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FAST RATE OF CATALYST PROMOTED BY BIOACTIVE SYNTHESIS OF 2, 4, 5-TRIPHENYL IMIDAZOLE DERIVATIVES EMPLOYING METHANE SULPHONIC ACID.

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ABSTRACT

A simple, highly versatile and an efficient synthesis of 2, 4, 5-trisubstituted imidazole that was obtained by three component cyclocondensation of benzil, substituted aromatic aldehydes and ammonium acetate in solvent free condition using methane sulphonic acid acts as catalyst and solvent .The main advantages of this process are cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, excellent yields and very low reaction time. One pot multicomponent reactions are very important an outstanding status in organic synthesis and medicinal chemistry for their high degree of atom economy and application in the diversity-oriented convergent conventional synthesis of complex organic molecules from simple and readily available substrates in a single vessel. The newly obtained derivatives were confirmed by advanced spectroscopic data such as FTIR, 1HNMR, 13CNMR and LCMS and the structural determination of the desired compounds were determined by elemental analysis.

KEYWORDS: 2,4,5 -Triarylimidazole, benzil, substituted aromatic aldehydes, Ammonium acetate, Methane sulphonic acid.

1. INTRODUCTION

Infectious diseases caused by bacterial pathogens represent a major public health issue in recent years due to the emergence and spread of new strains of bacteria and the widespread occurrence of drug resistance. Thus, the development of new types of antibacterial drugs, especially those with a new drug target and/or with the ability to overcome drug resistance is

an urgent need. Structural modification of antimicrobial drugs to which resistance has developed, has been shown to be an effective way to prolong the lifespan of antifungal agents such as azoles, antiviral agents such as no nucleoside reverse transcriptase inhibitors [5], and various antibacterial agents including imidazole and benzimidazoles.[1-5]

In recent time, Nitrogen containing heterocyclic compounds is highly interest because of their several applications in different fields such as pharmaceutical, cosmetics, pesticides, fungicides, disinfectant, agro chemicals, dye stuff, antifreeze, anti- inflammatory, anticancer, optical electronics, OLEDs and dye sensitized solar cells (DSSC), etc.[6-10] Imidazole is five membered heterocyclic compounds that contain two nitrogen atoms at position "1"and "3" and also it was under intensive focus mainly due to their broad range of applications in organic synthesis and medicinally chemistry. The study of synthesis of imidazole moiety is very significant play a role due to their potent biological activity and synthetic utility. Imidazole is the most important class of heterocyclic compounds which have being developed the core fragment of various natural products and biological systems. Most of the imidazoles core structures has present in many biological systems like histidine, histamine and biotin. Notably tri aryl imidazoles are used in photography as photo sensitive compounds.[11-13] Compounds possesses imidazole moiety which have many pharmacological properties and also play an important role in biochemical processes. The potent activity and wide applicability of the imidazole pharamacophores can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active sites. Naturally occurring substituted imidazole and its synthetic derivatives exhibit wide ranges of biological properties, making them attractive compounds for organic chemists As a result the role of imidazoles is noteworthy in the field of organic chemistry. The synthesis and characterization of trisubstituted imidazole that are used to satisfy the current requirements is one of the important research topics. Literature scanning clearly reveals that the number of divergent methods for the synthesis of tri substituted imidazoles. In general, synthesis comprises the condensation of acetate. It was first suggested by Radsziszewki in 1882, though this method has lot of potential, some of the reported variants were not applied for the synthesis of structurally diverse imidazoles.

METHODS AND MATERIALS

All reagents, chemicals and solvents were purchased from Sigma Aldrich and Merck chemicals and they are used without further purification. The melting points of the newly

synthesized compounds were measured by an instrument Agarwal thermo meter open capillary method using a Galen Kamp melting point apparatus and are uncorrected. The desired Products were characterized by spectroscopy data (FTIR, 1HNMR and 13CNMRspectra and LCMS). Bruker spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded on a Bruker Avance (400-MHz) NMR and $CDCl_3$ was used as a solvent. The purity of the substances and the progress of the reactions were checked on TLC.

