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MICROWAVE ASSISTED SYNTHESIS OF HALO-ARYL-SUBSTITUTED-1H-PYRAZOL-PYRIDNE MOIETY AND STUDY ON "EFFECT OF HALOGEN SUBSTITUTION ON ANTIMICROBIAL ACTIVITY"

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ABSTRACT:
16 Derivatives of halo-aryl-substituted-1H-pyrazol-pyridine moiety **3a-p** were synthesized by microwave irradiated one pot cyclocondensation of 3-substituted-1H-pyrazole-4-carbaldehyde **1a-d** and 4-substituted-acetophenone **2a-d** in presence of ceric ammonium nitrate (CAN). Various halogen substitutions were made for the study of effect on antimicrobial activity by halogen substitution on aryl-1H-pyrazol-pyridine moiety. The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and FT-IR spectral data, the molecular weight of compounds are confirmed by mass spectrometry. All compounds are screened for their antimicrobial activity against S.aureus; B.subtilis; C.tetani; E.coli; S.typhi; P.aeruginosa; C.albicans; T.rubrum.

KEY WORDS: Aryl-1*H*-pyrazol-pyridine, microwave irradiation, antimicrobial activity, halogen substitution.

INTRODUCTION

2,4,6-Trisubstituted pyridine is a general class of polysubstituted pyridines. Polysubstituted pyridines have been synthesized using an enormous number of preparative approaches such as Hantzsch synthesis from a 1,5-diketone and a nitrogen derivatives[I-II], cyclization of chalcones and iminophosphoranes[III], reactions of unsaturated imines with enolates[IV] and cyclization of α,β-unsaturated compounds with α-substituted ketones and a nitrogen source.[V] Among these approaches, the later approach is the most frequently employed. The two-step kröhnke synthesis[V-VIII] via condensation of α,β-unsaturated ketones with pyridinium salts in the presence of a mixture of ammonium acetate and acetic acid gives a variety of polysubstituted pyridines and has distinct advantages over the other routes. Therefore, it is worthwhile investigating new types of reactions and synthetic applications of multicomponent reactions (MCRs), which offer significant advantages and are increasingly important in organic and medicinal chemistry. Herein we wish to describe a simple and effective synthesis of pyridines in one-pot reactions of aromatic aldehydes and acetophenones

in the mixture of ammonium acetate and CAN under microwave irradiation to give polysubstituted pyridine derivatives.

Since the middle of the last century, pyridine has assumed an important role in our understanding of the chemistry of biological systems. It plays a key role catalyzing both biological and chemical systems. The incorporation of pyridine nucleus, a biologically established pharmacophore in medicinal compounds, has made it a versatile heterocyclic moiety possessing extensive variety of biological activities. Polysubstituted pyridines have been reported to possess biological activities such as antihypertensive, antianginal and antimicrobial activities[IX].

In recent times, ceric ammonium nitrate ($Ce(NH_4)_2(NO_3)_6$, CAN) has gained interest in organic synthesis due to its advantages such as admirable solubility in water, cost effectiveness, low toxicity, easy managing, high reactivity, and easy work-up procedures. Cerium ($^{140}Ce_{58}$) has an electron configuration of $[Xe]4f^1 5d^1 6s^2$. The electronic configuration of the Ce^{+3} ion is $[Xe]4f^1$, while that of Ce^{+4} ion is $[Xe]4f^0$. Due to the weak shielding of the 4f electron (lanthanide contraction), cerium (IV) compounds exhibit the distinctive nature of oxidation and Lewis acidity. Also, Ce salts are the ones that have the lowest affinity for oxygen, making them potential complementary to other extensively studied Lewis acids. In this connection, it is worth mentioning that CAN is a useful alternative to the other expensive catalysts. Recently, CAN has attracted much consideration because it can be used in the reactions like carbon-carbon, carbon-heteroatom bond formation and single-electron oxidation as well as in many chemical transformations[X].

