*IOSR Journal Of Pharmacy* *www.iosrphr.org*
*(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219*
*Volume 9, Issue 7 Series. I (July 2019), PP. 11-15*

# Synthesis of some novel Pyridine derivatives as potent MTCC inhibitors and compared to available antimicrobial drugs.

B.P. Yadav [1]; Meenakshi Thakur [2]
*1. Department of Chemistry, Meerut College, Meerut (U.P.) 250001, India*
*2. Department of Chemistry, Mewar University, Chittorgarh (Raj.) 312901, India*

**Abstract -** The upswing of antimicrobial resistance (AMR) is an intricate and severe health subjectat the present time as voluminous of microbial strains had turn out to be resistant to obtainable antibiotics. For discovery of new compoundsPyridine derivatives are chosen as they are well known for their wide range of biological activities.The synthesis of novel pyridine derivatives containing substituted Aryl- alkoxy group and sulfonyl group was done by multi step and multicomponent reactions in good yields. Since the activity of antibacterial drugs depends upon its concentration *in vitro* characterization of antibacterial activity commonly includes the determination of minimum inhibitory concentration (MIC)[2-5].The objective of this study was to evaluate antibacterial activity i.e. MIC[6] value of newly designed pyridinederivatives to serve the humanity.

**Key words:** Multi-component reactions, Pyridine derivative, antimicrobial activity, minimum inhibitory concentration.

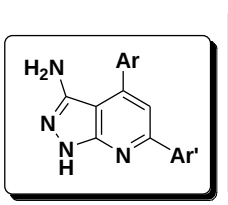
---

Date of Submission: 11-07-2019 Date of acceptance: 26-07-2019

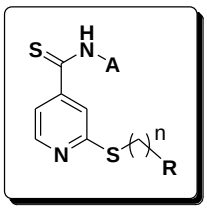
---

## I. INTRODUCTION

Antimicrobial contagion have occupied centre stage as they are the most communal disease and it is be anxious about that they would be most widespread disease in human in future. The upswing of antimicrobial resistance isintricate and unembellished health subject. The augmented rate of contagion due to confrontation of existing drugs has touched itsdisquietinglevel [1]. Communicable disease due to gram-positive bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus faecium* (VREF), and penicillin resistant *Streptococcus pneumoniae* are the prominent cause of indisposition and impermanence to the civicat present [2]. For the period of last few years an escalation of intrusive microbial and fungal contagion has been perceived, principally in immune- inhibited patients, which are now the cause of indisposition and impermanence as well. Therefore, there is exigentrequisite to develop new antimicrobial agents[3].Heterocyclic compounds have attracted attention due to their diverse biological and pharmacological properties. Pyridine derivatives are significant moieties in medicinal chemistry because of their wide range of biological activities like antibacterial[4], antifungal [5-6], antiviral[7], and antitumor[8].F. E. Gowda et al reported that 1H-pyrazolo[3,4-b]pyridines (Srtucture-1) comprise a very interesting class of compounds because of their significant and versatile biological and pharmacological activities, such as antimicrobial, antimalarial, antiviral and antiproliferative [9_17].Vera Klimesiva, Martin Svoboda et al reported the synthesis and in vitro antimycobacterial and antifungal activities of various thioalkylpyridine derivatives bearing anthioalkyl group in position 2 or 4 [18–22], as given by the general formula in structure- 2.




**Structure-1**




**Structure-2**

## II. RESULTS AND DISCUSSION

In the contemporaneousstudyPyridine derivatives was chosen for synthesis of novel molecules as antimicrobial agents due to testified antimicrobial activity of pyridine nucleus. 2- & 6-substituted Arylalkoxy and sulfone derivatives were synthesized using multistep procedure by following alkylation general procedure with base like caesium carbonate or sodium hydride followed by coupling of halo substituted pyridine with respective thiols. Synthetic pathways for the synthesis of targets compounds are shown in general scheme with the hope of discovering new antimicrobial agents. In comparison with several control drugs available in market in different categories. Newly synthesized derivatives have been evaluated for antibacterialandantifungal activity against standard strains. So it was aimed to investigate the efficacy of the antimicrobial effect of different derivatives on the same homologous structure of pyridine derivatives. Their Structures were elucidated with $^1$H NMR, and mass spectroscopy. Mass spectra of the compoundsshowed [$M^+$ + H] peaks, since the electrospray ionization method was employed. The structures of all derivatives were confirmed by spectral analysis and results are presented in the experimental section. In the $^1$H NMR spectra of the compounds, the signals of aromatic protons were observed at δ 7.84–7.03, as singlet bands, doublet bandsand multiplet bands.

