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Synthesis of Some New 2-Amino/Methoxy-4-(3-Methoxy-4-((3-Methyl-4-(2,2,2-Trifluoroethoxy) Pyridin-2-Yl) Methoxy) Phenyl)-6-Arylnicotinonitrile Derivative and Its Biological Activity

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Abstract: A series of novel 2-Amino-3-cyanopyridine derivatives **2a-l** and 2-Methoxy-3-cyanopyridine derivatives **3a-l** have been synthesized as potential antibacterial agents. The 2-Amino-3-cyanopyridine derivatives **2a-l** have been synthesized by reaction of various Chalcones **1a-l** with malononitrile and ammonium acetate in Ethanol. The 2-Methoxy-3-cyanopyridine **3a-l** were prepared by the reaction of Chalcone with malononitrile and sodium methoxide in Methanol. The structures of the new compounds were established on the basis of ¹H-NMR, Mass, IR and elemental analysis data. All the newly synthesized compounds were screened for their antibacterial activity against *E. coli*, *S. typhi* (Gram-negative bacteria), *S. aureus*, *M. luteus* (Gram-positive bacteria) and antifungal activity against *Candida albicans* (Fungi).

Keywords : 2-Amino-3-cyanopyridine, 2-Methoxy-3-cyanopyridine, Antimicrobial activity.

I. INTRODUCTION

Heterocyclic rings containing nitrogen atom plays important roles as the scaffolds of bioactive substances.[1] The pyridine moiety is of great importance to chemists and biologists as it is found in a large variety of naturally occurring compounds, pharmaceuticals and functional materials [2]. Substituted 3-Cyanopyridines were found to have anti-tubercular [3], antimicrobial [4], anticancer [5], A2A adenosine receptor antagonist [6], anti-inflammatory [7], antihistaminic [8]. The importance of cyanopyridines in organic synthesis has increased over the past few decades because they are among the most versatile organic synthetic intermediates [9,10]. As a result, several methods describing the synthesis of functionalized pyridines are available in the literature [11,12].

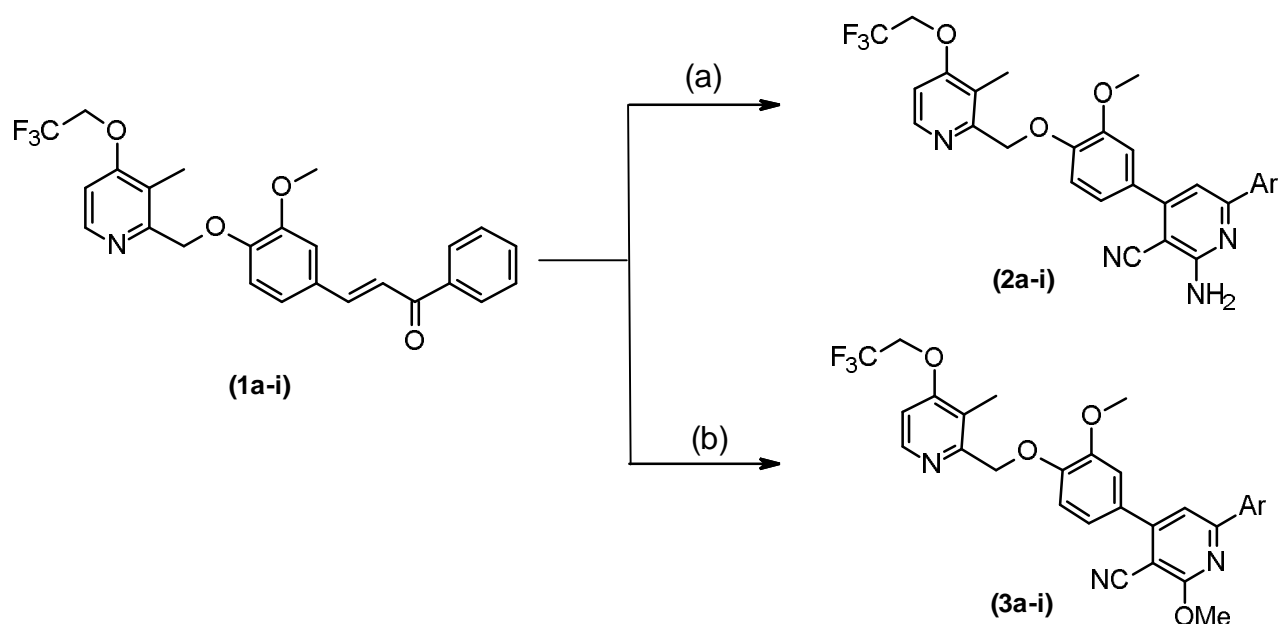
Recently, vanillin containing aryl substitution reported as anticancer [13], antimitotic and apoptotic [14] and antimalarial [15] activities. Considering importance of vanillin and 3-cyanopyridines in medicinal chemistry, we prompted to incorporate these moieties in ongoing research program [16]. In this article, we have reported synthesis of 2-Amino-3-cyanopyridine **2a-l** and 2-Methoxy-3-cyanopyridine derivatives **3a-l** and study of biological activities.

