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An efficient synthesis of substituted Imidazole via Multi Component Synthesis and their Antimicrobial evolution

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Abstract: One pot three component synthesis of 2-(substitutedphenyl)-4,5-diphenyl-1*H*-imidazole (**1a-d)** in moderate to high yield is achieved via a one pot synthesis reaction of benzyl, substituted aromatic aldehyde & ammonium acetate in glacial acetic acid. Which is further treated with different halogen derivatives to give final 1-substituted-2-(substitutedphenyl)-4,5-diphenyl-1*H*-imidazole [**2-5(a-d)]** via condensation process. All the synthesized compounds were supported by spectral and analytical analysis. Also the synthesized compounds were tested for their antimicrobial activity.

Keywords: Benzil, Ammonium Acetate, triphenyl imidazole, p-toluene sulfonyl chloride, n-butyl bromide.

INTRODUCTION

Imidazole derivatives possess diverse pharmacological activities, including antimicrobial[1-2], antiviral[3], antineoplastic[4], analgesic[5], anti-inflammatory[6-7], antihypertensive[8], and vasodilating activities[9]. Benzimidazolone derivatives are also medicinally important. They exhibit a wide variety of interesting biochemical and pharmacological properties[10-11]. They antagonize neurotransmitters[12-13], inhibit aldose reductase [14], show antiulcer and antisecretory properties[15-16], enhance pulmonary surfactant secretion and modulate ion channels[17-18]. Imidazole-based heterocyclic molecules play important roles in various

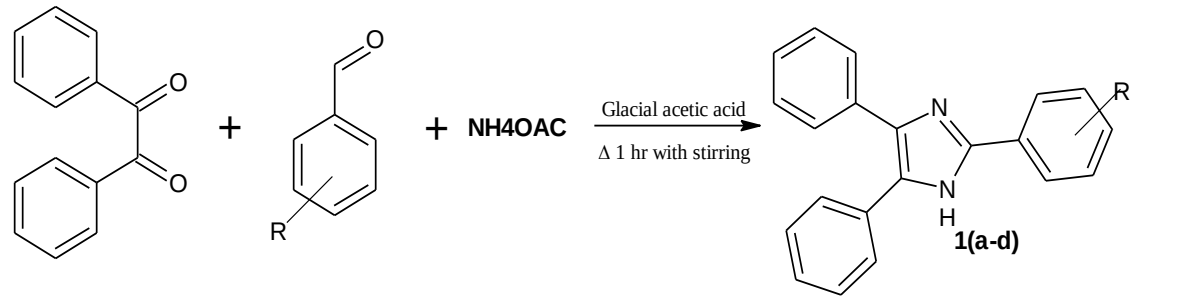
biochemical processes[19-20]. Therefore, the imidazolyl moiety is being used as a building block in developing new drugs[21-22]. Moreover, imidazole derivatives have wide range applications in coordination chemistry[23], organometallic catalysis[24], and asymmetric catalysis[25]. There are several reports for the synthesis and functionalization of the imidazole moiety[26-27-28].

RESULT & DISCUSSION

In the present work, an attempt has been made to undertake the synthesis of N-substituted (2-(substitutedphenyl)-4, 5-diphenyl imidazole [2-5(a-d)] through a multi-step process. For this purpose, the required 2-(substitutedphenyl)-4, 5-diphenyl-1*H*-imidazole were prepared by cyclization of benzil with substituted benzaldehyde in the contribution of ammonium acetate, formation of the product is confirmed by the presence of a singlet δ: 8.12 (s, 1H, NH) in NMR and 3412 cm-1 (N-H str.) in IR. Further compound (1a-d) was converted to N-substituted 2-(substitutedphenyl)-4, 5-diphenyl imidazole by the condensation process of compound (1a-d) with some halogen containing derivatives.

