Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2014, 6(6):435-441
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antimicrobial activity studies of microwave irradiated in (4-chlorophenyl) (6-methylpyridin-3-yl) derivatives

S. M. Reddy, Bijivemula N. Reddy and Madhvesh Pathak*

Department of Chemistry, Vellore Institute of technology, Vellore, T. N., India

---

ABSTRACT

*In view of generating new compounds for future drug development, we have synthesized some (4-chlorophenyl)(5-methylpyrazin-2-yl)derivatives of 5-methylpyrazine-2-carboxylic acid **(1a)** in presence of triethylamine followed, NH(OCH_3)CH_3.HCl and 4-chlorophenyl)magnesium bromide to obtaine (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone **(4a)** as one of the major product which was then used as an intermediate to synthesize a new series of compounds (5**a-j**). All the synthesized compounds were fully characterized on the basis of their detailed spectral studies and were evaluated for their antimicrobial activities in two Gram-positive bacteria (Staphylococcus aureus, Bacillus subtillis) and two Gram-negative bacteria (Echerichia coli and Pseudomonas aeuroginosa) and two fungi (Aspergillus niger and Aspergillus fumigatus) strains using Cup plate method*

Keywords: - Antimicrobial activity, 5-methylpyrazine-2-carboxylic acid NH (OCH_3) CH_3.HCl, microwave.

INTRODUCTION

Azomethines are generally known as Schiff bases to honour Hugo Schiff, who synthesized such compounds. These are the compounds containing characteristic -C=N- group. Several methods have been reported for the preparation of azomethines. Selvam et. al [1] have prepared sulfonamide and its derivatives as anti-HIV agents. More et. al [2] have marked the biological activity of Schiff bases synthesized from aminothiazoles. Ernst Bayer [3] has reported some metallocomplex Schiff bases derived from *o*-amino phenol. Schiff bases can be synthesized from an aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine [4]. They are well known intermediates for the preparation of azetidinones, thiazolidinones, oxadiazolines and many other derivatives. Azomethines exhibit a wide range of pharmacological activities like antimicrobial [5], antiparasitic [6], anti-inflammatory [7], anticancer [8] etc. A large number of substituted pyrazole derivatives are prepared and tested for variety of biological activities like anti HIV [9], anti-inflammatory [10], antimicrobial [11], fungicidal [12] etc. Pyridine derivatives also possess wide therapeutic activities such as antiviral [13], anti HIV [14], anticancer [15], antitumor [16], antimicrobial [17].

In view of their biological activity, Methylpyridin represent one of the most interesting groups of alkaloids. In particular, Methylpyridin alkaloids such as sedative hypnotic drug Methaqualone. The development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds, we became interested in the possibility of developing the methods reported in the literature for constructing Methylpyridin ring system, containing ortho-amino benzanilides as starting materials, we have successfully tried to minimize the number of steps, in which the intermediate.

MATERIALS AND METHODS

2.1 General conditions

All the reagents were obtained commercially (SD fine, India) and used with further purification. Melting points were determined by open capillary method. The IR spectra (in KBr pellets) were recorded on a Perkin-Elmer FTIR spectrophotometer.^{1}H NMR ($CDCl_3$ 400 MHz)and^{13}C NMR (DMSO-d_6, 100.6 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of n-hexane and ethyl acetate.

2.2 Synthesis

2.2.1 Synthesis of N-methoxy-N,5-dimethylpyrazine-2-carboxamide (2a-j)

To a stirred solution of 5-methyl pyrazine-2-carboxylic acid (**1a)** (1.0g, 1.0 eq) in DCM (20 mL) was added triethylamine (1.5 eq) followed by HATU (1.5 eq) and NH (OCH_3) CH_3.HCl (1.5 eq) at 0 °C. The resulting reaction mixture was stirred at RT for 4 h. After the completion of reaction, reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine dried over sodium sulfate and solvent was evaporated under reduced pressure to afford crude residue. The residue was triturated with diethyl ether to afford N-methoxy –N, 5-dimethyl pyrazine-2-carboxamide **(2a)** as thick liquid (yield 80%).

