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One-Pot Multi Component Microwave Assisted Synthesis of 4H-Pyrano [2, 3-c] Pyrazoles in Methanol and their Antibacterial Study

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Abstract: Upon literature studies, pyrano-pyrazoles were found to exhibit the biological activity as antimicrobial agents. So literature employed conventional stirring and reflux condensing to afford different pyrano-pyrazoles. Recent researches adopted the Microwave method, which is a simple and convenient method for organic synthesis. In this work, we reported the synthesis of different 4H-pyrano [2, 3-c] pyrazoles via two different methods, such as microwave & conventional stirring at room temperature. Ethyl acetoacetate, hydrazine hydrate, malanonitrile, and different substituted carbonyl compounds were made to react in the presence of methanol solvent & potassium ter-butoxide, a base catalyst. The microwave method was adopted for all the reactions and found to be more potent than the conventional method. The prepared compounds were characterized by FT-IR, ^{1}HNMR, and ^{13}CNMR. These compounds were screened for anti-bacterial activity against *Staphylococcus aureus* and *E. coli* by well diffusion method and showed the excellent antibacterial property. Our *In vitro* test for antibacterial study involves excellent MIC (µg/ml) and zone inhibition (mm) measurements of all synthesized compounds. Microwave irradiation synthesis hastens the reaction and is completed very fast. Potassium ter-butoxide, a base catalyst, is proved to be a good catalyst for accelerating the reactions. The yield of all synthesized compounds was good. Different 4H-pyrano [2, 3-c] pyrazoles exhibited good potency against *Staphylococcus aureus* and *E. coli.* In the presence of a base catalyst, the reactions are faster than in the absence of a catalyst. The microwave method is a good methodology for the green syntheses. Derivatives of 4H-pyrano [2, 3-c] pyrazoles exhibited excellent MIC (µg/ml) and proved to be as good antibacterial agents.

Keywords: 4H-pyrano [2, 3-c] pyrazoles; microwave method; potassium ter-butoxide; methanol solvent; in vitro antibacterial screening; minimum inhibition concentration.

1. Introduction

Upon studying literature, so many heterocycles have featured characteristics in the medicinal field [1]. Over the past decades, these category molecules have been emerging new trends day by day. Recently they have made it more adventurous for the chemists to involve in the research. We studied pyrazoles and made it more interesting to participate in their

medicinal characters [2-4]. Pyrano [2,3-c] pyrazoles have various Pharmacological applications such as antiviral, anticancer, anti-microbial and so on [5, 6]. The microwave method could reach the green chemistry phenomenon.

In this work, 4H-Pyrano [2, 3-c] Pyrazole molecules were synthesized under microwave irradiation and conventional stirring at room temperature. Potassium ter-butoxide, a strong base, catalyzed the reaction in the presence of methanol as a solvent. Both conventional and microwave methods were compared on their excellence of the reaction. The microwave method was found to be better potent than conventional.

2. Materials and Methods

2.1. Materials used.

Required chemicals were purchased by SDFCL Company and facilitated by Dept. of Chemistry, Government Science College, Karntaka, India. The melting point was determined into pen capillary tubes in the Buchi B-540 melting point apparatus. The reaction was monitored by thin-layer chromatography using silica gel glass plates. The reaction was visualized by a short Ultraviolet lamp & isolated in an iodine chamber. FT-IR spectrometer (Vertex series from Bruker), ^{1}H NMR (400MHz) & ^{13}C NMR (100MHz) were used. Glass Petri plates for MIC study were used.

2.1.1. General Procedure for 4H-Pyrano [2, 3-c] Pyrazoles synthesis.

A mixture of Ethyl acetoacetate (10 Mmol), hydrazine hydrate (10 Mmol), malanonitrile (10 Mmol), and Aromatic aldehydes was taken in a flask. A catalytic amount of Potassium t-butoxide (10mmol) in the presence of methanol solvent (25-30ml) was added to the mixture and allowed for microwave irradiation. The reaction progressed was monitored by TLC (Pet. Ether: Ethyl acetate). The precipitate thus formed was filtered off, washed with hot water.