General Methods for Synthesis of 2,4,5- Trisubstituted Imidazole

Taken clean and dry four neck rounded bottom flask fitted on the magnetic stirrer. The mixture of benzil (1mol), substituted aromatic aldehydes (1.150mol), and ammonium acetate (2mol) were introduced in a RBF and the appropriate amount catalyst such as methane sulphonic acid was added (3mmol). Then the reaction mixture was heated to reflux for the appropriated period of time. After completion of the reaction which was monitored by TLC as mobile phase (4:6-EtOAc: n-hexane), the mixture taken in an ethyl acetate and washed with water, the solid product can be separated and purified by recrystallization from ethanol. All of the desired product(s) were characterized by comparison of their physical data with those of known compounds.

Some characterization data for selected known products are given below

Spectral and Analytical Data

1). 2, 4, 5-Triphenyl-1H-imidazole (4a)

Paleyellowsolid;Rf:0.45(EtOAc:n-hexane=4:6);.Yield-85%:FTIR(KBr, cm−1):3487(NH), 2927, 2458, 1622(C=C), 1512(C=N);1HNMR(400MHz, CDCl3)ppm:11.241(s, 1H, NH-imidazole), 8.119-8.0174(m, 2H, Ar-H), 7.835-7.280(m, 13H, Ar-H);13CNMR (100MHz, CDCl3) ppm:148.54, 138.05, 136.12, 131.89, 130.66, 129.84, 128.68, 128.12, 127.89, 127.15, 125.96; LCMS(m/z): 297.26(M+H); Molecular formulae: $C_{21}H_{16}N_2$; Elemental analysis: Calculated: C-85.10, H-5.43, N-9.44, Obtained : C- 85.02 , H-5.42 , N-9.50.

2). 4-(4, 5-Diphenyl-1H-imidazol-2-yl)-phenol (4b)

Whitesolid;Rf:0.55(EtOAc:n-hexane=5:5);.Mp-230–232°C.Yield-86%;FTIR(KBr, cm−1): 3608 (OH), 3469 (NH), 3231, 3089, 1693(C=C), 1287; ^{1}HNMR(400 MHz, CDCl3): 11.115 (s, 1H, -NH-imidazole), 9.124 (s, 1H, OH), 7.789-7.692(m, 2H, Ar-H), 7.538–7.281(m, 10H, Ar-H), 7.089-6.986(m, 2H, Ar-H);^{13}CNMR(100MHz, $CDCl_3$):158.77, 148.09, 137.78, 133.65, 130. 87, 129.55, 128.54, 127.27, 126.84, 124.63, 121.95, 114.72, 112.82, 98.65,

95.48;LCMS(m/z):312. 03(M+); Molecularformulae:$C_{21}H_{16}N_{2O}$.Elementalanalysis: Calculated: C-80.75, H-5.16, N-8.97, Obtained: C- 80.68 , H-5.14 , N-9.04.

3).4-(4, 5-diphenyl-H-imidazol-2-yl)-2-hydroxy phenyl acetate (4c)

Whitesolid;Rf:0.50(EtOAc:n-hexane=5:5);Mp-236–238°C.Yield-89%; Rf-0.40(EtOH:n-hexane-4:6); FTIR(KBr, cm−1):3592(OH), 3469(NH), 3236, 3069, 1698(C=C), 1280; ^{1}HNMR(400MHz, CDCl3):11.096(s, 1H, -NH-imidazole), 9.167(s, 1H, OH), 7.558–7.284(m, 12H, Ar-H), 7.125(s, 1H, Ar-H), 1.986(s, 3H, -OCOCH$_3$);^{13}CNMR(100MHz, $CDCl_3$):163.08, 143.65, 140.34, 136.74, 129.81, 128.90, 128.56, 127.44, 125.68, 123.77, 118.76, 116.55, 60.33;LCMS(m/z):370.44(M+); Molecular formulae:$C_{23}H_{18}N_2O_3$.Elementalanalysis: Calculated: C-74.58, H-4.90, N-7.56:Obtained:C-74.51, H-4.89, N-7.64.