2.2.2 Synthesis of (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone (4a-j)

To a stirred solution of compound N-methoxy –N,5-dimethyl pyrazine-2-carboxamide (**2a)** (1.0 g 1.0 eq) in tetrahydrofuran (10 mL) was added 4-Chloro phenyl magnesium bromide (1.2 eq,1M) under nitrogen atmosphere at 0 $^{\circ}$C and stirred for 30 min, reaction mixture was quenched with saturated ammonium chloride solution under cooling condition and extracted with ethyl acetate . The combined organic layers were washed with brine and dried over sodium sulfate. Solvent was evaporated under reduced pressure to afford crude .The crude residue was purified by column chromatography to give pure compound (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone (**4a**) as a thick liquid (yield 70%).

2.2.3 General procedure for the synthesis of title compound (4-Chlorophenyl) (6-Methylpyridin-3-yl) (5a-j)

To a stirred solution of (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone (**4a)** (1.0 g, 1.0 eq) in ethanol (10 mL) was added ammonium acetate (15 eq) and Sodium cynoborohydride (1.5eq) at 0 °C. The resulting reaction was irradiated with microwave at 90 °for 30 min. After completion of the reaction, reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine (500 mL), dried over sodium sulfate and solvent was evaporated under reduced pressure to get a pure compound (4-Chlorophenyl) (5-methylpyrazin-2-yl) methanamine (**5a)** as a thick liquid (yield 90%) (**5a-k)**. Characterization data of 5**a-k** are given below.

2.2.3.1 (4-Chlorophenyl)(5-methylpyrazin-2-yl)methanamine (5a)

Mp: 132-133 °C. IR (DCM, cm^{-1}): 3369.93, 1593.90, 1485.66, 1339.79, 1151.06, 1089.71, 1034.04, and 895.24. ^{1}H NMR (400 MHz, DMSO d_6) δ: 8.65 (d, *J* = 1.2 Hz, 1 H), 8.40 (d, *J* = 0.8 Hz, 1 H), 7.42-7.40 (m, 2 H), 7.35-7.32 (m, 2 H), 5.16 (s, 1 H), 2.51-2.49 (brs, 2 H), 2.44 (s, 3 H). ^{13}C NMR (100.57 MHz, DMSO d_6) δ: 156.34, 151.52, 144.08, 143.02, 141.72, 131.18, 128.74, 128.05, 57.81, 20.65. DIPMS: m/z at 234.0 $[M+H]^{+}$).

2.2.3.2 (4-Chlorophenyl) (6-methoxypyridin-3-yl)methanamine (5b)

Mp: 130-134 °C. IR (DCM, cm^{-1}): 3372.9, 2945.4, 2845.7,1606, 1573.9, 1489.2, 1394.5, 1287.6, 1090.5, 1025.2 and 828.82. ^{1}H NMR (400 MHz, DMSO d_6) δ: 8.15 (d, *J* = 2.0 Hz, 1 H), 7.62 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1 H), 7.41 (d, 2 H, *J* = 8.4 Hz), 7.34 (d, 2 H *J* = 8.8 Hz), 6.72 (d, *J* = 8.8 Hz, 1 H), 5.08 (s, 1 H), 3.8 (s, 3 H), 2.34 (brs, 2 H). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ: 163.4, 144.9, 143.4, 137.4, 133.3, 132.8, 128.6, 127.9, 110.9, 56.3, 53.37. DIPMS: m/z at 249.0 $[M+H]^{+)}$

2.2.3.3 Phenyl (pyridazin-3-yl)methanamine (5c)

Mp: 122-123 °C. IR (KBr, cm^{-1}): 3420.66, 2922.80, 2592.48, 1611.02, 1525.35, 1439.12, and 1009.71. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29-9.27 (m, 3 H), 7.79-7.71 (m, 2 H), 7.56-7.54 (m, 2 H), 7.47-7.38 (m, 4 H), 5.98-5.95 (m, 1 H). ^{13}C NMR (100.57 MHz, D_2O) δ: 160.10, 148.86, 134.80, 133.42, 132.79, 130.55, 129.79, 128.69, 56.64. DIPMS: m/z at 186.1 $[(M-HCl)+H]^{+}$.