RESULTS AND DISCUSSION

Most medicinal compounds are small synthetic organic molecules, many of which contain primary heterocyclic rings like pyridine. However, the range of easily accessible and suitably functionalized heterocyclic building blocks is still surprisingly limited and the construction of even a small array of relevant heterocyclic compounds is often far from trivial. Heterocyclic chemistry therefore continues to attract the attention of the chemistry community and the development of novel methodologies to access heterocycles efficiently is highly appreciated[XI].

Many naturally occurring and synthetic compounds bearing pyridine scaffold possess interesting biological properties[XII]. Literature survey manifests that number of pyridine derivatives have been synthesized using various aldehydes but not a single reference have been found where 3-substituted-1*H*-pyrazole-4-carbaldehyde is used. We wish to report herein this heterocyclic aldehyde which is biologically active with a view to obtain more active and hybrid heterocyclic system containing two biologically active moieties, 1*H*-pyrazole[XIII-XV] and pyridine[XVI-XVIII] together.

The most suitable protocol for the synthesis of functionalized organic compounds would be microwave assisted one pot reaction due to the fact that the synthesis can be performed without the isolation of the intermediates, without discharging any functional groups in short reaction time, In addition to this use of ceric ammonium nitrate (CAN), is increases the rate of reaction and yield of targeted product with enormous purity, Hence, we wish to report an efficient microwave assisted one-pot multicomponent, CAN catalyzed synthesis of polysubstituted pyridine derivatives having 1*H*-pyrazole nucleus which have also been recognized as promising new scaffold to endow a very good biological properties.

The constitution of all the products was characterized using elemental analysis, FT-IR, ^1H NMR, ^{13}C NMR and mass spectrometry. All the derivatives were screened for their antibacterial activity against *Bacillus subtilis*, *Clostridium tetani*, *Streptococcus pneumoniae*,

Escherichia coli, *Salmonella typhi*, *Vibrio cholerae* as well as for antifungal activity against *Aspergillus fumigatus* and *Candida albicans*, using broth microdilution MIC method.

ANTIMICROBIAL SCREENING

The *in vitro* antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method[XIX]. Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to 10^8 CFU [Colony Forming Unit] per milliliter by comparing the turbidity.

The compounds **3a-p** were screened for their antibacterial activity against *Bacillus subtilis* (MTCC 441), *Clostridium tetani* (MTCC 449), *Streptococcus pneumoniae* (MTCC 1936), *Escherichia coli* (MTCC 443), *Salmonella typhi* (MTCC 98), *Vibrio cholerae* (MTCC 3906) as well as antifungal activity against *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227). DMSO was used as vehicle to get desired concentration of compounds to test upon microbial strains. The lowest concentration, which showed no visible growth after spot subculture was considered as MIC for each compound. The standard antibiotics used for comparison in the present study were ampicillin for evaluating antibacterial activity as well as griseofulvin and nystatin for antifungal activity. The protocols are summarized in (Table 1).

Table 1: Antimicrobial screening data of titled compounds **3a-p**

MINIMUM INHIBITION CONCENTRATION (MIC, µg/mL)