4). 2-(4-Methoxyphenyl)-4, 5-diphenylimidazole (4d)

Whitesolid;Rf:0.42(EtOAc:n-hexane=4:6);Mp.223-225°C.Yield-85%, FTIR(KBr, cm−1): 3452 (NH), 3074, 1616, 1496(C=C), 1180, 1026, 834, 765;1HNMR(400MHz, CDCl3): 11.064(s, 1H, -NH-imidazole), 8.121-8.108(m, 2H, Ar-H), 7.607-7.286(m, 10H, Ar-H), 7.157-7.109(m, 2H, Ar-H), 3.596 (s, 3H, OCH3);^{13}CNMR(100MHz, $CDCl_3$)ppm:158.98, 146.79, 136.25, 134.12, 131.16, 130.57, 128.04, 126.54, 123, 40, 113.78, 55.65;LCMS(m/z): 327.12(M+H);Molecularformulae: $C_{22}H_{18}N_2O$. Elemental analysis: Calculated: C-80.95, H-5.55, N-8.57, Obtained: C-80.87, H-5.54, N-80.80.

5).2-(2, 4, 6-trimethoxyphenyl)-4, 5-diphenylimidazole (4e)

White solid: Mp-248–250°C.Rf:0.40(EtOAc: n-hexane=5:5); Yield-92%; FTIR(KBr, cm−1):3487(NH), 3144, 3098, 1694(C=C), 1280;1HNMR(400MHz, $CDCl_3$): 11.258 (s, 1H, -NH), 7.884 (d, J=6.8 Hz, 2H, Ar-H), 7.554–7.289 (m, 10H, Ar-H), 6.862 (d, J=7.4 Hz, 2H, Ar-H), 3.696(s, 6H, -OCH$_3$), 3.578(s, 3H, -OCH$_3$);13CNMR(100MHz, $CDCl_3$):158.64, 147.36, 128.54, 127.27, 124.63, 121.95, 114.72, 112.82, 98.65, 95.48;LCMS(m/z): 386.36(M+); Molecular formulae: $C_{24}H_{22}N_2O_3$. Elemental analysis: Calculated: C-74.55, H-5.74, N-7.25, Obtained- 74.47, H-5.72, N-7.34.

6). 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N, N-diethyl aniline(4f)

Mp-229-231°C.Rf-0.45(EtOAc: n-hexane=4:6) FTIR (KBr, cm-1):3396(NH), 3068(C-H), 3012, 2958, 1594 (C=N), 1515, 1264, 1021, 763;1HNMR(400MHz, $CDCl_3$):11.542(s, 1H, NH-imidazole), 7.685-7.554(m, 2H, Ar-H), 7.512-7.294(m, 10H, Ar-H), 7.045-6.962(m, 2H, Ar-H);3.332-3.089(q, j=6.8Hz, 2H, Ar-H), 1.073(t, j=7.6Hz, 3H, CH3), 13CNMR(400MHz,

CDCl3) ppm:160.76, 140.08, 135.67, 129.79, 128.84, 128.07, 127.66, 11870, 115.75, 46.38, 13.06;LCMS (m/z):368.09(M+H)+: Molecularformulae:$C_{25}H_{25}N_3$.Elemental analysis: Calculated: C- 81.37, H-6.23, N-12.37:Obtained: C-81.31, H-6.21 , N-12.44.

7) 2-(4-Chlorophenyl)-4, 5-diphenyl-1H-imidazole (4g)

Mp-247-249°C. Rf-0.40(EtOAc: n-hexane=4:6); FTIR (KBr, cm-1): 3148 (NH), 3082(C-H), 2959, 2912, 1601(C=N), 1502, 1128, 1072, 730, 694, 634. 1HNMR (400MHz, CDCl3) ppm: 11.154 (S. 1H, NH-imidazole), 8.211 (d, J=8.4 Hz, 2H, Ar-H), 7.782-7.356 (m, 12H, Ar-H); ^{13}CNMR(100 MHz, $CDCl_3$): 149.42, 138.29, 136.65, 132.74, 130.92, 129.82, 128.77, 128.66, 128.35, 128.29, 128.02, 127.57, 127.07, 126.83, 126.59; LCMS (m/z):332.17(M+2); Molecular formulae: $C_{21}H_{15}ClN_2$. Elemental analysis : Calculated: C-76.25, H-4.57 , N-8.47 , Obtained: C- 76.18, H-4.56, N-8.57.