In that process Hydrogen of NH from the imidazole ring was replaced by halogen derivative. NH group of compound (1a-b) was replaced by phthallimidoxyethyl bromide in the presence of Na metal as a base to furnish 2-{2-[2-(substitutedphenyl)-4, 5-diphenyl-imidazol-1-yl]-ethoxy}-isoindole-1, 3-dione (2a-b). In another route NH group of compound (1a-b) were replaced by p-toluene sulfonyl chloride in the presence of K_2CO_3 as a base to furnish 2-(substitutedphenyl)-4,5-diphenyl-1-(toluene-4-sulfonyl)-1H-imidazole (3b-c). as above compound (4a-b) was prepared by a process in which NH group of compound (1a-b) were replaced by 1,2-dibromoethane in the presence of Na metal as a base. Another compound (5d) was prepared by a process in which NH group of compound (1a-b) were replaced by 1, 2-dibromoethane in the presence of Et_3N as a base. All the derivatives were confirmed by disappearance of a band of stretching of NH group in IR & singlet of NH in NMR.

All the synthesized compounds are tested for antibacterial and anti-fungal activity. In these compounds 2a and 3c shows good activity against bacterial and 2a, 3b and 3c gave good activity against fungal and rest of compounds show moderate activity.



R= a) 4-Cl b) 2-Cl c) 4-F d) 3-NO_2

Scheme 1

METHOD & MATERIALS

All the chemicals and solvents (analytical grade) were purchased from commercial sources and used without further purification. All melting points were determined in open capillary tube and are uncorrected. TLC aluminum sheets were used for thin-layer chromatography (TLC) and spots were visualized under UV light. Melting points were taken in open capillary tubes and therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spots was carried out in an UV/Iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm^{-1} ranges using KBr discs on FTIR Perkin Elmer spectrometers and 1H NMR were recorded on a Bruker DRX-300 MHz spectrometer (DMSO) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Structure of all the synthesized compounds was assigned on basis of their analytical Data and spectral data.

EXPERIMENTAL SECTION

Synthesis of 2-(4-chlorophenyl)-4, 5-diphenyl-1*H*-imidazole (1a): Benzyl (25 mmol), 4-chlorobenzaldehyde (25 mmol) and Ammonium acetate (130 mmol) was dissolved in glacial acetic acid (100 ml) in 250 ml round bottom flask containing a magnetic stirring bar. The mixture was heated to reflux in oil bath with stirring for 1 hr. After the completion of reaction according TLC the reaction mixture is allowed to cool to room temperature and it was filtered to remove any precipitate which may be present. After cooling 500 ml of water was added to the filtrate to collect the precipitated solid which was filtered at Buchner funnel with suction. The filtrate was neutralized with ammonium hydroxide to collect the second crop of solid. The two crops of solid was combined and recrystallized with aqueous ethanol.

Yield: 76%; M.P.:- 264-266^{o}C; IR (KBr) cm^{-1}: 3397 (N-H str.), 3066 (C-H str., Ar-H), 1650 (C=N str.). ^{1}H NMR ($CDCl_3$/DMSO) δ: 8.12 (s, 1H, NH), 7.18-7.68 (m, 14H, Ar-H), 13C-NMR (CDCl3/DMSO): 123 126.3, 127.4, 128, 128.5, 129, 133.9, 134.8, 136.4, 136.7. MS: (*m/z*) M+ 330, 295, 219, 175, Anal. calcd for C21H15N2Cl: C 76.24; H 4.57; Cl 10.72 N 8.47%. Found: C 76.09; H 4.34; Cl 10.51, N 8.34%

Similarly Compound (1b-1d) were synthesized with minor change in reflux time.