2.2.3.4 (4-Chlorophenyl) (6-methylpyridin-3-yl)methanamine (5d)
Mp: 130-131 °C. IR (DCM, cm^{-1}): 3368.70, 1600.25, 1488.00, 1396.39, 1297.53, 1089.68, 1013.96, and 827.18. ^{1}H NMR (400 MHz, DMSO d_6) δ: 8.44 (d, *J* = 2.0 Hz, 1 H), 7.60 (d, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1 H), 7.42-7.40 (m, 2 H), 7.35-7.33 (m, 2 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 5.10 (s, 1 H), 2.51-2.49 (m, 3 H), 2.35 (br s, 2 H). ^{13}C NMR (100.57 MHz, DMSO d_6) δ: 155.95, 147.57, 145.33, 138.63, 134.46, 130.99, 128.49, 128.08, 122.58, 56.05, 23.54. DIPMS: m/z at 233.0 $[M+H]^+$).

2.2.3.5 2-(3-Mehylisoxazol-5-yl)-1-phenylehanamine (5e)
Mp: 130-133 °C. IR (KBr, cm^{-1}): 3436.59, 2907.83, 2745.76, 2608.78, 2583.99, 2530.35, 2464.65, 1613.75, 1576.07, 1417.10, 1497.09, 1458.45, 1442.65, 1413.72, 1238.82, 1111.52, 1022.48, 1001.25, and 896.75. ^{1}H NMR (400 MHz, DMSO d_6) δ: 9.08-9.07(m, 3 H), 7.58 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 2 H), 7.40-7.33 (m, 3 H), 6.05 (s, 1 H), 4.64-4.58 (m, 1 H), 3.61 (dd, J_1 = 4.8 Hz, J_2 = 15.2 Hz, 1 H), 3.50-3.43 (m, 1 H), 2.0 (s, 3 H). ^{13}C NMR (100.57 MHz, DMSO d_6) δ: 167.30, 159.39, 136.47, 128.92, 128.66, 127.89, 103.95, 52.63, 31.24, 10.93. DIPMS: m/z at 203.1, $[(M-HCl)+H]^+$).

2.2.3.6 2, 2, 2-Trifluoro-1(pyridine-2-yl)ethanamine(5f)
Mp: 125-127 °C. IR (KBr, cm^{-1}): 3436.53, 3062.13, 2846.22, 2595.56, 1635.13, 1620.31, 1264.22, 1206.21, and 1123.20. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.70 (br s, 3 H), 8.71 (d, *J* = 4.4 Hz, 1 H), 7.99 (t, *J* = 7.6 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.57 (dd, J_1= 4.8 Hz, J_2 = 7.6 Hz, 1 H) 5.74 (t, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 149.47, 147.97, 137.91, 127.57, 125.41, 124.96, 124.96, 119.15, 54.80, 54.49, 54.18, 53.87. DIPMS: m/z at 176.9 $[(M-HCl)+H]^+$

2.2.3.7 1-(4-mehoxypyridin-2-yl) ethanamine (5g)
Mp: 132-133 °C. IR (DCM, cm^{-1}): 3358.93, 3285.71, 2971.57, 1598.67, 1438.62, 1306.79, and 1036.35. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.28 (d, *J* = 5.4 Hz, 1 H), 7.02 (d, *J* = 5.4 Hz, 1 H), 6.78 (dd, J_1 = 2.5 Hz, J_2 = 5.5l Hz, 1 H), 3.92 (q, *J* = 6.9 Hz, 2 H), 3.815 (s, 3 H), 1.91 (br s, 2 H), 1.25 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.70, 165.68, 149.77, 107.78, 105.55, 55.04, 52.14, 24.63. DIPMS: m/z at 153.0 $[M+H]^+$.