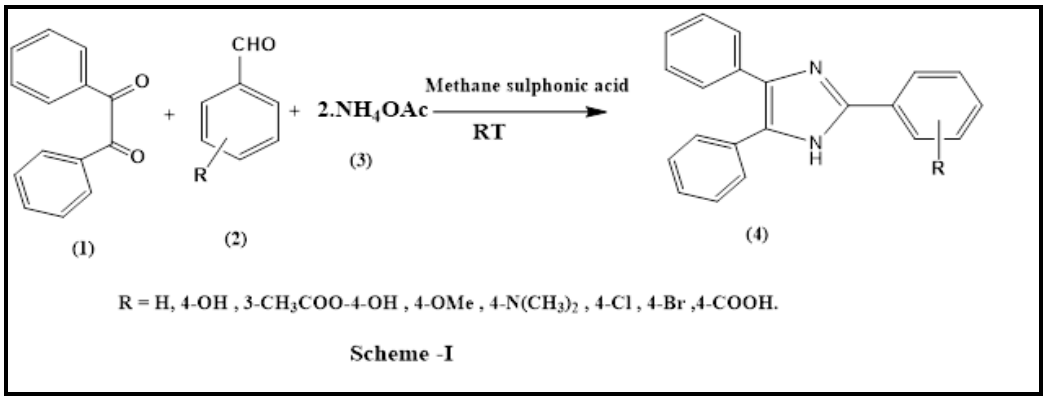
8) 2-(4-Bromophenyl)-4, 5-diphenyl-1H-imidazole (4h)

Mp-262-264°C. Rf-0.43(EtOAc: n-hexane=4:6); FTIR (KBr, cm-1): 3456(NH), 3044(C-H), 2932, 2848, 16028(C=N), 1513, 1124, 1063, 829, 732, 716, 694.1HNMR(400MHz, $CDCl_3$)ppm: 10.835(S, 1H, NH-imidazole), 8.156 (d, J=8.8 Hz, 2H, Ar-H), 7.714 -7.284 (m, 11H, Ar-H), ; 13C NMR (100 MHz, $CDCl_3$):149.45, 138.35, 136.19, 132.68, 130.56, 129.62, 128.95, 128.56, 128.08, 127.88, 127.51, 127.02, 126.80, 126.32:LCMS (m/z):375.32: Molecularformulae: $C_{21}H_{15}BrN_2$. Elemental analysis : Calculated: C-67.21 , H- 4.03 , N-7.47, Obtained: C- 67.14, H-4.01, N- 7.56.

9) 4-(4, 5-diphenyl-1H-imidazol-2-yl)benzoic acid (4i)

Mp-250-252°C. Rf-0.45(EtOAc: n-hexane=5:5); FTIR (KBr, cm-1):3400(NH), 3057(C-H), 2980, 2875, 1696(C=O), 1613(C=N), 1585, 1180, 1072, 721, 697.^{1}HNMR(400MHz, $CDCl_3$): 11.474(s, 1H, NH-imidazloe), 8.254-8.120(m, 2H, Ar-H), 8.091-7.794(m, 2H, Ar-H), 7.708-7.397(m, 10H, Ar-H);^{13}CNMR(100MHz, CDCl3):168.59, 158.74, 153.58, 144.65, 136.44, 133.07, 132.51, 131.03, 130.55, 129.77, 129.23, 129.09, 128.72, 128.77, 128.18, 127.80, 127.45, 127.03, 126.65, 126.48, 126.14, 124.68;LCMS(m/z):340.31(M+);Molecularformulae: $C_{22}H_{16}N_2O_2$;Elemental analysis: calculated: C-77.63 , H- 4.74 , N-8.23, Obtained : C- 77.55, H- 4.73, N- 8.31.