The crude solid was then recrystallized by hot ethanol many times to afford pure Pyrano-pyrazoles and finally dried.

2.2. Antibacterial assay.

All the compounds synthesized in the present work were screened for antibacterial activity against *Staphylococcus aureus,* and *E. coli* by well diffusion method (Kirby-Bauer method) (Çiğdem Eda Balkan *et al*., 2016) [7, 8]. The bacteria cultures were collected from Vasavi diagnostic laboratory and sub-cultured on nutrient agar slants. They were pre-cultured on nutrient broth overnight and incubated at 37^{o}C. The culture broths were centrifuged at 1000 rpm for 5minutes; bacterial pellet was suspended in double-distilled sterile water.

In this assay, a concentration of 1mg/ml of synthesized compounds was placed into respective wells cut in nutrient agar plates inoculated with test bacteria. Similarly, reference antibiotics streptomycin and ampicillin and solvent dimethyl sulphoxide were also placed into their respective wells. All the plates were incubated at 37^{o} C for 24 hours. After incubation, the plates were observed for the inhibition zone surrounding the well, and its diameter was measured.

6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a): White solid, M.P 245-2460℃ , yield (%): 85.00; FT-IR: υ cm^{-1} 3374 (-NH stretch, weak), 3172 (-NH_2 stretch, weak), 3023 (Ar-H, strong), 2200 (-CN, medium), 1650 (C=C stretch), 1612 ((C=C, Pyrazole ring); ^{1}H-NMR (DMSO, 300MHz): 1.7 (3H, s), 2.4-3.2(3H, s), 4.5 (1H, s), 6.8 (2H, dtd, J= 7.9, 1.3, 0.6 Hz), 7.1 (dddd, J= 7.9, 7.7, 1.9, 0.6 Hz), 7.1 (tt, J=7.7, 1.3 Hz), 12.0 (C=NH, s); ^{13}C-NMR (100 MHz, DMSO-d6) δ: 9.6, 36.1, 57.1, 97.6, 120.7, 126.6, 127.4, 128.3, 135.5, 144.4, 154.7, 160.8; Elemental analysis: calculated for $C_{14}H_{12}N_4O$ (C, H, N) 66.65, 4.79, 22.21, Found: 66.66, 4.77, 22.20.

6-amino-4-(2-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5b): Brown solid, M.P 246-248℃ , yield (%): 84.00; FT-IR: υ cm^{-1} 3392 (-NH stretch, weak), 3169 (-NH_2 stretch, weak), 2190(-CN, medium), 1654 (C=C stretch), 1611 ((C=C, Pyrazole ring), 1490 (Ar-C-C stretch, medium), 1053 (C-Cl, stretch, strong), 760 (C-Cl).

6-amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5c): Dark Yellow solid, M.P 218-220℃, yield (%): 80.00; FT-IR: υ cm^{-1} 3356 (-NH stretch, weak), 3230 (-NH_2 stretch, weak), 3062 (Ar-H stretch, strong) 2189 (-CN stretch, medium), 1691 (C=N, bend), 1600 (Ar-C-C, Pyrazole ring), 1495 (N=O, stretch, Strong), 1453 (CH_2 & CH_3, strong); ^{1}H-NMR (DMSO, 300MHz): 2.1-2.5 (3H, s), 3.3(1H, s), 6.5-7.4 (1H, ddd, J= 8.4, 8.0, 0.4 Hz), 7.7 (1H,ddd, J= 8.0, 1.5, 1.4 Hz), 8.1-8.2 (2H, 7.8 (dddd, J= 1.7, 1.5, 0.4 Hz), 7.8 (ddd, J=8.4, 1.7, 1.4 Hz), (C=NH, s). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 12.6, 18.5, 55.9, 99.9, 119.3, 125.5, 127.1, 127.8, 128.5, 142.3, 143.1, 144.2, 144.6, 147.5, 159.1; Elemental analysis: calculated for $C_{14}H_{11}N_5O_3$ (C, H, N) 56.56, 3.73, 23.56, Found: 56.58, 3.70, 23.52.