2.2.3.8 Cyclopropyl (1-methyl-1H-pyrazol-5-yl) methanamine (5h)
Mp: 130-133 °C. IR (KBr, cm^{-1}): 3555.41, 3435.37, 3122.64, 2862.67, 1590.14, 1507.92, 1411.49, 1320.59, 1286.36, 1119.68, and 828.07. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 5.4 Hz, 1 H), 7.42 (d, *J* = 2.0 Hz, 1 H), 6.56 (d, *J* = 2.0 Hz, 1 H), 5.28 (br s, 5 H) 4.02 (q, *J* = 5.4 Hz , 1 H), 3.82 (s, 3 H), 1.41-1.35 (m, 1 H), 0.66-0.61 (m, 1 H), 0.55-0.47 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 139.82, 137.55, 105.66, 49.55, 36.91, 14.83, 4.58, 3.29. DIPMS: m/z at 152.0, $[(M-HCl)+H]^+$).

2.2.3.9 6-(1-aminoethyl) pyridin-3-ol (5i)
Mp: 135-136 °C. IR (KBr, cm^{-1}): 3451.39, 2929.47, 2661.00, 1621.39, 1567.94, 1321.42, 1226.02, and 858.03. ^{1}H NMR (400 MHz, DMSO d_6) δ: 10.4 (br, 1 H), 8.456 (br s, 3 H), 8.20 (d, *J* = 2.4 Hz, 1 H), 7.46 (d, *J* = 8.7 Hz, 1 H), 7.38 (dd, J_1 = 2.6 Hz, J_2 = 8.5 Hz, 1 H), 4.45 (t, *J* = 6.15 Hz, 1 H). ^{13}C NMR (75 MHz, D_2O) δ: 155.94, 141.47, 133.08, 131.00, 125.80, 47.68, 17.78. DIPMS: m/z at 139.1[(M-HCl) +H]$^+$).

2.2.3.10 4-(4-fluorophenyl) buane-2-amine (5j)
Mp: 129-131 °C. IR (KBr, cm^{-1}): 2929.24, 1607.29, 1509.48, 1457.15, 1219.96, 1194.66, and 826.00. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.12 (br s, 3 H), 7.28-7.23 (m, 2 H), 7.16-7.08 (m, 2 H),4.25 (d, *J* = 4.2 *Hz*, 2 H), 2.75 (s, 3 H), 2.68–2.62 (m, 2 H), 2.53-2.41 (m, 1 H), ^{13}C NMR (100.57 MHz, DMSO-d_6) δ: 161.85, 159.45, 137.15, 137.12, 130.00, 129.91, 115.14, 114.93, 46.28, 35.90, 29.93, 18.01. DIPMS: m/z at 168.0, $[(M-H)+H]^+$

RESULTS AND DISCUSSION

3.1 Chemistry

We have successfully ten novel compounds 5**a-j** in good yields via (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone **(4a)** by employing the reaction sequences shown in (scheme 1).

Esterification of compound **2** was brought out in presence of 5-methyl pyrazine-2-carboxylic acid (**1a)** was added triethylamine followed by HATU and NH (OCH_3) CH3.HCl at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. After the completion of reaction, reaction mixture was diluted with water and extracted

with ethyl acetate. The combined organic layer was washed with brine dried over sodium sulfate and solvent was evaporated under reduced pressure to afford crude residue. The residue was triturated with diethyl to afford N-methoxy –N, 5-dimethyl pyrazine-2-carboxamide **(2a)** yield 80% as a thick liquid. To a solution of N-methoxy –N, 5-dimethyl pyrazine-2-carboxamide (**2a)** in tetrahydrofuran was added 4-Chloro phenyl magnesium bromide **(3a)** under nitrogen atmosphere at 0 $^{\circ}$C and stirred for 30 min. reaction mixture was quenched with saturated ammonium chloride solution under cooling condition and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Solvent was evaporated under reduced pressure to afford crude, the crude residue was purified by column chromatography o give pure compound (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone **(4a)** as thick liquid (yield 70%).