4. RESULTS AND DISCUSSION



Scheme -I

In continuation of our research work on the use of simple inorganic non-toxic catalysts, we report herein the efficacy of methane sulphonic acid as catalyst as well as solvent. In this study the multicomponent reaction strategy for the preparation of 2, 4, 5-triaryl-1H-imidazole by using benzil, various substituted aldehydes and ammonium acetate in presence of methane sulphonic acid as catalyst, in ethanol at reflux condition is introduced.

In a model reaction, the presence of the catalyst (5 mol %), the mixture of substituted aromatic aldehyde (1 mmol), benzil (1 mmol) and NH4OAc (2 mmol) as ammonia source, stirred at RT under solvent free conditions. The 2, 4, 5-triphenyl imidazole are obtained in 92% yield. Various kinds of functionalised substituted benzaldehyde were also subjected in the presence of methane sulphonic acid at RT under solvent free conditions (Table 1).

We observed that for aldehydes having either electron withdrawing or electron-releasing substituents in the meta or para positions; the reaction proceeded very efficiently in all cases. This procedure provides trisubstituted imidazoles directly, in relatively short reaction times, high yields. Furthermore, we used benzoin instead of benzil and in this case corresponding products were achieved in good yields. In all cases, complete conversion was observed after appropriate time and the products were readily isolated in very high yields.

In summary, a one-pot, multicomponent procedures have been developed for the synthesis of trisubstituted imidazoles derivatives catalyzed by methane sulphonic acid in high yields. Moreover, easy work-up, clean reaction profiles, low cost, availability, low toxicity, stable under normal temperatures and pressures of the catalyst, and short reaction time make this methodology a valid contribution to the existing processes in the field of 2-aryl-4,5-diphenyl imidazole derivatives synthesis.

Table I: Physical data of titled compounds.

Entry	Aldehyde	Yield (%)	M.Wt	MP (^{0}C)	M.Formula
4a	C6H5	84	297.26	212-214	$C_{21}H_{16}N_2$
4b	4-OHC6H4	90	512.03	230-232	$C_{21}H_{16}N_2O$
4c	3-CH3COO-4-OH-C6H3	89	370.44	236-238	$C_{21}H_{16}N_2O$
4d	4-OCH3-C6H5-		327.12	223-225	$C_{21}H_{16}N_2O$
4e	2,4,6-(OCH3)3-C6H2	91	386.36	248-250	$C_{21}H_{16}N_3$
4f	4-(N,N-(CH3)2)C6H4	88	368.17	229-231	$C_{21}H_{16}ClN_2$
4g	4-ClC6H4	89	332.17	247-249	$C_{21}H_{16}ClN_2$
4h	4-Br-C6H4-	89	375.32	262-264	$C_{21}H_{16}BrN_2$
4i	4-COOH-C6H5-	86	340.31	250-252	$C_{21}H_{16}N_2O_2$

Table-II: The various catalysts applied during the synthesis.

S.NO	catalyst	Solvent	Time (hrs.)	Yield (%)
1	Silicasulphuricacid.	Ethanol	8	49
2	Methane sulphonic acid	Ethanol	2	92
3	P-Toluene sulphonic acid	Ethanol	4	61
4	P-Toluenesuphuryl chloride	Ethanol	6	69
5	Camphor sulphonic acid.	Ethanol	6	56
6	Sulphanilic acid	Ethanol	7	67

Hence, the various organic based Bronsted acid catalysts applied above synthesis. But all the catalyst used to perform as the catalysts during this condition. Methane sulphonic acid performed as a catalyst and solvent. The advantages of this catalyst such as obtained excellent yield, easy to workup, as well as fast rate of reaction with low time bound. It is available commercially, cost effectiveness compared to other catalyst showed table above.

Vibrational Spectroscopy

The evidence of FT-IR spectroscopy data reveals that the presence of various functional group were observed. A strong absorption band around 1285 cm1 and 3608 cm-1 for all the synthesized compounds in FT-IR confirms the presence of C=N and N-H stretching, in addition weak bending at 1400-1684cm-1 indicates the presence of aromatic C=C. In Particular, a broad peak around 3608cm-1is obtained shows the existence O-H stretching in compounds.