6-amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5d): Pale Yellow solid, M.P 210-2110℃, yield (%): 79.00; FT-IR: υ cm^{-1} 3363 (-NH stretch, strong), 3308 (-NH_2 stretch, strong), 3062 (Ar-H stretch, strong) 2193 (-CN stretch, medium), 1648 (C=N, bend), 1594 (C-O, stretch), 1486 (Ar-C-C, stretch, medium), 1426 (Ar-C-C, stretch); ^{1}H-NMR (DMSO, 300MHz): 1.807 3H,s), 2.481-3.301 (3H, s), 4.47 (1H, s), 6.60 (2H, ddd, J= 8.8, 1.2, 0.6 Hz), 7.10 (2H, ddd, J= 8.8, 1.0, 0.6 Hz), 12.05 (C=NH); ^{13}C-NMR (100 MHz, DMSO-d6) δ: 12.33, 29.86, 55.66, 57.28, 99.95, 111.47, 119.17, 119.80, 20.84, 125.03, 128.43, 129.12, 130.66, 142.42, 144.20, 144.99, 147.27, 156.64, 159.76; Elemental analysis: calculated for $C_{15}H_{14}N_4O_2$ (C, H, N) 63.82, 5.00, 19.85, Found: 63.78, 5.05, 19.82.

6-amino-4-[4-(dimethylamino)phenyl]-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5e): Light Brown solid, M.P 274-276℃, yield (%): 90.00; FT-IR: υ cm^{-1} 3454 (-NH stretch, strong), 3211 (-NH_2 stretch, strong), 3062 (Ar-H stretch, strong) 2203 (-CN stretch, medium), 1634 (C=N, bend), 1508 (C-O, stretch), 1352 (CH_3& CH_2, bend); ^{1}H-NMR (DMSO, 300MHz): 2.0 (3H, s), 2.4-2.4 (3H, s),4.4-4.6 (1H, s),6.5-6.6 (2H, ddd, J= 8.2, 1.3, 0.5 Hz), 7.5-7.8 (2H,ddd, J= 8.2, 1.1, 0.5 Hz), 12.0 (C=NH). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 9.7, 35.3, 57.9, 98.1, 112.2, 120.9, 127.9, 132.0, 135.4, 149.1, 154.7, 160.5; Elemental analysis: calculated for $C_{16}H_{17}N_5O$ (C, H, N) 65.07, 5.80, 23.71, Found: 65.08, 5.78, 23.70.

6-amino-4-(3-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5f): Pale Yellow solid, M.P 209-210℃, yield (%): 89.00; FT-IR: υ cm^{-1} 3363 (Ar-OH, strong), 2216 (CN, medium),1619 (C=N, bend), 1602 (Ar-C-C, stretch); ^{1}H-NMR (DMSO, 300MHz): 2.4-2.4 (3H, s), 2.4-3.3 (3H, s), 7.0 (1H, dd, J=10.1, 9.5 Hz), 7.0-7.7 (3H, 7.4 (tt, J=7.3, 1.5 Hz), 7.7 (dddd, J= 7.9, 7.3, 2.0, 0.4 Hz)), 7.7 (2H, dddd, J= 7.9, 1.5, 1.5, 0.4 Hz), 7.8 (1H, d, J= 9.5 Hz), 8.6 (1H, d, J=10.1 Hz). ^{13}C-NMR (100 MHz, DMSO-d) δ: 9.7, 36.1, 57.2, 97.6,

113.7, 114.0, 118.1, 120.7, 129.2, 135.5, 145.9, 154.7, 157.3, 160.8; Elemental analysis: calculated for $C_{14}H_{12}N_4O_2$ (C, H, N) 62.68, 4.51, 20.88, Found: 62.61, 4.39, 20.90.