Compd.	R_1	R_2	Gram positive bacteria			Gram negative bacteria			Fungi	
			B.S. MTCC 441	C.T. MTCC 449	S.P. MTCC 1936	E.C. MTCC 443	S.T. MTCC 98	V.C. MTCC 3906	A.F. MTCC 3008	C.A. MTCC 227
3a	**H**	**H**	1000	**500**	500	125	125	200	1000	1000
3b		**F**	500	**200**	**100**	500	500	500	1000	**500**
3c		**Cl**	1000	**250**	**100**	125	500	250	1000	**500**
3d		**Br**	500	**500**	500	500	500	250	500	**250**
3e	**F**	**H**	**200**	**250**	500	**100**	150	500	1000	**500**
3f		**F**	**62.5**	**200**	100	200	100	**100**	100	>1000
3g		**Cl**	**100**	**250**	100	250	100	500	100	**250**
3h		**Br**	500	500	250	500	500	250	500	**500**
3i	**Cl**	**H**	**250**	**250**	250	**100**	200	250	>1000	>1000
3j		**F**	**200**	**250**	200	**100**	200	250	500	**250**
3k		**Cl**	500	**100**	**100**	250	250	500	500	>1000
3l		**Br**	**250**	**100**	**100**	200	150	500	1000	**500**
3m	**Br**	**H**	**200**	500	200	**62.5**	**100**	**100**	1000	**500**
3n		**F**	**100**	**250**	250	125	200	250	>1000	1000
3o		**Cl**	500	500	**62.5**	125	125	**62.5**	>1000	1000
3p		**Br**	**250**	500	125	**100**	150	500	1000	**500**
Ampicillin			**250**	**250**	**100**	**100**	**100**	**100**	**-**	**-**
Ciprofloxacin			**50**	**100**	**50**	**25**	**25**	**25**	**-**	**-**
Griseofulvin			**-**	**-**	**-**	**-**	**-**	**-**	**100**	**500**
Nystatin			**-**	**-**	**-**	**-**	**-**	**-**	**100**	**100**

B.S = Bacillus subtilis, *C.T = Clostridium tetani*, *S.P = Streptococcus pneumoniae*, *E.C = Escherichia coli*, *S.T = Salmonella typhi*, *V.C = Vibrio cholera*, A.F = *Aspergillus fumigates*, C.A = *Candida albicans,"-"= not tested*

An examination of the data (Table 1) reveals that amongst all the synthesized compounds **3a-p**, compound **3f** (R_1 = F, R_2 = F) exhibited excellent activity against Gram positive bacteria *Bacillus subtilis,* **3f** founds to be most active member of the series which is active against most of the scanned biological species. While **3g**, **3n** (MIC = 100 µg/mL), **3e**, **3j**, **3m** (MIC = 200 µg/mL) are showing more potency then ampicillin against *Bacillus subtilis*. For *Clostridium tetani,* **3k** and **3l** (MIC = 100 µg/mL) showing excellent potency, while **3b**, **3f** (MIC = 200 µg/mL) are more potent and **3c**, **3e**, **3g**, **3i**, **3j** and **3n** (MIC = 250 µg/mL) are equipotent as ampicillin. For *Streptococcus pneumonia,* **3o** (MIC = 62.5 µg/mL) founds as more potent while, **3b**, **3c**, **3f**, **3g**, **3k**, **3l** (MIC = 100 µg/mL) are equipotent as Ampicillin
Against Gram negative bacteria *Escherichia coli,* **3m** (MIC = 62.5 µg/mL) more potent than ampicillin while **3e**, **3i**, **3j**, **3p** are equipotent as ampicillin. The compound **3f**, **3g** and **3m** (MIC = 100 µg/mL) founds to be equipotent as ampicillin against *Salmonella typhi*. The compound **3o** founds (MIC = 62.5 µg/mL) more active and **3f** and **3m** are equipotent as amp against *Vibrio cholera.*
In case of antifungal character **3f** and **3g** (MIC = 100 µg/mL) founds equipotent as griseofulvin and nystatin against *Aspergillus fumigates.* While in case of *Candida albicans,* 3 compounds **3d**, **3g**, **3j** (MIC = 250 µg/mL) founds more active and **3b**, **3c**, **3e**, **3h**, **3l**, **3m**, and **3p** founds equipotent as nystatin.