The reaction sequence employed for the synthesis of title compounds is shown in (**Scheme 1**). To a stirred solution of (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone (**4a)** in ethanol was added ammonium acetate (15eq) and Sodium cynoborohydride (1.5eq) at 0 °C. The resulting reaction was irradiated with microwave at 90 for 30 min. reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine (500 mL) dried over sodium sulfate and solvent was evaporated under reduced pressure to get a pure compound (4-Chlorophenyl)(5-methylpyrazin-2-yl) methanamine (**5a)**,appeared at ^{1}H NMR (400 MHz, DMSO d_6) δ: 8.65 (d, *J* = 1.2 Hz, 1 H), 8.40 (d, *J* = 0.8 Hz, 1 H), 7.42-7.40 (m, 2 H), 7.35-7.32 (m, 2 H), 5.16 (s, 1 H), 2.51-2.49 (brs, 2 H), 2.44 (s, 3 H). ^{13}C NMR (100.57 MHz, DMSO d_6) δ: 156.34, 151.52, 144.08, 143.02, 141.72, 131.18, 128.74, 128.05, 57.81, 20.65. DIPMS: m/z at 234.0 $[M+H]^{+}$).

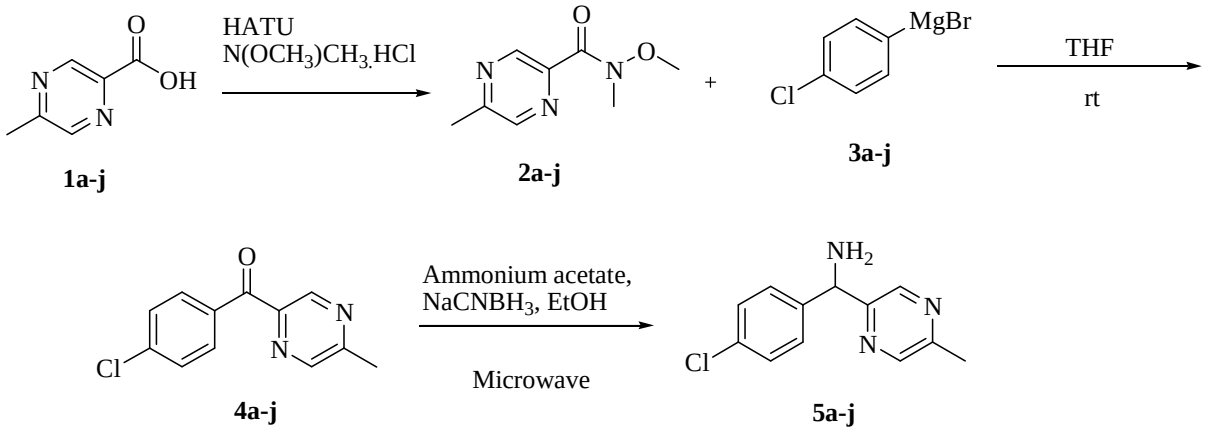
3.2. Antimicrobial Activity

In view of developing new class of antimicrobial agents, synthesized novel compounds were screened for their In vitro antimicrobial activities to determine zone of inhibition at 100 µg/mL against two Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis and two Gram-negative bacteria Escherichia coli, Pseudomonas aeruginosa, as well as two fungi Aspergillus niger, Aspergillus fumigates strains using Cup plate method where inoculated Muller-Hilton agar for bacteria and Sabouraud dextrose agar for fungi was poured onto the sterilized petri dishes (25–30 mL each petri dish). The poured material was allowed to set (30 min.) and thereafter the 'CUPS' (06mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution (0.1mL) was added with the help of a micro pipette. The plates were incubated at 37° C for 14h for bacteria and 30 h for fungi and the results were noted. The test solution was prepared by DMSO as solvent.

The obtained results, depicted in Table 1, revealed that all the synthesized compounds 5**a-j** could effectively, to some extent, inhibit the growth of all tested strains In vitro. In antibacterial studies, all the compounds tested were found less active towards Bacillus subtilis, as compared to other one strain of bacteria. Most of the compounds showed moderate to good activity against Staphylococcus aureus, Pseudomonas aeruginosa. Compounds **5a**, **5j** and **5i** have shown good antibacterial activity against Staphylococcus aureus. **5a, 5b** and **5i** have shown moderate activity against Escherichia coli. Out of two strains of fungi, these compounds were found to be less active against Aspergillus niger whereas showed moderate to good activity against Aspergillus fumigatus.