6-amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5g): Brown solid, M.P. 192-194℃, solid, yield (%) 80.00; FT-IR: υ cm^{-1} 3363 (Ar-OH, strong), 2216 (CN, medium),1619 (C=N, bend), 1602 (Ar-C-C, stretch); ^{1}H-NMR (DMSO, 300MHz): 2.4-2.4 (3H, s), 2.4-3.3 (3H, s), 7.0 (1H, dd, J=10.1, 9.5 Hz), 7.0-7.7 (3H, 7.4 (tt, J=7.3, 1.5 Hz), 7.7 (dddd, J= 7.9, 7.3, 2.0, 0.4 Hz)), 7.7 (2H, dddd, J= 7.9, 1.5, 1.5, 0.4 Hz), 7.8 (1H, d, J= 9.5 Hz), 8.6 (1H, d, J=10.1 Hz). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 9.7, 35.7, 55.5, 57.5, 97.8, 111.5, 115.3, 119.7, 120.8, 135.3, 135.5, 145.1, 147.2, 154.6, 160.4; Elemental analysis: calculated for $C_{14}H_{12}N_4O_2$ (C, H, N) 62.68, 4.51, 20.88, Found: 62.70, 4.48, 20.87

6-amino-4-(2,4-dihydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5h): Yellow solid, M.P. 200-202℃, yield (%) 82.00; FT-IR: υ cm^{-1} 3363 (Ar-OH, strong), 2216 (CN, medium),1619 (C=N, bend), 1602 (Ar-C-C, stretch); ^{1}H-NMR (DMSO, 300MHz): 2.4-2.5 (3H, s), 2.4-3.3 (3H, s), 7.0 (1H, dd, J=10.1, 9.5 Hz), 7.0-7.7 (3H, 7.4 (tt, J=7.3, 1.5 Hz), 7.7 (dddd, J= 7.9, 7.3, 2.0, 0.4 Hz)), 7.7 (2H, dddd, J= 7.9, 1.5, 1.5, 0.4 Hz), 7.8 (1H, d, J= 9.5 Hz), 8.6 (1H, d, J=10.1 Hz). Elemental analysis: calculated for $C_{14}H_{13}N_4O_3$ (C, H, N) 58.94, 4.56, 19.64, Found: 58.90, 4.58, 19.62.

6-amino-4-[(E)-2-phenylethenyl]-2,4-dihydropyrano[2,3-c]pyrazole-5-arbonitrile (5i): Yellow solid, M.P 269-271℃, yield (%): 84.00; FT-IR: υ cm^{-1} 3345 (-NH, stretch, strong), 3227 (NH_2 stretch, strong), 3027 (CH=CH stretch)2215 (CN, medium),1619 (C=N, bend), 1602 (Ar-C-C, stretch); ^{1}H-NMR (DMSO, 300MHz): 1.0-1.2 (3H, s), 2.0-2.5 (3H, s), 3.9-4.9 (1H, d, J= 4.4 Hz), 6.6-6.7 (2H, 6.8 (d, J= 17.1Hz), 7.2 (dd, J= 17.1, 4.4 Hz)), 7.5 (1H, s), 7.5 (1H, tt, J=7.7, 1.3 Hz), 7.8-7.9 (4H, 7.3 (dddd, J=7.7, 7.6, 1.8, 0.5 Hz), 8.0-8.9 (dddd, J=7.6, 1.8, 1.3, 0.5 Hz). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 10.4, 35.9, 57.1, 97.7, 120.8, 126.8, 127.6, 135.6, 142.7, 154.7, 160.8; Elemental analysis: calculated for $C_{17}H_{13}N_4O$ (C, H, N) 70.58, 4.49, 19.37, Found: 70.57, 4.50, 19.42.