II. RESULTS AND DISCUSSION

A. Chemistry

The synthetic route adopted to obtain the 3-Cyanopyridine derivatives **2a-l** and **3a-l** is shown in Scheme 1. The 2-Amino-3-Cyanopyridine derivative **2a-l** were prepared from Chalcones **1a-l** by refluxing with malononitrile and ammonium acetate in Ethanol. The isolated product was washed with 1,4-dioxane to get 2-Amino-3-Cyanopyridine derivatives in 51-70% yield. The 2-Methoxy-3-Cyanopyridine derivatives **3a-l** were prepared from Chalcones **1a-l** by refluxing with malononitrile and sodium methoxide in Methanol for 16hrs. The isolated product was washed with 1,4-dioxane to get 2-Methoxy-3-Cyanopyridine in 53-75% yield. The structures of all newly synthesized compounds were assigned on the basis of spectral data such as IR, ¹H-NMR, Mass and elemental analysis. Starting material Chalcone (**1a-l**) were synthesized as per procedure reported earlier [16].

1) *Scheme 1* : The Synthetic scheme for the preparation of compounds **2a-l** and **3a-l**.



Reagents and conditions: (a) Malononitrile, NH_4OAc , Ethanol, Reflux, 16hrs

(b) Malononitrile, NaOMe , Methanol, Reflux, 16hrs

The structural assignment of the title compounds **2a-l** and **3a-l** have been made on the basis of $^1\text{H-NMR}$, Mass, elemental analysis and IR spectral studies which were in full agreement with the proposed structures. IR spectrum of compound **2a** reveals absorption band in the region 3402 cm^{-1} corresponding to amine (C-N) stretching and 2225 cm^{-1} due to -CN. In $^1\text{H-NMR}$ spectra of **2a**, the two CH_3 protons absorbed as a singlet at δ 2.33 and methoxy group at δ 3.82 and broad singlet at δ 5.95 due to amine for 2H proton and rest of the aromatic proton appear at their respective position. Mass spectrum of 2-Amino-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-phenyl nicotinonitrile showed (M^+) peak at 521.3 which support the formation of product. The structure of **3a** is interpreted from spectroscopic data. The IR spectrum of **3a** showed a characteristic absorption band at 2234 cm^{-1} due to -CN stretching and 1568 cm^{-1} due to vinyl (C=C) stretching. $^1\text{H-NMR}$ spectrum of **3a** reveals the presence of methyl group at δ 2.22 and two methoxy group at δ 3.83 and δ 4.13 respectively. Mass spectrum of 2-Methoxy-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-phenyl nicotinonitrile showed (M^+) peak at 536.2.

B. Experimental

All the melting points were determined on electro-thermal apparatus using open capillaries and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5mm thickness, and spots were located by iodine and UV (254nm). The IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GCMS-QP2010 model using Direct Injection Probe technique. $^1\text{H-NMR}$ was determined in $\text{CDCl}_3/\text{DMSO}-d_6$ solution on a Bruker AC 400MHz spectrometer using TMS as internal standard and coupling constants (J) are expressed in Hertz (Hz). Elemental analysis of the all the synthesized compounds were carried out on Elementar Vario EL III Carlo Erba 1108 model, and the results are in agreements with the structures assigned. All the reagents were purchased from Rankem (New Delhi, India) and Sigma-Aldrich (New Delhi, India) and are used without further purification.

General procedure for synthesis of 2-Amino-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-arylnicotinonitrile (**2a-l**). A mixture of (E)-1-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (0.5gm, 1.09 mol), malononitrile (0.086g, 1.31 mol) and ammonium acetate (0.25g, 3.28 mol) in ethanol (10 ml) was refluxed for 16 hrs., The content was poured in to crushed ice. The solid was obtained filtered, washed with water and crystallised from 1,4-dioxane. The physical and spectral data of compound are as following.

2-Amino-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-phenyl nicotinonitrile. (**2a**) Yield

61% (off white solid); m.p 161-163 °C; IR (KBr, cm⁻¹): 3402 (-NH₂), 2225 (-CN), 1559 (C=C); ¹H-NMR (DMSO, d ppm): 8.32-8.36 (m, 1H, aromatic), 8.01-8.05 (m, 2H, aromatic), 7.19-7.29 (m, 3H, aromatic) 7.12-7.15 (m, 4H, aromatic), 6.88 (s, 1H, aromatic), 5.95 (bs, 2H, -NH₂), 5.23 (s, 2H), 4.88-4.94 (q, 2H, -O-CH₂-CF₃), 3.82 (s, 3H, -OCH₃), 2.33 (s, 3H, -CH₃); MS : (m/z) 521.3 (M⁺); Anal. Calcd. for C₂₈H₂₃F₃N₄O₃: C: 64.64 %, H: 4.45%, N: 10.48%; Found: C: 64.72%, H: 4.52%, N: 10.54%.