EXPERIMENTAL SECTION

MATERIALS:

All the reagents were obtained commercially and used with further purification. Solvents used were of analytical grade. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates coated with silica gel 60 F_{254}, 0.25 mm thickness, Merck) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer and all compounds are within ±0.4% of theory specified. The IR spectra were recorded on a Shimadzu FTIR 8401 spectrophotometer using KBr discs and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400 MHz spectrometer using solvent peak as internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Mode of ionization employed was ESI (electrospray ionization). The microwave oven used was specially modified by RAGA's Electromagnetic systems. Following are some specifications of microwave employed: Power output-700W 2450 MHz: 100% microwave power is associated with 700 Watt, Adjustable power levels: 10 Levels from 140 Watt to 700 Watt, Dimensions: W 36cm x H 21cm x D 43cm (Internal).

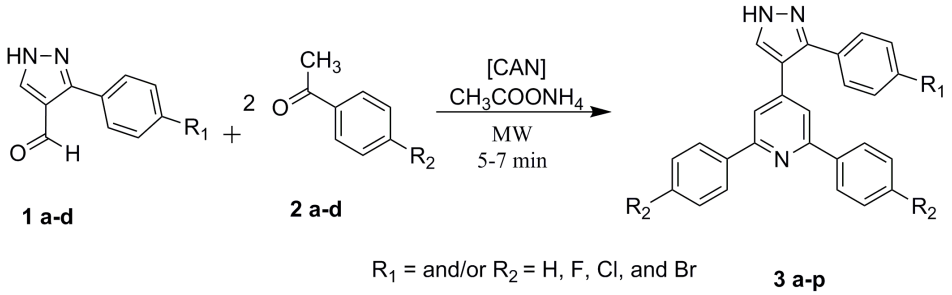
Synthesis of title compounds (3a-p)

Synthesis of title compounds involves following two steps:
(i) Synthesis of 3-substituted-1*H*-pyrazole-4-carbaldehydes **1a-d**.
3-substituted-1*H*-pyrazole-4-carbaldehydes were synthesized according to our previous work.[XV]
(ii) Synthesis of polysubstituted pyridine derivatives **3a-p**.

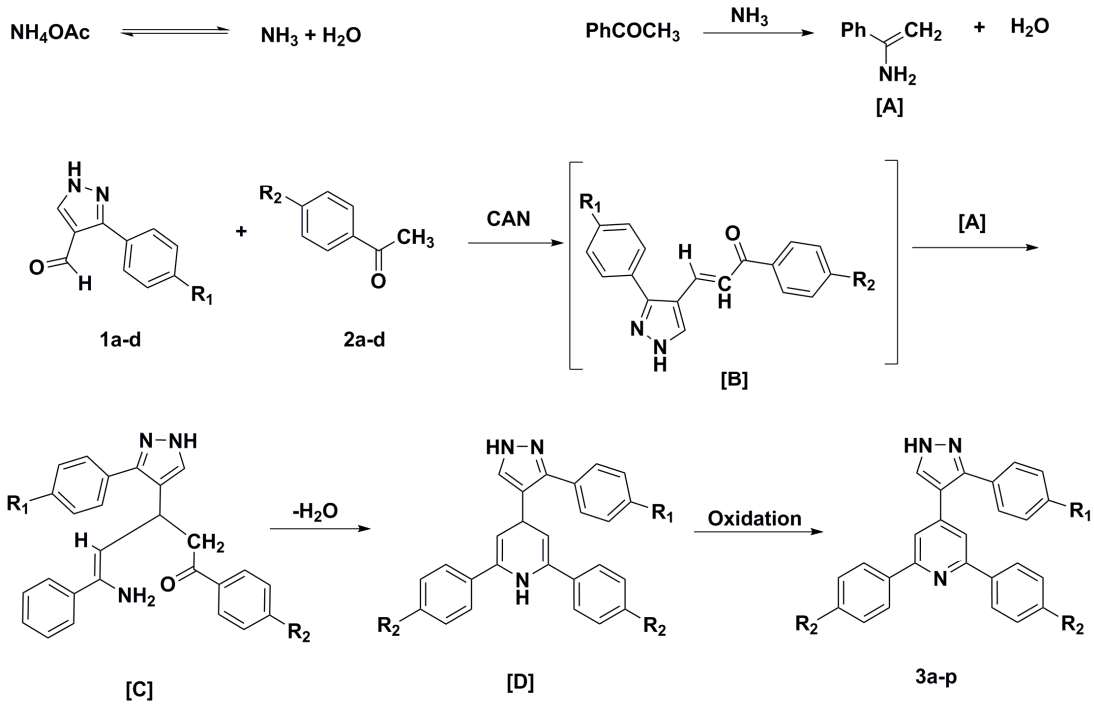
In a 50 mL round-bottom flask, 3-substituted-1*H*-pyrazole-4-carbaldehydes (**1a-d**, 1 mmol), and various methyl aryl ketone (**2a-d**, 2.2 mmol), Ammonium acetate (2.5 mmol) and 5 mol% ceric ammonium nitrate (CAN) as catalyst were taken in ethanol (5 mL), thoroughly mixed and irradiated in microwave oven at 420 W for 300 second. After the completion of reaction (checked by TLC; eluent, chloroform:methanol::9:1), the solution was cooled to