Synthesis of 2-(2-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (1b):

Yield: 79%; M.P.:- 274-276^{o}C; IR (KBr) cm^{-1}: 3412 (N-H str.), 3089 (C-H str., Ar-H), 1668 (C=N str.). ^{1}H NMR (DMSO) δ: 8.13 (s, 1H, NH), 7.24-7.57 (m, 14H, Ar-H), ^{13}C-NMR ($CDCl_3$/DMSO): 123 126.3, 127.4, 128, 128.5, 129, 133.9, 134.8, 136.4, 136.7. MS: (*m/z*) M+ 330, 295, 219, 175,111. Anal. calcd for $C_{21}H_{15}N_2Cl$: C 76.24; H 4.57; Cl 10.72 N 8.47%. Found: C 76.15; H 4.38; Cl 10.57, N 8.31%

Synthesis of 2-(4-fluorophenyl)-4,5-diphenyl-1*H*-imidazole (1c):

Yield: 66%; M.P.:- 256-259^{o}C; IR (KBr) cm^{-1}: 3397 (N-H str.), 3417 (N-H str.), 3026 (C-H str., Ar-H), 1647 (C=N str.). ^{1}H NMR ($CDCl_3$/DMSO) δ: 8.18 (s, 1H, NH), 7.29-7.63 (m, 14H, Ar-H), ^{13}C-NMR ($CDCl_3$/DMSO): 122 126.1, 127.5, 128.2, 128.5, 129.4, 133.2, 134.3, 136, 136.2. MS: (*m/z*) M+ 312, 295, 219, 175, 111. Anal. calcd for $C_{21}H_{15}N_2F$: C 80.24, H 4.81, F 6.04, N 8.91%. Found: C 80.15, H 4.76, F 6.01, N 8.85%.

Synthesis of 2-(3-nitrophenyl)-4, 5-diphenyl-1*H*-imidazole (1d):

Yield: 86%; M.P.:- 294-296°C; IR (KBr) cm^{-1}: 3375 (N-H str.), 3072 (C-H str., Ar-H), 1658 (C=N str.). ^{1}H NMR ($CDCl_3$/DMSO) δ: 8.11 (s, 1H, NH), 7.26-7.81 (m, 14H, Ar-H), 13C-NMR ($CDCl_3$/DMSO): 123 126.3, 127.4, 128, 128.5, 129, 133.9, 134.8, 136.4, 136.7. MS: (*m/z*) M+ 331, 295, 219, 175, Anal. calcd for $C_{21}H_{15}N_3O$: C 73.89 H 4.43 N 12.31 O 9.37%. Found: C 73.81, H 4.39, N 12.26, O 9.32%.

Synthesis of 2-{2-[2-(4-Chloro-phenyl)-4, 5-diphenyl-imidazol-1-yl]-ethoxy}-isoindole-1, 3-dione (2a): Bromoethoxy phthallimde (0.01 mole) and compound **(1a-b**) (0.01 mole) was dissolved in DMF (20 ml) and Na metal (0.01 mole) is added. Then the reaction mixture is stirred on a magnetic stirrer for 3 hrs at room temperature. After that the reaction mixture was refluxed for 4 hrs. After completion of reaction (TLC) the reaction mixture is cooled and poured in crushed ice and precipitate of compound (2a-b) was formed which was filtered, washed with cold water, dried and recrystallized from ethanol.

Yield: 65%; M.P.:-224-226°C; IR (KBr) cm^{-1}: 3026 (C-H str., Ar-H), 1661 (C=N str.), 1724, 1694 (CO-N-CO). ^{1}H NMR ($CDCl_3$/DMSO) δ: 7.26-7.81 (m, 18H, Ar-H), 4.45 (J= 6.2 Hz, t, OCH_2), 3.33 (J=6.2 Hz, t, NCH_2) ^{13}C-NMR ($CDCl_3$/DMSO): 34.6, 69.3, 122, 123 126.3, 127.4, 128, 128.5, 129, 131.6, 132.7, 133.9, 134.8, 136.4, 136.7, 139.8, 161.6. MS: (*m/z*) M+ 520, 436, 375, 359, 331, 295, 219, 175, 115. Anal. calcd for $C_{31}H_{22}ClN_3O_3$: C 71.61, H 4.26, Cl 6.82, N 8.08, O 9.23% Found: C 71.49, H 4.19, Cl 6.79, N 8.03, O 9.11%

Similarly Compound **(2b)** were synthesized with minor change in reflux time.