6-amino-4-(furan-2-yl)-1,3a,4,7a-tetrahydropyrano[2,3-c]pyrazole-5-carbonitrile (5j): Brown solid, M.P 255-256℃, yield (%): 80.00; FT-IR: υ cm^{-1} 3329 (-NH, stretch, strong), 3220 (NH_2 stretch, strong), 2214 (CN, medium),1595 (CO, stretch, furan ring), 1602 (Ar-C-C, stretch), 1453 (CH3 strong); ^{1}H-NMR (DMSO, 300MHz): 1.2 (3H, s), 2.0-2.5 (3H, s), 3.3-3.9 (1H, d, J= 4.4 Hz), 6.2-6.6 (2H, 6.8 (d, J= 17.1Hz), 7.0 (dd, J= 17.1, 4.4 Hz)), 7.5 (1H, s), 7.3 (1H, tt, J=7.7, 1.3 Hz), 7.6-7.9 (4H, 7.3 (dddd, J=7.7, 7.6, 1.8, 0.5 Hz), 7.9-8.0 (dddd, J=7.6, 1.8, 1.3, 0.5 Hz). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 9.6, 31.3, 57.5, 97.5, 120.5, 124.3, 124.9, 126.4, 136.0, 149.7, 154.2, 160.6; Elemental analysis: calculated for $C_{12}H_{10}N_4O_2$ (C, H, N) 59.50, 4.16, 23.13, Found: 59.48, 4.13, 23.11.

3. Results and Discussion

The synthesized compounds exhibited FT-IR ranges between 3300-3450 cm^{-1} and 2200-2230 cm^{-1} confirmed –NH of pyrazole ring and CN group, respectively. Likewise, ^{1}H-NMR spectra showed the range 6.5-8.0 ppm and 8.0-12.1 ppm which confirmed the aromatic protons of pyrazoles and -NH of pyrazole, respectively. Reddy M B *et al*. reported the synthesis of Pyrazolo [2,3-c] pyrazoles by the catalyst imidazole by conventional method [9].

This work consumes more reaction time as well as a lower yield of products. Khurana J M, *et al*. reported the work on Pyrazolo [2,3-c] pyrazoles synthesis in the presence of an Ionic liquid [bmim] OH under solvent-free conditions. This work revealed the reaction time of all the reactions at approx. 5 mins [10]. We studied some literature on the synthesis of Pyrano [2,

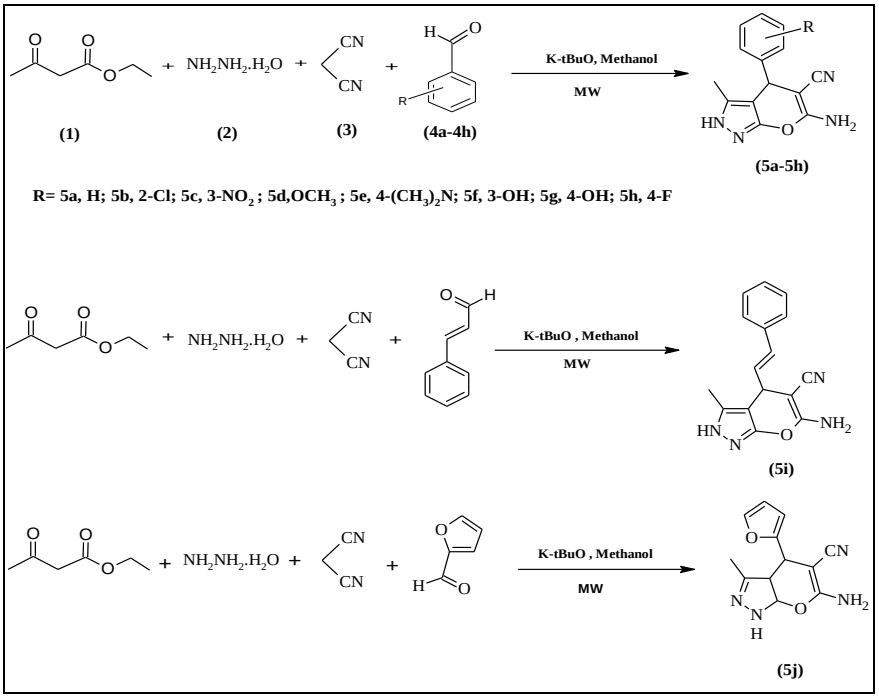
3-c] pyrazoles by different methods. These researches only revealed the synthesis of compounds by convenient methods but not focussed on shorter reaction times and the yield [11-15].