room temperature, the solid separated was filtered, washed well with R-spirit (10 ml), dried and recrystallized from chloroform-methanol (1:1) to get the pure solid sample **3a-p**.

REACTION SCHEMES



Scheme 1 Reaction scheme for **3a-p**



Scheme 2 Plausible reaction mechanism for **3a-p**

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2,6-diphenyl-4-(3-phenyl-1*H*-pyrazol-4-yl)pyridine [3a]

Yield: 85%; m.p.: 182-185 °C; IR (KBr, ν_{max}, cm^{-1}): 3145 (NH str.), 3005 (aromatic CH str.), 1600-1400 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21-8.32 (m, 18H, Ar-H), 12.62 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 99.4, 116.2, 126.3, 127.0, 127.8, 128.6, 129.1, 129.9, 133.5, 136.4, 139.7, 145.1, 147.3, 153.7; Mol. For.: $C_{26}H_{19}N_3$; Mol. Wt.: 373.16 gm/mole; MS: 373.45 gm/mole; Elemental analysis: Calcd: C 83.62, H 5.13, N 11.25 %; Found: C 83.35, H 4.96, N 11.18 %

2,6-bis(4-fluorophenyl)-4-(3-phenyl-1*H*-pyrazol-4-yl)pyridine [3b]
Yield: 78% ; m.p.: 175-178°C ; IR (KBr, ν_{max}, cm^{-1}): 3176 (NH str.), 2960 (aromatic CH str.), 1628-1425 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39-8.65 (m, 16H, Ar-H), 12.50 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 97.1, 116.1, 116.8, 127.4, 128.7, 129.9, 130.7, 133.2, 134.4, 136.8, 145.3, 147.6, 153.2, 161.1; Mol. For.: $C_{26}H_{17}F_2N_3$; Mol. Wt.: 409.14 gm/mole; MS: 409.43 gm/mole; Elemental analysis Calcd: C 76.27, H 4.19, N 10.26 % Found: C 76.38, H 4.42, N 10.14 %;

2,6-bis(4-chlorophenyl)-4-(3-phenyl-1*H*-pyrazol-4-yl)pyridine [3c]
Yield: 74% ; m.p.: 165-169°C; IR (KBr, ν_{max}, cm^{-1}): 3151 (NH str.), 3019 (aromatic CH str.), 1600-1420 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39-8.51 (m, 16H, Ar-H), 12.64 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 95.3, 116.5, 126.8, 127.2, 127.9, 128.3, 129.8, 132.4, 133.7, 135.2, 137.7, 144.5, 147.8, 152.4Mol. For.: $C_{26}H_{17}Cl_2N_3$; Mol. Wt.: 441.08 gm/mole; MS: 442.34 gm/mole; Elemental analysis Calcd: C 70.60, H 3.87, N 9.50 % Found: C 70.53, H 3.69, N 9.41 %;

