl)methylene)-3,4-dihydronaphthalen-1 (2H)-one(8f)

White solid, Chemical formula: $C_{22}H_{18}ClNO$; melting point: 173; IR (KBr, cm^{-1}): 3597, 3429, 3392, 3327, 2926, 2850, 1693, 1635, 1602, 1539, 1508, 1413, 1309, 1230, 1157, 1039, 972, 835, 781, 713, 594; ^{1}HNMR(400MHz,$CDCl_3$) (δ ppm): δ 8.196- 8.177(d, J=8Hz,1H), 7.965- 7.942(d,J=18Hz, 2H), 7.544-7.523(m, 1H), 7.447(m, 2H), 7.416- 7.378(m, 1H), 7.279-7.263(m, 1H), 3.058(t, 2H), 3.040(t,2H), 2.979(s,3H), 2.501(s,3,H); ^{13}CNMR(100 MHz) δ 191.68 (s), 149.53 - 135.62 (m), 135.38 - 124.05 (m), 29.86 (d, J = 17.1 Hz), 22.03 - 18.03 (m); MS (m/z):347.80.

3.1.7. (E)-2-((2-chloro-6-hydroxyquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2H)-one(8g)

White solid, Chemical Formula: $C_{20}H_{14}ClNO_2$; melting point: 177; IR (KBr, cm^{-1}): 3587,3501, 3431, 3395, 3337, 2936, 2859, 1647, 1655, 1622, 1559, 1518, 1417, 1306, 1231, 1158, 1040, 972, 834, 784, 717, 590; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm): 8.197-8.179(d, J = 15.5 Hz, 1H), 8.027- 7.982(m, 2H), 7.931- 7.910(m, 2H), 7.844- 7.822(m, 1H), 7.556-7.522(m, 1H), 7.426-7.391(m, 1H), 7.291-7.266(m, 1H), 5.353(s, 1H), 022-3.014(s, 4H); ^{13}CNMR (100 MHz) δ 191.64 (s),149.62(s) 144.74 (dd, J = 489.1, 228.3 Hz), 137.62 (s), 135.25 - 124.96 (m), 29.86 (d, J = 17.1 Hz), 23.02(s), 21.68 (s); Mass m/z: 355.70.

3.1.8. (E)-2-((2-chloro-6-nitroquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2H)-one(8h)

Brown solid, Chemical Formula: $C_{20}H_{13}ClN_2O_3$, melting point: 169; IR (KBr, cm^{-1}): 3599, 3394, 3328, 3177, 2916, 2852,1683, 1636, 1612, 1542, 1518, 1418, 1329, 1237, 1160, 1031, 974, 834, 783, 712, 597; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm): 8.197-8.179(d, J = 15.5 Hz, 1H), 8.027- 7.982(m, 2H), 7.931- 7.910(m, 2H), 7.844- 7.822(m, 1H), 7.556-7.522(m, 1H), 7.426-7.391(m, 1H), 7.291-7.266(m, 1H), 3.022-3.014(s, 4H); ^{13}CNMR (100 MHz) δ 191.67 (s),152.42(s), 149.02(s), 145.45(s), 144.71 (dd, J = 489.1, 228.3 Hz), 138.62 (s), 135.68(s)

134.25 - 124.98 (m), 29.86 (d, J = 17.1 Hz), 21.67 (s). Mass m/z: 364.78.

3.1.9. (E)-2-((2,7-dichloroquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1 (2H)-one(8i)

Yellow solid, Chemical Formula: $C_{20}H_{13}Cl_2NO$; melting point: 172; IR (KBr, cm^{-1}): 3429, 3349, 3327, 3315, 3245, 2945, 2868, 1641, 1539, 1481, 1460, 1435, 1413, 1321, 1309, 1167, 1072, 832,781,594; ^{1}HNMR(400MHz,$CDCl_3$)(δ ppm): 8.197-8.179(d, J = 15.5 Hz, 1H), 8.027- 7.982(m, 1H), 7.931- 7.910(m, 2H), 7.556- 7.522(m, 1H), 7.426-7.391(m, 2H), 7.291-7.266(m, 2H), 3.022-3.014(m, 4H); ^{13}CNMR (100 MHz) δ192.78 (s), 149.97 (dd, J = 362.4, 281.8 Hz), 147(s), 145.3(s), 136.66 (s), 134.24 - 124.24 (m), 122(s), 118.75 (s), 29.86 (d, J = 17.1 Hz). 23.3(s) 21.69 (s); Mass m/z: 354.06.