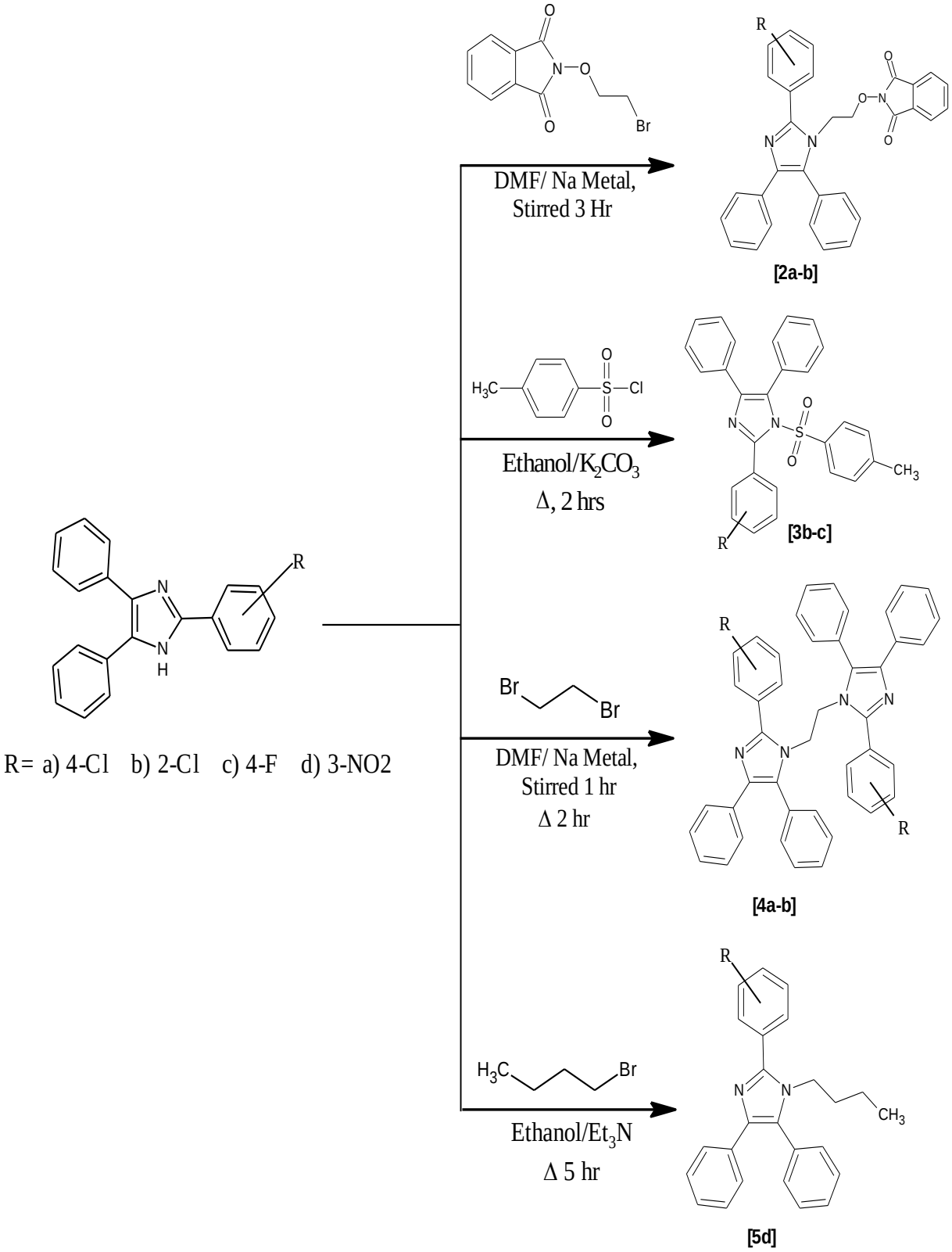
Synthesis of 2-{2-[2-(2-Chloro-phenyl)-4,5-diphenyl-imidazol-1-yl]-ethoxy}-isoindole-1,3-dione (2b):