We are herein reported that reactions under microwave irradiation were completed faster than the convention method (< 5 min). Meanwhile, compounds yielded excellent under the influence of microwave. K-tBuO, a catalyst, provoked the reactions in the presence of methanol solvent.

From Table 1, Under microwave, compounds 5a and 5d were found to be completed the reaction at a lesser time (> 3mins) and afforded the yields 85.00% and 79.00% respectively. Due to only the Phenyl group without any electron releasing group and electron-withdrawing group attached to the Pyrano-pyrazole moiety, the yield of 5a compound is excellent compared to 5d. The compounds 5a, 5b, 5d, 5e, 5f, 5g, and 5h possess electron releasing group attached to the phenyl group, completed the reaction within 4 mins and yielded excellent compared to 5c, which possess electron-withdrawing group at a phenyl substituent.

Table 1. Synthesis of Pyrano [2,3-c] pyrazoles by Microwave method.

Compounds	Time (min)		Yield (%)		M.P ^{0}C
	Microwave	Convention	Microwave	Convention	
5a	2.5	5-6	85.00	80.00	245-246
5b	4.5	10-12	84.00	75.00	246-248
5c	5.0	10	80.00	60.00	218-220
5d	2-3	8-10	83.00	62.00	210-211
5e	3-4	12	89.00	75.00	274-276
5f	4.0	11-12	84.00	72.00	209-210
5g	3-4	10	80.00	70.00	192-194
5h	4.0	10-11	82.00	72.00	200-202
5i	5.0	12	80.00	70.00	269-271
5j	4-5	10-12	90.00	78.00	255-256



Scheme 1. Base catalysed microwave assisted synthesis of Pyrano[2,3-c]pyrazoles in Methanol solvent.

3.1. Antibacterial assay.

After incubation, inhibition zones formed around the wells were measured in millimetres. This study was performed in triplicates. The results showed (in Fig. 1) *In vitro*

antibacterial activity of all the synthesized compounds tested at 1mg/ml concentration showed low to high activity against *Staphylococcus aureus*, and *E. coli*.

Mahavir Parshad *et al*. in 2015 revealed the study of antibacterial activity of Pyrano [2,3-c] pyrazoles. Zone inhibition and MIC of most synthesized compounds were found to exhibit less activity [16]. We referred to many kinds of literature of antibacterial activity of Pyrano [2,3-c] pyrazoles possess less activity (MIC) [17, 18].

Among the tested compounds and standard antibiotics, relatively 5d showed the highest activity (23 mm) against *Staphylococcus aureus*, and *E. coli*, which is higher than reference antibiotics (in Fig. 2)

The compound 5i has shown the highest activity against *Staphylococcus aureus*, which is slightly higher than ampicillin. The activity of compounds 5b and 5j against *Staphylococcus aureus* is equal to ampicillin. All other compounds showed moderate antibacterial activity. This showed that the compounds synthesized in our work are effective antibacterial activity.

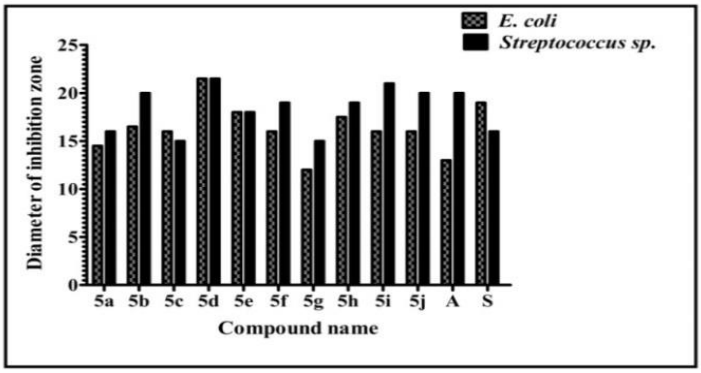


Figure 1. Graph representation for antibacterial activity of test compounds against *E. coli* and *Staphylococcus aureus in comparision with* reference antibiotics Ampicillin (A) and Streptomycin (S).