Table-1. Antimicrobial activity of title compounds 5a-j

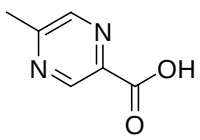
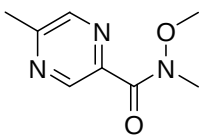
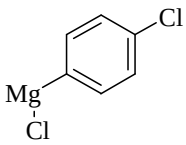
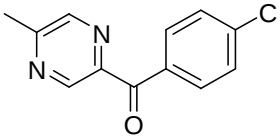
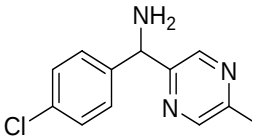
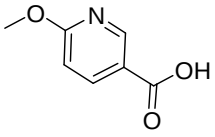
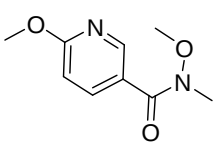
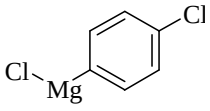
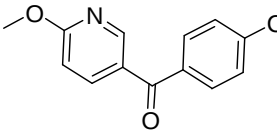
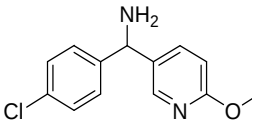
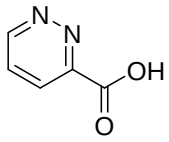
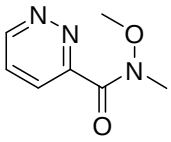
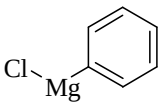
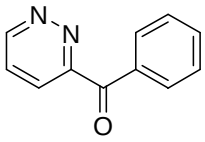
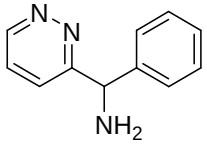
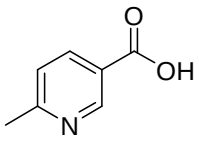
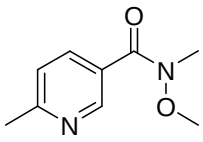
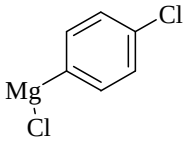
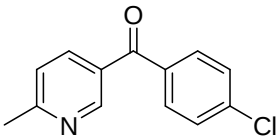
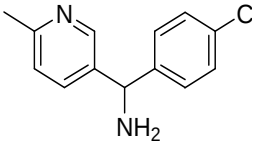
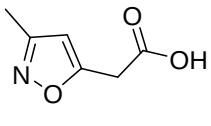
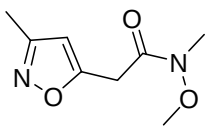
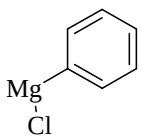
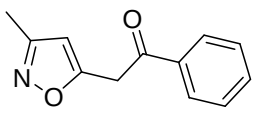
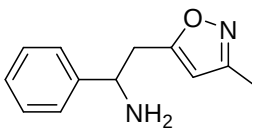
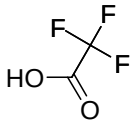
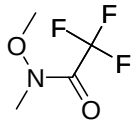
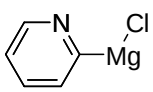
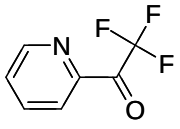
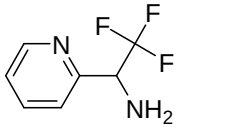
Compound	Gram positive bacteria		Gram negative bacteria		Fungi	
	Aureus	subtillis	coli	aeuroginosa	niger	fumigatus
5a	15	12	11	13	11	18
5b	13	12	15	12	10	18
5c	14	10	15	12	11	15
5d	13	11	12	11	12	18
5e	13	10	10	11	11	18
5f	14	11	10	13	13	16
5g	13	10	12	12	13	18
5h	16	10	14	14	14	18
5i	15	13	16	14	14	18
5j	13	11	13	13	13	18