Yield: 78%; M.P.: 253-257°C; IR (KBr) cm^{-1}: 3058 (C-H str., Ar-H), 1667 (C=N str.), 1734, 1691 (CO-N-CO). ^{1}H NMR ($CDCl_3$) δ: 7.16-7.91 (m, 18H, Ar-H), 4.35 (J= 6.5 Hz, t, OCH2), 3.29 (J=6.5 Hz, t, NCH2) 13C-NMR (CDCl3/DMSO): 34.6, 69.3, 122, 123 126.3, 127.6, 128.2, 128.4, 129.8, 131.6, 132.7, 133.1, 134.5, 136.2, 136.8, 139.3, 159.6. MS: (*m/z*) M+ 520, 436, 375, 359, 331, 295, 249, 219, 175, 115. Anal. calcd for $C_{31}H_{22}ClN_3O_3$: C 71.61, H 4.26, Cl 6.82, N 8.08, O 9.23% Found: C 71.51, H 4.21, Cl 6.76, N 8.01, O 9.06%

Synthesis of 2-(2-Chloro-phenyl)-4,5-diphenyl-1-(toluene-4-sulfonyl)-1H-imidazole (3b): P-Toluene sulphonyl chloride (0.01 mole) and compound **(1b-c**) (0.01 mole) was dissolved in Ethanol (20 ml) and K_2CO_3 (0.01 mole) is added. Then the reaction mixture was refluxed for 2 hrs. After completion of reaction (TLC) the reaction mixture is cooled and poured in crushed ice and precipitate of compound **(3b-c)** was formed which was filtered, washed with cold water, dried and recrystallized from ethanol.

Yield: 64%; M.P.:-210-212°C; IR (KBr) cm^{-1}: 3031 (C-H str., Ar-H), 2971 (C-H str. CH_3) 1646 (C=N str.), ^{1}H NMR ($CDCl_3$) δ: 7.21-8.09 (m, 18H, Ar-H), 2.36 (s, 3H str. CH_3) ^{13}C-NMR ($CDCl_3$/DMSO): 21.2, 123 126.3, 127.4, 128.5, 129.8, 131.6, 133.9, 134.8, 135.4, 136.7, 137.8, MS: (*m/z*) M+ 484, 469, 393, 329, 295, 219, 175 , 115. Anal. calcd for $C_{28}H_{21}ClSN_2O_2$: C 69.34, H 4.36, Cl 7.31, N 5.78, O 6.60, S 6.61% Found: C 69.31, H 4.32, Cl 7.28, N 5.72, O 6.58, S 6.59%

Similarly Compound **(3c)** were synthesized with minor change in reflux time.


DMF/ Na Metal,
Stirred 3 Hr
[2a-b]
Ethanol/K2CO3
Δ, 2 hrs
[3b-c]
DMF/ Na Metal,
Stirred 1 hr
Δ 2 hr
[4a-b]
Ethanol/Et3N
Δ 5 hr
[5d]
R= a) 4-Cl b) 2-Cl c) 4-F d) 3-NO2