2,6-bis(4-bromophenyl)-4-(3-phenyl-1*H*-pyrazol-4-yl)pyridine [3d]
Yield: 83% ; m.p.: 193-195°C; IR (KBr, ν_{max}, cm^{-1}): 3145 (NH str.), 3005 (aromatic CH str.), 1613-1400 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41-8.38 (m, 16H, Ar-H), 12.52 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 99.8, 115.7, 121.6, 126.8, 127.4, 128.1, 129.6, 132.2, 133.9, 136.5, 138.3, 144.6, 146.8, 152.9 Mol. For.: $C_{26}H_{17}Br_2N_3$; Mol. Wt.: 528.98 gm/mole; MS: 531.24 gm/mole; Elemental analysis; Calcd: C 58.78, H 3.23, N 7.91 % Found: C 59.02, H 3.47, N 8.12 %;

4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-2,6-diphenylpyridine [3e]
Yield: 77% ; m.p.: 174-176°C IR (KBr, ν_{max}, cm^{-1}): 3160 (NH str.), 2980 (aromatic CH str.), 1600-1420 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30-8.44 (m, 17H, Ar-H), 12.78 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 95.4, 116.5, 117.3, 126.7, 127.5, 128.6, 129.3, 131.5, 136.7, 139.1, 146.2, 147.4, 153.6, 163.2 Mol. For.: $C_{26}H_{18}FN_3$; Mol. Wt.: 391.15 gm/mole; MS: 391.44 gm/mole; Elemental analysis; Calcd: C 79.78, H 4.63, N 10.73 % Found: C 79.54, H 4.77, N 10.68 %;

2,6-bis(4-fluorophenyl)-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)pyridine [3f]
Yield: 76% ; m.p.: 163-166°C ; IR (KBr, ν_{max}, cm^{-1}): 3184 (NH str.), 3018 (aromatic CH str.), 1628-1421 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32-8.68 (m, 15H, Ar-H), 12.66 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 98.6, 115.4, 116.7, 117.2, 128.5, 130.2, 130.8, 133.5, 136.3, 145.7, 147.1, 152.8, 161.4, 163.0 Mol. For.: $C_{26}H_{16}F_3N_3$; Mol. Wt.: 427.13 gm/mole; MS: 427.42 gm/mole; Elemental analysis; Calcd: C 73.06, H 3.77, N 9.83 % Found: C 72.91, H 3.84, N 9.78 %;

2,6-bis(4-chlorophenyl)-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)pyridine [3g]
Yield: 73% ; m.p.: 169-171°C ; IR (KBr, ν_{max}, cm^{-1}): 3156 (NH str.), 3010 (aromatic CH str.), 1600-1426 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29-8.51 (m, 15H, Ar-H), 12.62 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 96.2, 116.1, 116.7, 128.4, 129.1, 129.7, 130.6, 132.8, 135.3, 137.1, 144.3, 146.7, 152.9, 162.5Mol. For.: $C_{26}H_{16}C_{l2}FN_3$; Mol. Wt.: 459.07 gm/mole; MS: 459.33 gm/mole; Elemental analysis; Calcd: C 67.84, H 3.50, N 9.13 % Found: C 67.90, H 3.61, N 8.91 %;

2,6-bis(4-bromophenyl)-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)pyridine [3h]
Yield: 75% ; m.p.: 155-159°C ; IR (KBr, ν_{max}, cm^{-1}): 3160 (NH str.), 2980 (aromatic CH str.), 1606-1420 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31-8.43 (m, 15H, Ar-H), 12.56 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 99.7, 116.8, 117.4, 121.6, 128.2, 128.9, 130.7, 132.3, 135.5, 138.7, 145.3, 146.7, 154.3, 163.1Mol. Wt.: 546.97 gm/mole; Mol. For.: $C_{26}H_{16}Br_2FN_3$; MS: 549.23 gm/mole; Elemental analysis; Calcd: C 56.86, H 2.94, N 7.65 % Found: C 56.59, H 3.19, N 7.74 %;