NMR Spectroscopy

The 1H NMR spectral analysis of the as synthesized compounds showed a characteristic peak at δ 11.474-10.474 ppm clearly indicates the presence of N-H proton, the presence of aromatic protons in all the compounds is clearly identified by the chemical shift value at 8.254-6.962, in addition the presence of hydroxyl proton in the compounds 4b, 4c showed

9.124 and 9.167.verified by the obtained chemical shift value at 3.596ppm respectively. The methoxy proton in the 4d, 4e derivatives are confirmed by the δ value at 3.596 ppm and 3.696, 3.578. The ^{13}C NMR spectroscopies were examined in order to predict the structure of the as synthesized imidazoles. It was in good agreement with the literature. The δ value at 141 ppm, 149 ppm, 152 ppm and 163 ppm are obtained. The molecular weight of the titled compounds was obtained (M+2), (M+H) and M^+ respectively.

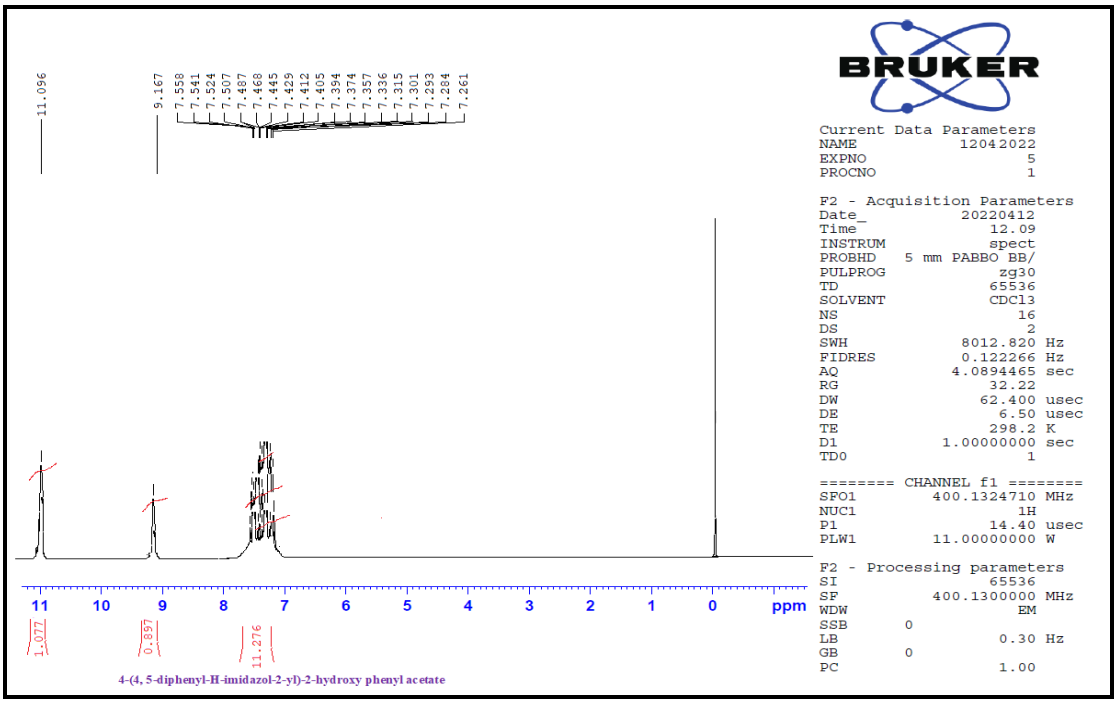
Antimicrobial Activity

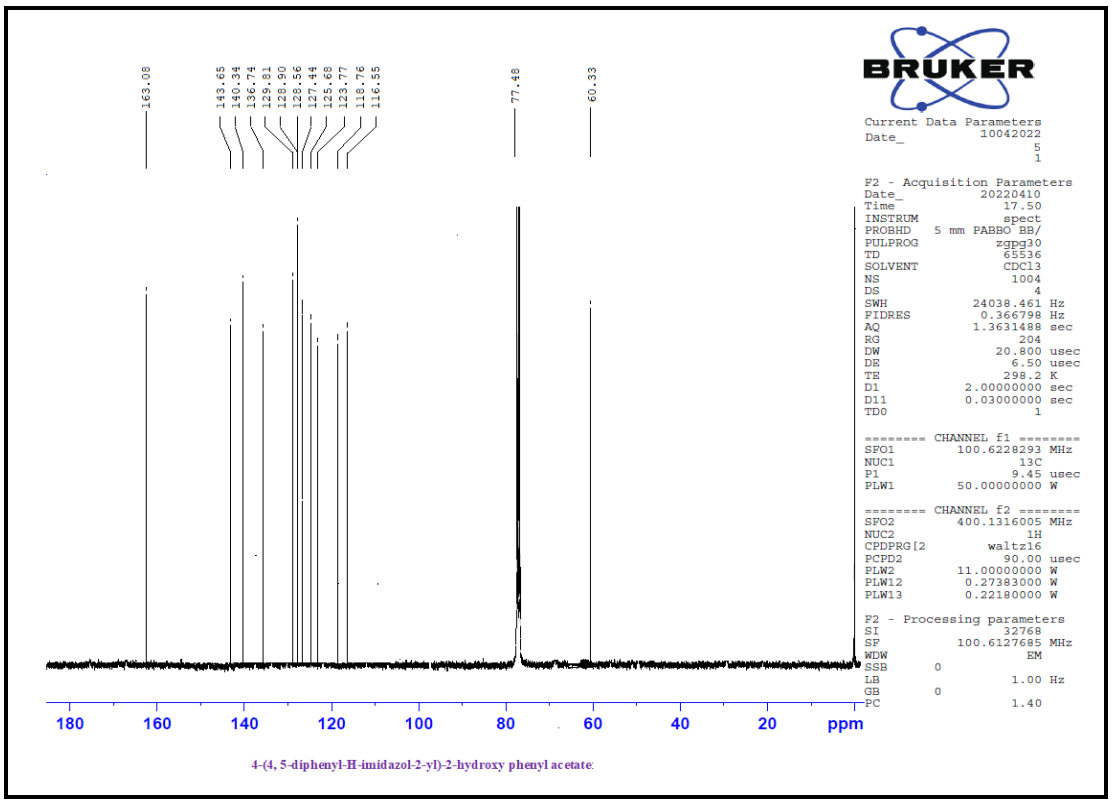
Antibacterial activity (Protocol): Preliminary investigation of anti-microbial activity of newly synthesized compounds (4a-4if) was evaluated by cup plate method. We used different pathogenic strains viz. Staphylococcus aureus, B-substills (gram positive), P.aeruginose, S.typhi, and E.coli (gram negative) using standard drug Streptomycin for antibacterial growth.