Scheme 2

Synthesis of 2-(4-Fluoro-phenyl)-4,5-diphenyl-1-(toluene-4-sulfonyl)-1H-imidazole (3c): Yield: 69%; M.P.:-196-198^{o}C; IR (KBr) cm^{-1}: 3091 (C-H str., Ar-H), 2978 (C-H str. CH_3) 1635 (C=N str.). ^{1}H NMR (CDCl3) δ: 7.26-8.11 (m, 18H, Ar-H), 2.43 (s, 3H str. CH_3) ^{13}C-NMR ($CDCl_3$/DMSO): 21.6, 123.3 126.6, 127.2, 128.4, 129.8, 131.6, 133.9, 134.8, 135.4, 136.7, 137.8, MS: (*m/z*) M+ 468, 393,377, 329, 295, 219, 175, 115. Anal. calcd for $C_{28}H_{21}FSN_2O_2$: C 71.78, H 4.52, F 4.05, N 5.98, O 6.83, S 6.84% Found: C 71.76, H 4.49, F 4.02, N 5.94, O 6.80, S 6.81%

Synthesis of 1,2 ethyl-bis-2-(4-Chloro-phenyl)-4,5-diphenyl--1H-imidazole (4a):1,2-dibromoethane (0.01 mole) and compound **(1a-b**) (0.01 mole) was dissolved in DMF (20 ml) and Na metal (0.01 mole) is added. Then the reaction mixture is stirred on a magnetic stirrer for 2 hrs at room temperature. After that the reaction mixture was refluxed for 5 hrs. After completion of reaction (TLC) the reaction mixture is cooled and poured in crushed ice and precipitate of compound (4a-b) was formed which was filtered, washed with cold water, dried and recrystallized from ethanol.

Yield: 61%; M.P.:- 234-238^{o}C; IR (KBr) cm^{-1}: 3033 (C-H str., Ar-H), 2971 (C-H str. CH_2), 1645 (C=N str.). ^{1}H NMR ($CDCl_3$) 7.18-7.68 (m, 28H, Ar-H), 3.39 (J=6.2 Hz, t, NCH_2), 4.11 (J=6.2 Hz, t, NCH_2). ^{13}C-NMR ($CDCl_3$): 22.7, 123 126.3, 127.4, 128, 128.5, 129, 133.9, 134.8, 136.4, 136.7. MS: (*m/z*) M+ 686, 331, 295, 219, 175, 115. Anal. calcd for $C_{44}H_{32}N_4Cl_2$: C 76.24; H 4.57; Cl 10.72 N 8.47%. Found: C 76.09; H 4.34; Cl 10.51 N 8.34%

Similarly Compound **(3c)** were synthesized with minor change in reflux time.

Synthesis of 1,2 ethyl-bis-2-(2-Chloro-phenyl)-4,5-diphenyl--1H-imidazole (4b):

Yield: 61%; M.P.:- 234-238^{o}C; IR (KBr) cm^{-1}: 3028 (C-H str., Ar-H), 2958 (C-H str. CH_2), 1634 (C=N str.). ^{1}H NMR ($CDCl_3$) 7.19-8.09 (m, 28H, Ar-H), 3.36 (J=4.7 Hz, t, NCH_2), 4.13 (J=4.72 Hz, t, NCH_2). ^{13}C-NMR ($CDCl_3$): 22.7, 123 126.3, 127.4, 128, 128.5, 129, 133.9, 134.8, 136.4, 136.7. MS: (*m/z*) M+ 686, 331, 295, 219, 175, 115. Anal. calcd for $C_{44}H_{32}N_4Cl_2$: C 72.44; H 4.77; Cl 10.82 N 8.27%. Found: C 72.42; H 4.74; Cl 10.78 N 8.32%

Synthesis of 1-Butyl-2-(3-nitro-phenyl)-4, 5-diphenyl-1H-imidazole (5d): n-butyl bromide (0.01 mole) and compound **(1d**) (0.01 mole) was dissolved in Ethanol (20 ml) and Et_3N (0.01 mole) is added. Then the reaction mixture was refluxed for 3 hrs. After completion of reaction (TLC) the reaction mixture is cooled and distill the excess of ethanol and then the remaining residue is poured in crushed ice and precipitate of compound **(5d)** was formed which was filtered, washed with cold water, dried and recrystallized from ethanol to give yellow-white needle shaped crystals.