3.2. Minimum inhibitory concentration of Compounds.

The compounds 5d, 5e, and 5h inhibited *E. coli* growth in lowest (7.8125 µg/ml) inhibitory concentration. The other compounds 5d, 5f, 5h, 5i, and 5j have the lowest (7.8125 µg/ml) inhibitory concentration against *Staphylococcus aureus* (Table 2.). This showed that the compounds synthesized in our work have great potential to inhibit+/kill the test bacteria in low concentration.

MIC is defined as the lowest concentration of the antibacterial agent where no visible growth is observed in the test tube (bacteriostatic concentration). The method of Volleka *et al*. (2001), modified by Usman *et al*. (2007), was used to determine the MIC of the compounds [19]. The compounds were diluted by double serial dilution method (1-2) to a working concentration ranging from 1000 µg/ml to 7.812 µg/ml using nutrient broth. Later all the test tubes containing nutrient broth and compounds in variable concentration were inoculated with 0.1ml respective test bacterial suspension. After 18 hours of incubation at 37ºC, the test tubes were observed for growth, and turbidity was determined calorimetrically. The least concentration of the compounds (or highest dilution of compounds) that completely inhibited the growth of the test organism, i.e., where no turbidity was observed, is the minimum inhibitory concentration (MIC) of the compounds. A control experiment was done parallel to check the influence of the solvents alone (without compound) on the growth of the test organisms. Solvents were diluted appropriately with sterile nutrient broth, followed by inoculation of test bacterial suspension and incubation. Positive control was prepared by using

2ml of sterile nutrient broth followed by inoculation of 0.1ml of test bacterial suspension and incubation (EL-Kamali *et al*., 2010) [20].

Table 2. Minimum Inhibitory Concentration (MIC).

Sl. No.	Compound name	MIC (µg/ml)	
		E. coli	***S. aureus***
1	5a	15.625	15.625
2	5b	15.625	31.125
3	5c	15.625	62.25
4	5d	7.8125	7.8125
5	5e	7.8125	15.625
6	5f	31.125	7.8125
7	5g	15.625	15.625
8	5h	7.8125	7.8125
9	5i	31.125	7.8125
10	5j	15.625	7.8125

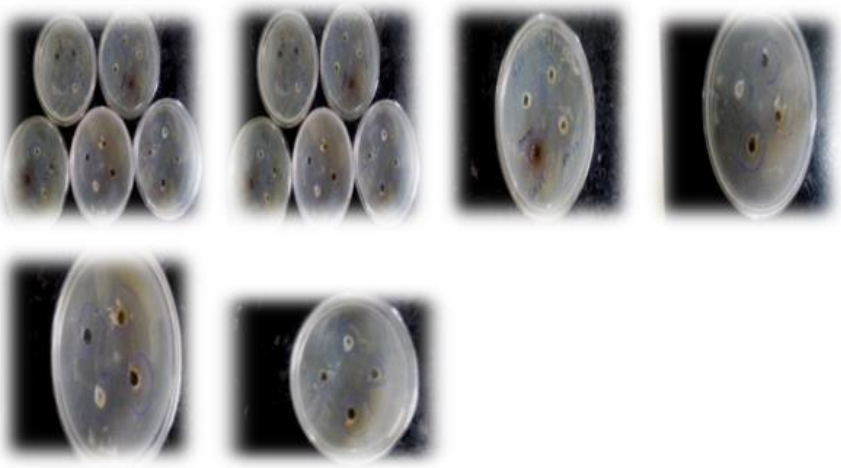


Figure 2. Images: Measurements of Zone Inhibition at 1mg/ml concentration of compounds 5a-5j against *Staphylococcus aureus*, and *E. coli*.

4. Conclusions

We reported that Multicomponent reactions are instant reactions under the microwave. But in the case of convention, the reaction time is high compared to microwave. The yield of all synthesized compounds is excellent in the microwave. Potassium t-butoxide is proved as a promising catalyst. Most of the synthesized compounds showed good activity against Gram-+ve and Gram--ve bacteria. Some of the synthesized compounds showed moderate antibacterial activity.

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Conflicts of Interest

No Conflicts of interest declared by all the Authors.

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