Compounds were evaluated for the antimicrobial and compared with the activity of standard drugs available. All the derivatives synthesized were tested in vitro for antibacterial activity against *E. coli***MTCC442**, *P. aerugenosa***MTCC441**, *S. aureus***MTCC96** and *S. Pyogenus***MTCC443.** All the derivatives were tested for the antifungal activity against *C. albicans***MTCC227**, *A. niger***MTCC282** and *A. clavatus***MTCC1323**.The activity of antibacterial drugs depends upon its concentration *in vitro* characterization of antibacterial activity commonly includes the determination of minimum inhibitory concentration (MIC)[23-26]. Each synthesized drugs was diluted with DMSO obtaining 2000 µg/ml concentrations as a stock solution for biological screening. For primary screening 1000 µg/ml to 250 µg/ml concentrations and for secondary screening 200 µg/ml to 6.25 µg/ml concentrations was used. The standard drugs employed while assessing antimicrobial activities were Gentamycin, Chloramphenicol, Ampicillin, Ciprofloxacin and Norfloxacin for antibacterialactivity; Nystatin and Greseofulvin for antifungal activity. We have used the Broth Dilution Method[27]to evaluate the antibacterial activity. This archetypal method produces a quantifiable result for the amount of antimicrobial agents that is needed to inhibit growth of unambiguous microorganisms.

Some compounds exhibits broad antibacterial activity with MIC values of 25 – 250 µg/ml against *E. coli*, *P. aerugenosa*, *S. aureus* and *S. Pyogenus* and its isolate except for derivative **MT-07** that had a MIC value of 12.5 µg/ml -50µg/ml against all four stains and compound **MT-03** had a MIC values of 12.5µg/ml - 100µg/ml against all four stains (Table- 1).

In the antifungal assay compounds exhibits broad antifungal activity with MIC valuesof 125 – >1000µg/ml against *C. albicans*, *A. niger*and *A. clavatus*and its isolate except for derivative **MT-07** that had a MIC value of 125 µg/ml against *C. albicans*, and 100 µg/ml against*A. niger*and *A. clavatus*. All the derivatives had lower antifungal activities than the standard drugs (Table-2).

## III. EXPERIMENTAL SECTION

### 3.1 Materials & Methods

The chemicals and solvents were purchased from Sigma-Aldrich Co. (Taufkirchen, Munich, Germany), Merck Lifescience Pvt. Ltd. (Vikhroli, Mumbai, India) and Fisher Scientific (Pittsburgh, PA, USA) and usedwithout further purification. Silica gel (with Mesh size 230-400) was used for column chromatography and TLCplates were purchased from Merck Lifescience Pvt. Ltd. (Vikhroli, Mumbai, India) and ethyl acetate: hexaneswere used as mobile phase. NMR spectra were recorded on Bruker 400 MHz NMR spectrometer in CDCl3and DMSO; tetramethylsilane (TMS) was used as an internal standard. The mass spectra were recorded o Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA) usingthe ESI(+) method.

### 3.2 General Procedure

**Step-1: Synthesis of 2-(4-chlorobenzyloxy)-6-bromopyridine:**

Compound 1 (1.0 Eq.) was taken in a RBF with 1.5 eq. of caesium carbonate and N, N- Dimethylformamide at room temperature and stirred for 10 min. Now compound 2 (1.1 Eq.) was added under $N_2$ atmosphere and reaction mixture was allowed to stirred at 80 deg. C till completion of reaction. After that it was diluted with ethyl acetate and organic layer was washed with water, sodium bicarbonate solution and then with brine solution. Organic layer was concentrated and purified by column chromatography to afford desired product **(3).**

**1 H NMR (2-(4-chlorobenzyloxy)-6-bromopyridine) CDCl3:** 7.512-7.473 (1H, t, *J*= 8.0 Hz); 7.34-7.29 (6H, m); 7.16-7.14 (1H, d, *J*= 7.6 Hz); 7.09-7.07 (1H, d, *J*= 7.6 Hz); 4.67 (2H, s).

**Alternate route: Synthesis of 2-(4-chlorobenzyloxy)-6-bromopyridine:**

Compound 1 (1.0 Eq.) was taken in a RBF with 1.5 eq. of sodium hydride and N, N- Dimethylformamide at room temperature and stirred for 20 min. Now compound 2 (1.1 Eq.) was added under $N_2$ atmosphere and reaction mixture was allowed to stirred at room temperature till completion of reaction. After that it was

quenched with ice-water and extracted with ethyl acetate and organic layer was washed with brine solution. Organic layer was concentrated and purified by column chromatography to afford desired product **(3). 1 H NMR (2-(4-chlorobenzyloxy)-6-bromopyridine) CDCl3:** 7.512-7.473 (1H, t, *J*= 8.0 Hz); 7.34-7.29 (6H, m); 7.16-7.14 (1H, d, *J*= 7.6 Hz); 7.09-7.07 (1H, d, *J*= 7.6 Hz); 4.67 (2H, s).