Yield: 70%; M.P.:- 184-186^{o}C; IR (KBr) cm-1:3071 (C-H str., Ar-H), 2870 (C-H str. CH_3) 1650 (C=N str.). ^{1}H NMR ($CDCl_3$/DMSO) δ: 7.11-8.11 (m, 14H, Ar-H), 4.43 (t, 2H, NCH_2), 2.73 (m, 2H, CH_2), 2.37 (t, 2H, CH_2), 2.15(s, 3H, CH_3) ^{13}C-NMR ($CDCl_3$/DMSO): 123 126.3, 127.4, 128, 128.5, 129, 133.9, 134.8, 136.4, 136.7. MS: (*m/z*) M+ 397, 331, 295, 219, 175, 111. Anal. calcd for $C_{25}H_{23}N2O_2$:. C 75.54, H 5.83, N 10.57, O 8.05%. Found: C 75.51, H 5.79, N 10.53, O 8.01%

ANTIMICROBIAL ACTIVITY

Eleven synthesized compounds were *in vitro* screened for their antibacterial and antifungal activity using 500 ppm concentrations in DMF by cup and well method. The micro-organisms *Proteus mirabilis, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli* were used as antibacterial, *Candida albicans* and *Aspergillus fumigatus* were used as fungal strains. The activity is presented as zone of inhibition in

mm and compared with activity of controls C1 and C2 (for antibacterial activity CI= ciprofloxacin for antifungal activity C2=flucanazole) to give activity index value **(**Table **1).** All the compounds showed poor activity against *K pneumonia* and *E. colt* whereas moderate to strong activity was shown against *P. mirabilis* and *B. subtilis.* Activity index value against *P. mirabilis* and *B. subtilis* was more than one for majority of compounds. It was interesting to note that all the compounds showed stronger activity than the standard used against *Candida albicans* and *Aspergillus fumigatus.* It was concluded from the activity study that compound 3c was found to be the strongest amongst all synthesized compounds. Compounds under study showed more comprehensive fungus-inhibiting properties than that of the bacterial. Even two folds antifungal activity was observed for these compared to standard.

Table 1: Antimicrobial activity of the synthesized compounds (**2a-b), (3b-c)** and **5d**

	Antibacterial activity				Antifungal activity	
S.No.	**Protius Mirabilis**	**Bacillus Subtilis**	**Klebsilla Pneumonia**	**Escherichia Coli**	**Candida Albicans**	**Aspergillus Fumigatus**
2a	24(.1.34)	22 (1.29)	20 (.97)	22(1.03)	22 (1.08)	21 (1.02)
2b	14 (.72)	16 (.97)	18 (1.05)	23 (1.25)	18 (.90)	20 (1.0)
3b	16 (.88)	17 (1.00)	16 (.83)	23 (1.29)	23 (1.19)	24 (1.27)
3c	21 (1.17)	23 (1.29)	21 (1.08)	24 (1.25)	23 (1.05)	24 (1.13)
4a	17 (.98)	18 (1.11)	19 (.97)	17 (.94)	18 (.90)	20 (.01)
4b	18 (1.09)	17 (.86)	16 (.77)	19 (1.17)	20 (1.14)	19 (.97)
5d	19 (1.17)	16 (.67)	17 (.86)	18 (.90)	20 (1.0)	19(.95)
C1	18	17	18	18	-	-
C2	-	-	-	-	20	20

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug
For antibacterial activity: C1 = Ciprofloxacin
For antifungal activity: C2 = flucanazole

CONCLUSION

In the synthesized compounds **2a** and 3**c** give good activity and others show moderate activity against all four bacterial and 2**a**, **3b** and 3**c** give good activity against two fungal.

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