Table 1: Optimization table for compound 8b

Solvent	Base	Temperature °C	Time (min)	Yield (%)
H_2O	-	RT	25	Trace
EtOH	-	RT	25	Trace
H_2O	NaOH	RT	20	50
EtOH	NaOH	RT	20	70
H_2O	KOH	RT	20	60
EtOH	KOH	RT	20	75
H_2O: EtOH	NaOH	RT	10	79
H_2O: EtOH	NaOH	50	10	69
H_2O: EtOH	KOH	50	10	71
H_2O: EtOH	KOH	60	10	65

All the optimization conditions were performed under ultra-sound irradiation method to choose the most efficient condition with minimum time.

To find the optimal reaction condition, we have studied the synthesis of (E)-2-((2-chloro-6-methylquinolin-3-yl)methylene)-3,4-dihydronaphthalen-1(2H)-one from 2-chloro-4-methyl quinoline-3-carbaldehyde and the 3,4-dihydronaphthalen-1(2H)-one under various optimazation reaction conditions shown in table1.

Table 2: Optimization table of various substitutions with respect to their % of yield and melting points

Code	Substitution	Molecular formula	% Yield	Melting Point
8a	H	$C_{20}H_{14}ClNO$	73	167
8b	6-CH_3	$C_{21}H_{16}ClNO$	79	172
8c	6-Br	$C_{20}H_{13}BrClNO$	76	174
8d	6-Cl	$C_{20}H_{13}Cl_2NO$	80	170
8e	6-F	$C_{20}H_{13}ClFNO$	75	168
8f	6,7-CH_3	$C_{22}H_{18}ClNO$	78	173
8g	6-OH	$C_{20}H_{14}ClNO_2$	63	177
8h	6-NO_2	$C_{20}H_{13}ClN_2O_3$	83	169
8i	8-Cl	$C_{20}H_{13}Cl_2NO$	81	172

3.2. Biological activity

All the derivatives were screened for their antimicrobial activities. The activities against two gram positive and two gram negative bacterial strains and three fungal strains were shown in table-3. All the activities were recorded using Ampicilin and Nystatin as standard drugs in Minimum-bacterial Inhibitory Concentration (MIC). Broth dilution technique was used to evaluate all the values and as diluents DMSO was used as diluent. MIC values of the appraised compounds were recorded in table 3.

Table 3: Antimicrobial activity of synthesized compounds

Sr. No.	Code	MIC (µg/mL)						
		antibacterial activity				antifungal activity		
		S.aureus	*B.cereus*	*E.coli*	*P.aeruginosa*	*C.albicans*	*A.niger*	*A.clavatus*
1	8a	500	500	200	500	1000	>1000	>1000
2	8b	100	250	250	500	1000	500	500
3	8c	1000	1000	83.5	500	500	500	500
4	8d	250	500	200	500	1000	1000	1000
5	8e	1000	62.5	250	250	200	>1000	>1000
6	8f	250	1000	500	76.5	500	500	500
7	8g	200	500	250	500	500	500	500
8	8h	1000	500	1000	500	>1000	100	100
9	8i	100	500	500	250	1000	100	1000
Ampicilin		100	100	100	100	-	-	-
Nystatin		-	-	-	-	500	100	100

S. aureus: Staphpyococcus aureus, B. Cereus: Bacillus Cereus, E. coli: Escherichia coli, P.aeruginosa: Pseudomonas aeruginosa, C.albicans: Candida.albicans, A.niger: Aspergillus niger, A.clavatus: Aspergillus clavatus

Derivatives **8b** and **8i** were exhibited moderate activity against *S. Aureus* (MTCC-96), derivative **8e** was possessed moderate activity agaist *B.cereus* (MTCC-430), compound **8c** was possessed moderate activity against *E. Coli* (MTCC-443) and compound **8f** was showed moderate activity agaist *P. aeruginosa* (MTCC-1688) by comparing Ampicilin as a standard drug. Compound **8e** was possessed moderate activity against *C.albicans* (MTCC-227), compounds **8h** and **8i** were exhibited moderate activity against *A.niger* (MTCC-282) and derivative **8h** was showed moderate activity against *A.clavatus* (MTCC-8123) by comparing Nystain as a standard drug.

4. CONCLUSION

In the present studies we have developed novel α, β unsaturated carbonyl derivatives using simple, greener ultra sound irradiation method with good yield. All the novel chalcone structures were successfully characterized by ^{1}HNMR, ^{13}CNMR, Mass & IR spectral analysis. All the synthesized compounds were screened for their antimicrobial activity against two gram positive, two gram negative bacterial and three fungal strains. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed potency to inhibit the micro-organisms. The best microbial activity was shown by 8b, 8c, 8e, 8f, 8h and 8i compounds.

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