**Step-2: Synthesis of 2-(4-chlorobenzyloxy)-6-(ethylthio)pyridine:**

To the stirred solution of compound **3** (1.0 Eq.) in THF was added sodium ethane thiolate (1.2 Eq.) at $0^{O}$ C under $N_2$ atmosphere and reaction mixture was allowed to stir at room temperature for 6 hrs. After that it was quenched with ice-water and extracted with ethyl acetate and organic layer was concentrated under reduced pressure. Crude product was purified by column chromatography to afford compound (**4)**. **1H NMR (2-(4-chlorobenzyloxy)-6-(ethylthio)pyridine):** 7.512-7.473 (1H, t, *J*= 8.0 Hz); 7.38-7.32 (4H, m); 6.79-6.77 (1H, d, *J*= 7.6 Hz); 6.48-6.46 (1H, d, *J*= 7.6 Hz); 5.36 (2H, s); 3.125-3.07 (2H, q, *J*= 7.2 Hz); 1.35-1.31 (3H, t, *J* = 7.2 Hz).

**Step-3: Synthesis of 2-(4-chlorobenzyloxy)-6-(ethylsulfonyl)pyridine:**

To the stirred solution of compound **4** (1.0 Eq.) in dichloromethane was added *meta*-Chloro per-oxy benzoic acid (1.2 Eq.) at $0^{O}$ C under $N_2$ atmosphere and reaction mixture was allowed to stir at room temperature for 2 hrs. After that it was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane and organic layer was concentrated under reduced pressure. Crude product was purified by column chromatography to afford compound (**5)**. **1H NMR (2-(4-chlorobenzyloxy)-6-(ethylsulfonyl)pyridine):** 7.84-7.80 (1H, dd, *J*= 7.2 Hz); 7.70-7.68 (1H, dd, *J*= 6.8 Hz); 7.41-7.37 (2H, d, *J*= 2.4 Hz); 7.35-7.33 (2H, d, *J*= 2.4 Hz); 7.09-7.03 (1H, m); 5.39 (2H, s); 3.31-3.25 (2H, q, *J*= 7.2 Hz); 1.27-1.23 (3H, t, *J* = 7.2 Hz).

## IV. FIGURES & TABLES

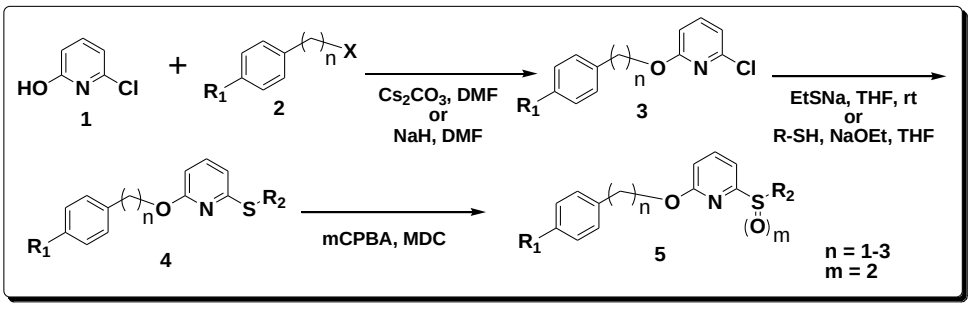
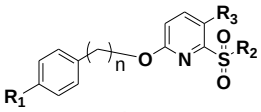