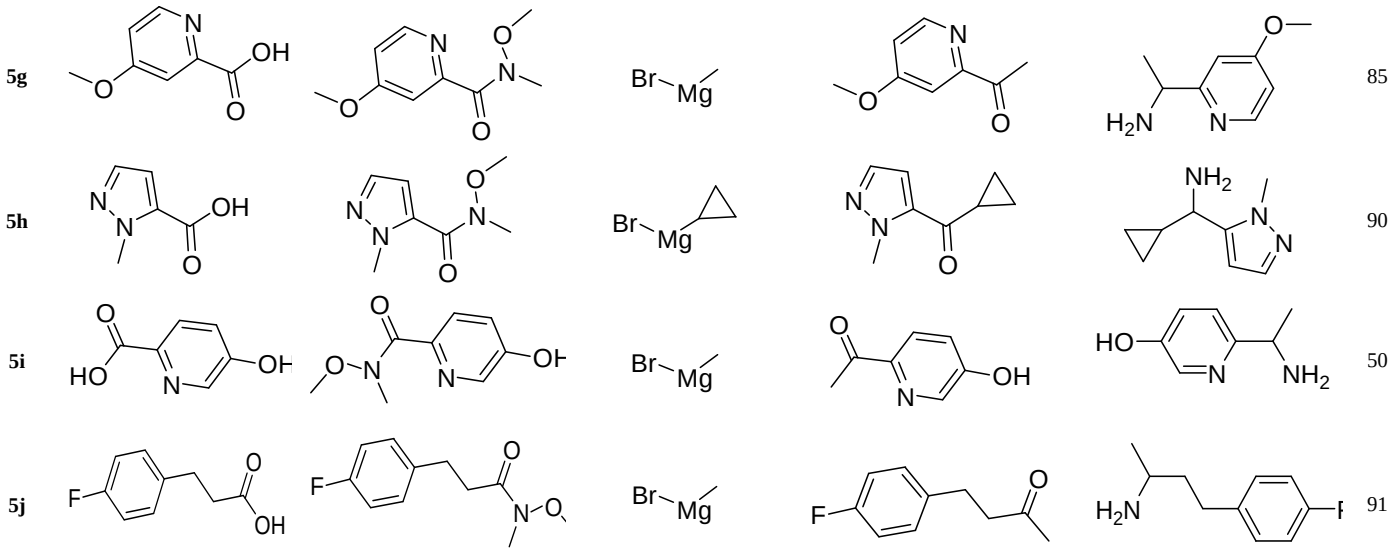


1a-j **2a-j** **3a-j** **4a-j** **5a-j**

Scheme-1.Synthesis of title compounds 5a-j

Table:-1 characterization (4-Chlorophenyl) (6-Methylpyridin-3-yl) derivatives (5a-j)

S.No	1	2	3	4	5	Yield
5a						90
5b						91
5c						87
5d						91
5e						82
5f						80



CONCLUSION

We have successfully synthesized ten novel (4-Chlorophenyl) (6-Methylpyridin-3-yl) **(5a-j)** containing (4-chlorophenyl) (5-methylpyrazin-2-yl) methanone **(4a)** in good yields. The structures of all the compounds were confirmed by their spectral data. All the newly synthesized compounds were screened for their MIC and zone of inhibition against four strains of bacteria and two strains of fungi. Amongst the compounds screened, most of the compounds have shown moderate to good antibacterial and antifungal properties whereas some compounds have shown promising antifungal properties, which were further used to determine MBC and MFC against some selected strains of bacteria and fungi. It is also suggested (4-Chlorophenyl) (6-Methylpyridin-3-yl) are worthy for further investigations as potential antimicrobial agents.