4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-2,6-diphenylpyridine [3i]
Yield: 72% ; m.p.: 162-166°C ; IR (KBr, ν_{max}, cm^{-1}): 3145 (NH str.), 3005 (aromatic CH str.), 1600-1400 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53-8.38 (m, 17H, Ar-H), 12.71 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6): 98.4, 115.4, 126.3, 127.6, 128.2, 128.8, 129.5, 132.7, 134.1, 136.9, 139.5, 145.1, 147.6, 153.8 Mol. For.: $C_{26}H_{18}ClN_3$; Mol. Wt.: 407.12 gm/mole; MS: 407.89 gm/mole; Elemental analysis; Calcd: C 76.56, H 4.45, N 10.30 % Found: C 76.43, H 4.23, N 10.39 %;

4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-2,6-bis(4-fluorophenyl)pyridine [3j]
Yield: 79% ; m.p.: 173-175°C ; IR (KBr, ν_{max}, cm^{-1}): 3166 (NH str.), 2980 (aromatic CH str.), 1609-1427 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55-8.71 (m, 15H, Ar-H), 12.64 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 98.9, 116.2, 117.7, 128.1, 129.5, 130.7, 131.2, 134.0, 134.5, 136.7, 144.3, 146.8, 154.4, 161.1 Mol. For.: $C_{26}H_{16}ClF_2N_3$; Mol. Wt.: 443.10 gm/mole; MS: 443.88 gm/mole; Elemental analysis; Calcd: C 70.35, H 3.63, N 9.47 % Found: C 70.61, H 3.80, N 9.34 %;

2,6-bis(4-chlorophenyl)-4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)pyridine [3k]
Yield: 83% ; m.p.: 186-188°C; IR (KBr, ν_{max}, cm^{-1}): 3182 (NH str.), 3010 (aromatic CH str.), 1610-1420 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57-8.62 (m, 15H, Ar-H), 12.77 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 95.3, 116.3, 127.8, 128.4, 129.6, 130.1, 131.5, 132.8, 134.2, 136.7, 137.7, 145.2, 147.1, 152.3Mol. For.: $C_{26}H_{16}Cl_3N_3$; Mol. Wt.: 475.04 gm/mole; MS: 475.78 gm/mole; Elemental analysis; Calcd: C 65.50, H 3.38, N 8.81 % Found: C 65.36, H 3.62, N 8.96 %;

2,6-bis(4-bromophenyl)-4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)pyridine [3l]
Yield: 72% ; m.p.: 181-184°C; IR (KBr, ν_{max}, cm^{-1}): 3147 (NH str.), 3005 (aromatic CH str.), 1600-1400 (C=N and C=C aromatic str. of pyridine);^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51-8.38 (m, 15H, Ar-H), 12.67 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 97.1, 115.8, 120.7, 127.6, 128.4, 129.1, 131.6, 132.8, 134.3, 136.1, 138.9, 146.5, 146.3, 154.5Mol. For.: $C_{26}H_{16}Br_2ClN_3$; Mol. Wt.: 562.94 gm/mole; MS: 562.69 gm/mole; Elemental analysis; Calcd: C 55.20, H 2.85, N 7.43 % Found: C 54.95, H 2.67, N 7.52 %;

4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-2,6-diphenylpyridine [3m]
Yield: 83% ; m.p.: 190-192°C ; IR (KBr, ν_{max}, cm^{-1}): 3160 (NH str.), 2980 (aromatic CH str.), 1612-1420 (C=N and C=C aromatic str. of pyridine);^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66-8.30 (m, 17H, Ar-H), 12.62 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 99.4, 116.5, 122.8, 127.3, 127.7, 128.3, 129.8, 132.4, 133.9, 136.7, 139.7, 145.4, 147.1, 153.9 Mol. For.: $C_{26}H_{18}BrN_3$; Mol. Wt.: 451.07 gm/mole; MS: 451.35 gm/mole; Elemental analysis; Calcd: C 69.04, H 4.01, N 9.29 % Found: C 68.73, H 4.22, N 9.47 %;