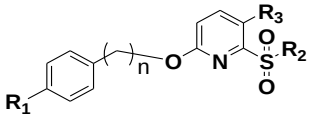

**Table-1:** Invitro antibacterial activity of novel pyridine derivatives in comparision with standard drugs:




**General Structure**

| Sr. No. | Sample ID | R1 | R2 | R3 | n | *E. coli* MTCC442 | *P. aerugenosa* MTCC441 | *S. aureus* MTCC96 | *S. pyogenus* MTCC443 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | MT-01 | Cl | Et | - | 1 | 500 | 500 | 250 | 250 |
| 2 | MT-02 | Cl | CH2CF3 | - | 1 | 250 | 500 | 500 | 500 |
| 3 | MT-03 | Cl | Et | - | 2 | 100 | 25 | 12.5 | 125 |
| 4 | MT-04 | Cl | Pr | - | 2 | 250 | 250 | 200 | 125 |
| 5 | MT-05 | CF3 | Et | - | 1 | 125 | 200 | 100 | 100 |
| 6 | MT-06 | CF3 | CH2CF3 | - | 1 | 100 | 25 | 125 | 100 |
| 7 | MT-07 | CF3 | Et | - | 2 | 12.5 | 25 | 25 | 50 |
| 8 | MT-08 | CF3 | Pr | - | 2 | 125 | 200 | 500 | 250 |
| 9 | MT-09 | Cl | Et | Me | 1 | 125 | 200 | 500 | 250 |
| 10 | MT-10 | Cl | CH2CF3 | Me | 1 | 200 | 500 | 100 | 12 |
| 11 | MT-11 | Cl | Et | Me | 2 | 100 | 100 | 125 | 100 |
| 12 | MT-12 | t-Bu | Et | Me | 2 | 126 | 125 | 200 | 200 |
| **Reference Drugs:** | | | | | | | | | |
| Gentamycin | | | | | | 0.05 | 1 | 0.25 | 0.5 |
| Chloramphenicol | | | | | | 50 | 50 | 50 | 50 |
| Ciprofloxacin | | | | | | 25 | 25 | 50 | 50 |
| Norfloxacin | | | | | | 10 | 10 | 10 | 10 |

**Table-2:** Invitro antifungal activity of novel pyridine derivatives in comparision with standard drugs:




**General Structure**

| Sr. No. | Sample ID | R1 | R2 | R3 | n | *C. albicans* | *A. niger* | *A. clavatus* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | **MTCC227** | **MTCC282** | **MTCC1323** |
| 1 | MT-01 | Cl | Et | - | 1 | 125 | 1000 | 500 |
| 2 | MT-02 | Cl | CH2CF3 | - | 1 | 150 | 1000 | 500 |
| 3 | MT-03 | Cl | Et | - | 2 | 500 | 1000 | 1000 |
| 4 | MT-04 | Cl | Pr | - | 2 | 1000 | 1000 | 500 |
| 5 | MT-05 | CF3 | Et | - | 1 | 500 | >1000 | >1000 |
| 6 | MT-06 | CF3 | CH2CF3 | - | 1 | 500 | >1000 | >1000 |
| 7 | MT-07 | CF3 | Et | - | 2 | 125 | 100 | 100 |
| 8 | MT-08 | CF3 | Pr | - | 2 | >1000 | 500 | 500 |
| 9 | MT-09 | Cl | Et | Me | 1 | 500 | 500 | 1000 |
| 10 | MT-10 | Cl | CH2CF3 | Me | 1 | 1000 | 1000 | 1000 |
| 11 | MT-11 | Cl | Et | Me | 2 | >1000 | >1000 | >1000 |
| 12 | MT-12 | t-Bu | Et | Me | 2 | 1000 | 1000 | 1000 |
| **Reference Drugs:** | | | | | | | | |
| Nystatin | | | | | | 100 | 100 | 100 |
| Gresiofulvin | | | | | | 500 | 100 | 100 |

## V. CONCLUSION

In conclusion, the right hand and left hand region of our lead MTCC inhibitor structure appears tobe quite tolerant to structural modifications. Few derivatives showed good antibacterial and antifungal activity, but less as compared to the standard drugs. So, these types ofderivatives of Pyridine can serve as future therapeutic leads for the discovery of antimicrobial drugs. It can be concluded that this class of compounds certainly holds promise towards good active leads in medicinal chemistry. The results of our efforts to further optimize the biologicalprofile of this series of dual MTCC inhibitors will be forthcoming.

## ACKNOWLEDGEMENTS

The authors would like to thank to Dr. Dhanji P. Rajani and Mr. Kalpesh of Microcare Laboratory, Surat for conducting the antibacterial and antifungal activity.