REFERENCES

[1] Selvam P, Chandramohan M, De Clercq E, Witvrouw M and Pannecouque C, *Eur J Pharm Sci*., **2001**, 14(4), 313-316.
[2] More P G, Bhalvankar R B and Pattar S C, *J Indian Chem Soc.*, **2001**, 78, 474-475.
[3] Bayer E, *Chem Ber*., 1957, 90(10), 2325-2338.
[4] Amanda J Gallant, Brian O Patrick and Mark J MacLachlan, *J Org Chem*., **2004**, 69(25), 8739-8744.
[5] Chambhare R V, Khadse B G, Bobde A S and Bahekar R H, *Eur J Med Chem*., **2003**, 38(7), 89-100.
[6] Rathelot P, Azas N, El-Kashef H and Delmas F, *Eur J Med Chem***.,** **2002**, 37(8), 671-679.
[7] Holla B S, Malini K V, Rao B S, Sarojini B K and Kumari N S, *Eur J Med Chem*., **2003**, 38(7), 313-318.
[8] Holla B S, Veerendra B, Shivananda M K and Poojary B, *Eur J Med Chem*., **2003**, 38(7), 759-767.
[9] Michael J G and Carolyn B, *J Med Chem*., **2000**, 43(5), 1034-1040.
[10] Bekhit A A, Fahmy H T Y and Baraka A M, *Eur J Med Chem*., 2003, 38(1), 27-36.
[11] Freddy H and Fernandes P S, *J Indian Chem Soc*., **1988**, 65(10), 691-694.
[12] Itaru O and Kazuhiko K, *Chem Abstr*., **2003**, 138, 401728x
[13] Tabarrini O, Manfroni G, Fravolini A, Cecchetti V, Sabatini S, De Clercq E, Rozenski J, Canard B and Dutartre H, *J Med Chem***.,** **2006**, 49(8), 2621-2627.
[14] Balzarini J, Stevens M, De Clercq E, Schols D. and Pannecouque C, *J Antimicrob Chemother*. , **2005**, 55(2),135-138.
[15] Cocco M T, Congiu C, Lilliu V and Onnis V, *Eur J Med Chem*., **2005**, 40(12),1365.
[16] Kovala-Demertzi D, Boccarelli A, Demertzis M A and Coluccia M, *Chemother*., **2007**, 53,148-152.
[17] Almeida V D, Mauro, Souza V N, Marcus, Barbosa R Nadia, Silva P, Frederico, Amarante W, Giovanni Cardoso H and Sílvia, *Letters in Drug Design and Discovery*, **2007**, 4, 149.
[18] Weitzel, K. W.; Wickman, J. M.; Augustin, S. G.; Strom, J. G. *Clinical Therapeutics* **2000**, *22*, 1254.
[19] Ming, L.; Wei-Si, G.; Li-Rong, W.; Bo, Q. *Jiegou Huaxue* **2006**, *25*, 108.

[20] Mirza, N. R.; Rodgers, R. J.; Mathiasen, L. S. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 1291.
[21] Ibrahim, H. M.; Makhseed, S.; Abdel-Motaleb, R. M.; Makhloof, A. A.; Elnagdi, M. H. *Heterocycles* **2007**, *71*, 1951.
[22] Khalil, K. D.; Al-Matar, H. M.; Al-Dorri, D. M.; Elnagdi, M. H. *Tetrahedron* **2009**, *65*, 9421.
[23] McFadden, H.G.; Huppatz, J.L.; Halladay, P.K. *Austral. J. Chem.* **1993**, *46*, 873.
[24] Jianguo, S.; Peiyu, W.; Ming, Z.; Qi, Z. *Yangzhou, Daxue Xuebao, Ziran Kexueban* **1998**, *1*, 17.
[25] Abdel-Motaleb, R. M.; Makhloof, A. A.; Ibrahim, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 109.
[26] Slatt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, 2760.
[27] Aziz, S. I.; Anwar, H. F.; Felita, D. H.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 725.
[28] Kenawi, I. M.; Elnagdi, M. H. *Spectrochim. Acta Molecul. Biomolecul. Spectroscopy* 2006, *65A*, 805.
[29] Ghozlan, S. A. S.; Abdelhamid, I. A.; Ibrahim, H. M.; Elnagdi, M. H. *Arkivoc* **2006**, (*xv*), 53.
[30] Al-Matar, H.M.; Riyadh, S.M.; Elnagdi, M. H., *Arkivoc* **2007**, (xiii), 53.