4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-2,6-bis(4-fluorophenyl)pyridine [3n]
Yield: 74% ; m.p.: 168-170°C ; IR (KBr, ν_{max}, cm^{-1}): 3178 (NH str.), 2969 (aromatic CH str.), 1600-1425 (C=N and C=C aromatic str. of pyridine);^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61-8.69 (m, 15H, Ar-H), 12.69 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 99.8, 115.3, 116.7, 123.4, 128.8, 130.2, 132.0, 132.6, 134.7, 136.5, 145.5, 146.8, 152.5, 162.3Mol. For.: $C_{26}H_{16}BrF_2N_3$; Mol. Wt.: 487.05 gm/mole; Elemental analysis; Calcd: C 63.95, H 3.30, N 8.60 % Found: C 64.07, H 3.46, N 8.51 %; MS: 487.33 gm/mole;

4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-2,6-bis(4-chlorophenyl)pyridine [3o]
Yield: 79% ; m.p.: 196-198°C ; IR (KBr, ν_{max}, cm^{-1}): 3145 (NH str.), 3007 (aromatic CH str.), 1602-1404 (C=N and C=C aromatic str. of pyridine);^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60-8.53 (m, 15H, Ar-H), 12.61 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 98.4, 116.7, 123.9, 128.1, 129.3, 129.8, 132.5, 133.3, 133.8, 135.3, 137.4, 145.7, 147.2, 153.4 Mol. For.: $C_{26}H_{16}BrCl_2N_3$; Mol. Wt.: 518.99 gm/mole; MS: 518.24 gm/mole; Elemental analysis; Calcd: C 59.91, H 3.09, N 8.06 % Found: C 60.13, H 3.20, N 7.94 %;

2,6-bis(4-bromophenyl)-4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)pyridine [3p]
Yield: 71% ; m.p.: 177-179°C ; IR (KBr, ν_{max}, cm^{-1}): 3181 (NH str.), 3018 (aromatic CH str.), 1614-1421 (C=N and C=C aromatic str. of pyridine); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65-8.67 (m, 15H, Ar-H), 12.66 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 95.3, 115.1, 121.7, 123.1, 128.3, 128.8, 131.0, 132.1, 132.6, 137.2, 138.4, 145.3, 148.4, 153.6 Mol. For.: $C_{26}H_{16}Br_3N_3$; Mol. Wt.: 606.89 gm/mole; Elemental analysis; Calcd: C 51.18, H 2.64, N 6.89 % Found: C 51.29, H 2.87, N 6.71 %; MS: 606.14 gm/mole;

CONCLUSION:

A series of some new 1*H*-pyrazole bearing polysubstituted pyridine derivatives has been synthesized through a facile one pot, microwave assisted, multicomponent reaction. This synthetic strategy allows the construction of relatively complicated nitrogen containing heterocyclic system as well as the introduction of various halo-aromatic substitutions into 2-, 4- and 6- positions of pyridine. We also believe that the procedural simplicity, the efficiency and the easy accessibility of the reaction partners gives access to a wide array of pyridine frameworks equipped with a 1*H*-pyrazole unit. It can be concluded from Table 1 that compound 3f is highly active against mostly all of the biological species. From the activity data, it is worth mentioning that halogen substitution on these compounds profoundly influences the activity. From the activity chart analysis we found that pyrazole aldehyde with fluorine substitution and pyridine ring with fluoro and chloro aryl substitution is the most active composition. The governing factors for the antimicrobial potency of synthesized 1*H*-pyrazole bearing polysubstituted pyridine derivatives is still a confront needing further investigations

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