## REFRENCES

[1]. Desai N C, Bhatt N B, Somani H C, & Bhatt K A, *Indian Journal of Chemistry*, 55B, **2016**, 94-101.
[2]. Moustafa M A, Gineinah M M, Nasr M N & Bayoumi W A, *Arch Pharm*, 337,**2004,** 427.
[3]. Andriole V T, *J Antimicrob Chemother*, 44, **1999**, 151.
[4]. Panwar H., Verma R. S., Srivastava V. K., Kumar A., *India J Chem* 45B, **2006**, 2099.
[5]. Abele E, Abele R, Dzenitis O, Lukevics, *E.Chem Heterocycl Compd* 39, **2003**, 3.
[6]. Skii N. M. P., Magedov I. V., Drozed V. N., *Chem Heterocycle Compd* 33, **1997**, 1475.
[7]. Panday V K, Mishra D & Shukla S, *Indian Drug* 31, **1994**, 532.
[8]. Poonam Khloya, Pawan Kumar, Arpana Mittal, Neeraj K Aggarwal, Pawan K Sharma, *Organic and Medicinal Chemistry;* 3:9, **2013**, 1-7.
[9]. Gowda F. E., Alaa A. M. Abdel Aziz, Omer A. Attef; *Bioorganic and Medicinal Chemistry*; 12. **2004,** 1845-1852.
[10]. Sanna, M. E.;Wahid, M. B.; Laila, I. I. Egypt J. Pharm. Sci. 1998, 39, 197.
[11]. Carla, M. S. M.;Carlos, M. R. S. A.;Carlos, R. R.; Eliezer, J. B. Journal of Molecular Structure (Theochem)2002, 579, 31.
[12]. Poreba, K.;Opolski, A.;Wietrzyk, J.; Kowalska, M. Arch Pharm (Weinheim) 2001, 334, 219.
[13]. Poreba, K.;Opolski, A.;Wietrzyk, J. Acta Pol. Pharm. 2002, 59, 215.

[14]. Bernardino, A. M. R.;Ferreira, V. F.;Fontoura, G. A. T.; Frugulhetti, I. C. P. P.;Lee, M. M.;Romeiro, G. A.; souza, M. C. B.;Sa ´, P. M. J. Braz. Chem. Soc. 1996, 7, 273.
[15]. Kuo, S. C.;Huang, L. J.;Nakamura, H. J. Med. Chem. 1984, 27, 539.
[16]. Arita, M.;Saito, T.; Sato, H.;Uehata, M.; Okuda, H. JP App. 91/255, 689; Chem. Abstr. 1993, 119, 95006u.
[17]. Sato, Y.;Shimogi, Y.;Kumakura, S.;Takagi, H. Ja pan, Kokai 75,151,896;Appl. 74,61,149; Chem. Abstr. 1976, 84, 164771.
[18]. Veˇra Klimesˇova´, Martin Svoboda , Karel Waisser , Milan Pour, Jarmila Kaustova´, *II Farmaco,* 54, **1999**, 666-672.
[19]. V. Klimesˇova´, M. Otcˇena´sˇek, K. Waisser, Potential antifungal agents. Synthesis and activity of 2-alkylthiopyridine-4-carbothioamides, Eur. J. Med. Chem. 31 (1996) 389–395.
[20]. V. Klimesˇova´, M. Svoboda, K. Waisser, M. Macha´cˇek, V. Buchta, Z& . Odlerova´, Research on antifungal and antimycobacterial agents. Synthesis and activity of 4-alkylthiopyridine-2-carbothioamides, Arch. Pharm. Pharm. Med. Chem. 329 (1996) 438–442.
[21]. V. Klimesˇova´, M. Svoboda, K. Waisser, M. Pour, J. Kaustova´, Synthesis and antimicrobial activity of new 4-(benzylsulfanyl)-pyridine derivatives, Collect. Czech. Chem. Commun. 64 (1999) 417–434.
[22]. V. Klimesˇova´, M. Svoboda, K. Waisser, J. Kaustova´, V. Buchta, K. Kra´lova´, Synthesis of 2-benzylthiopyridine-4-carbothioamide derivatives and their antimycobacterial, antifungal and photosynthesis-inhibiting activity, Eur. J. Med. Chem. 34 (1999) 433–440.
[23]. Clinical microbiology procedure handbook, vol. II, chapter 5 pages no 5.0.1, Henry d. Isenberg, 2nd edition.
[24]. Desai N C, Shihora P N & Moradia D L, "Synthesis and characterization of new quinazolines as potential antimicrobial agent" *Indian journal of chemistry, Sec-b*, 46b, **2007**, 550-553.
[25]. Shadomy, S. In Manual of Clinical Microbiology; Albert, B. Ed.; ASM Press: Washington, DC, **1991**, 1173.
[26]. V. M. Barot, B. G. Rathod, *Asian Journal of Biochemical and Pharmaceutical Research*, Issue 1(3), **2013**, 80-85.
[27]. Donal R. Stalons & Clyde Thornsberry, "Broth-dilution method for determining the antibiotic susceptibility of anaerobic bacteria", *Antimicrobial Agents & Chemotherapy*, 7(1), **1975**, 15-21.

B.P. Yadav. "Synthesis of some novel Pyridine derivatives as potent MTCC inhibitors and compared to available antimicrobial drugs." IOSR Journal of Pharmacy (IOSRPHR), vol. 9, no. 7, 2019, pp. 11-15