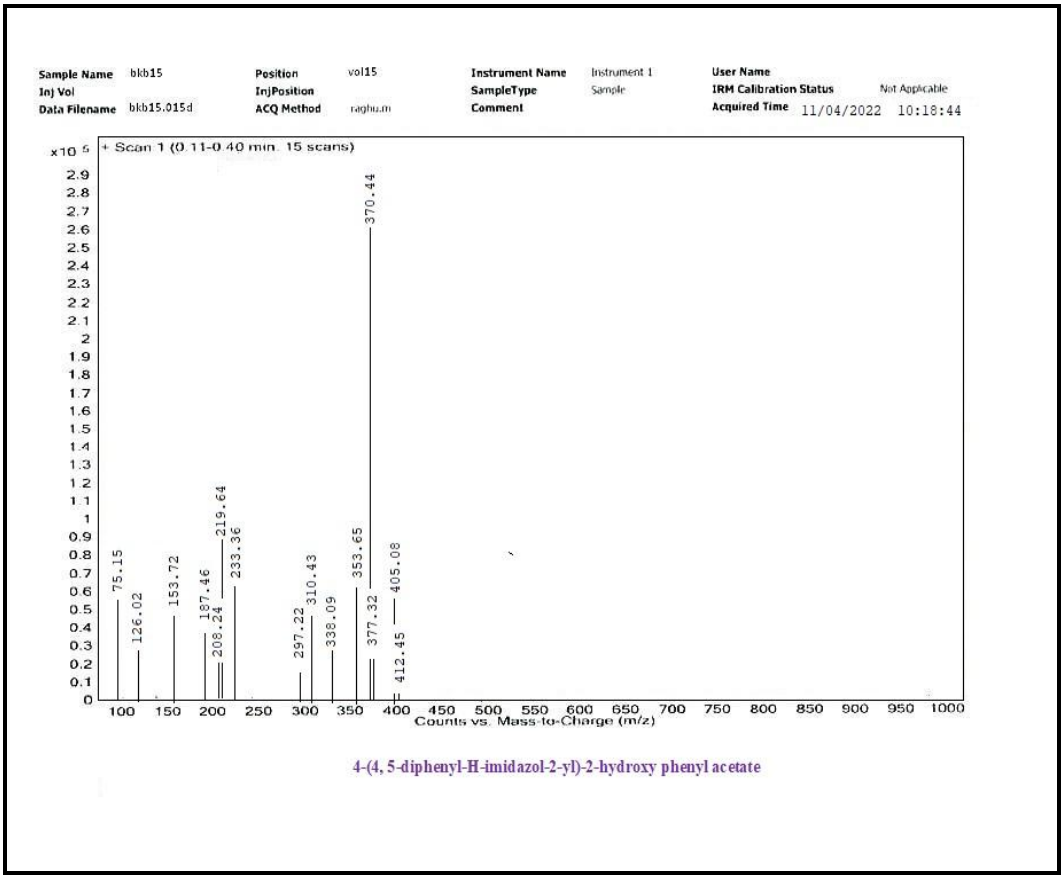
Nutrient agar medium (NAM) is used to test for the anti-bacterial activity of titled compounds; NAM was prepared with beef extract (4g), peptone (7g), NaCl (5g) agar (20g) en 1000 ml distilled water and PH was maintained to 7.1. NMA was sterilized in an auto clave at 121℃ 15 lbs pressure for 45 min. After sterilization, 20 ml of NAM was poured into petro dishas in a laminar air flow and allowed to solidity. After solidification, NMA was in oculated with 100 µl of derived bacteria. The tested derivatives were dissolved in DMSO with a concentration of 100 ppm, 250 ppm and whatsman No.1 filter paper disks were placed in the solution and kept for one minute. After drying the disks were placed as NAM inoculated with bacteria and NAM plates were incubated at 37 ℃. Zones of inhibition were measured after 24 hrs. compared with Streptomycin.

S.NO	Compound	Gram Negative						Gram Positive			
		P.aeruginose		S.typhi		E.coli		S.aureus		B.substill	
		250	500	250	500	250	500	250	500	250	500
1	4a	05	10	06	12	05	10	03	06	05	09
2	4b	10	14	10	16	09	14	11	16	08	14
3	4c	06	12	09	15	11	17	11	15	08	15
4	4d	11	16	10	16	11	18	09	16	09	12
5	4e	08	14	9	15	8	14	07	13	08	15
6	4f	07	12	08	14	07	14	08	10	08	11
7	**4g**	**10**	**17**	**11**	**17**	**09**	**16**	**11**	**18**	**10**	**18**
8	**4h**	**11**	**18**	**10**	**18**	**08**	**17**	**10**	**17**	**08**	**18**
9	4i	03	05	06	07	05	08	04	06	05	07

The compound ‘4a &4i’ exhibited poor active potential due to aryl substituent containing electron with dragging groups whereas compounds such as ‘4f’ showed moderate active potential containing electron donating groups .Other hand ,the compounds 4b , 4d , 4e having good active potential due to highly electron donating groups. From the above table, we observed that the compound “4g and 4h “exhibited good active potential.







5. CONCLUSION

Multicomponent reactions enjoy an outstanding status in organic and medicinal chemistry for their high degree of atom economy and application in the diversity-oriented convergent synthesis of complex organic molecules from simple and readily available substrates in a single vessel. A simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazole is achieved by three component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes and ammonium acetate as ammonia source in thermal solvent free condition using Bronsted acidic methane sulphuric acid as catalyst. The key advantages of this process are cost effectiveness of catalyst, reusability of catalyst, easy work-up and purification of products by no chromatographic methods, excellent yields and very short time reaction. In additionally, the compounds showed satisfactorily antibacterial activity.

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