General procedure for synthesis of 2-Methoxy-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-aryl nicotinonitrile (3a-l). To a solution of (E)-1-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one (0.5gm, 1.09 mol), malononitrile (0.086gm, 1.31 mol) and sodium methoxide (0.06gm, 1.09mmol) in methanol (10ml). The content was heated under reflux with stirring for 16 hrs. The reaction mixture was diluted with water and extracted with chloroform. The excess solvent was distilled out and product was crystallized from ethanol. 2-Methoxy-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-phenyl nicotinonitrile (3a) : Yield 63% (off white solid); m.p 140-142 °C; IR (KBr, cm⁻¹): 2234 (-CN), 1568 (C=C); ¹H-NMR (DMSO, d ppm): 8.26-8.36 (m, 2H, aromatic), 7.95-7.97 (m, 2H, aromatic), 7.48-7.54 (m, 2H, aromatic) 7.28-7.36 (m, 2H, aromatic), 7.11-7.16 (m, 1H, aromatic), 6.89-6.96 (d, 1H, aromatic), 5.26 (s, 2H), 4.86-4.94 (q, 2H, -O-CH₂-CF₃), 4.13 (s, 3H, -OCH₃), 3.83 (s, 3H, -OCH₃), 2.22 (s, 3H, -CH₃); MS : (m/z) 536.2 (M⁺); Anal. Calcd. for C₂₉H₂₄F₃N₃O₄: C: 65.04 %, H: 4.52%, N: 7.85%; Found: C: 65.15%, H: 4.45%, N: 7.79%.

Similarly other 3-cyanopyridine were synthesized and data were shown in table 1.

| Sr No | R | Molecular Formula | M.W | M.P °C | Yield % | % of Nitrogen | |
|-------|---|--|-------|--------|---------|---------------|--------|
| | | | | | | Calcd. | Found. |
| 2a | C ₆ H ₅ - | C ₂₈ H ₂₃ F ₃ N ₄ O ₃ | 520.3 | 161 | 65 | 10.76 | 10.82 |
| 2b | 4-CH ₃ -C ₆ H ₄ - | C ₂₉ H ₂₅ F ₃ N ₄ O ₃ | 534.3 | 125 | 68 | 10.48 | 10.54 |
| 2c | 4-OCH ₃ -C ₆ H ₄ - | C ₂₉ H ₂₅ F ₃ N ₄ O ₄ | 550.2 | 165 | 61 | 10.18 | 10.25 |
| 2d | 4-OH-C ₆ H ₄ - | C ₂₈ H ₂₃ F ₃ N ₄ O ₄ | 536.4 | 214 | 54 | 10.44 | 10.56 |
| 2e | 3-Br-C ₆ H ₄ - | C ₂₈ H ₂₂ BrF ₃ N ₄ O ₃ | 599.3 | 194 | 59 | 9.35 | 9.48 |
| 2f | 4-Br-C ₆ H ₄ - | C ₂₈ H ₂₂ BrF ₃ N ₄ O ₃ | 599.3 | 183 | 63 | 9.35 | 9.40 |
| 2g | 3-Cl-C ₆ H ₄ - | C ₂₈ H ₂₂ ClF ₃ N ₄ O ₃ | 555.1 | 183 | 69 | 10.10 | 10.18 |
| 2h | 4-Cl-C ₆ H ₄ - | C ₂₈ H ₂₂ ClF ₃ N ₄ O ₃ | 555.1 | 179 | 71 | 10.10 | 10.15 |
| 2i | 3-NO ₂ -C ₆ H ₄ - | C ₂₈ H ₂₂ F ₃ N ₅ O ₅ | 565.3 | 199 | 50 | 12.38 | 12.47 |
| 2j | 2-Thiophenyl- | C ₂₆ H ₂₁ F ₃ N ₄ O ₃ S | 526.2 | 174 | 53 | 10.64 | 10.73 |
| 2k | 2-Furanyl- | C ₂₆ H ₂₁ F ₃ N ₄ O ₄ | 510.3 | 170 | 51 | 10.98 | 10.89 |
| 2l | 2-Pyridinyl | C ₂₇ H ₂₂ F ₃ N ₅ O ₃ | 521.3 | 149 | 59 | 13.43 | 13.52 |
| 3a | C ₆ H ₅ - | C ₂₉ H ₂₄ F ₃ N ₃ O ₄ | 535.3 | 140 | 61 | 7.85 | 7.79 |
| 3b | 4-CH ₃ -C ₆ H ₄ - | C ₃₀ H ₂₆ F ₃ N ₃ O ₄ | 549.3 | 105 | 70 | 7.65 | 7.72 |
| 3c | 4-OCH ₃ -C ₆ H ₄ - | C ₃₀ H ₂₆ F ₃ N ₃ O ₅ | 565.2 | 145 | 75 | 7.43 | 7.51 |
| 3d | 4-OH-C ₆ H ₄ - | C ₂₉ H ₂₄ F ₃ N ₃ O ₅ | 551.4 | 202 | 58 | 7.62 | 7.70 |
| 3e | 3-Br-C ₆ H ₄ - | C ₂₉ H ₂₃ BrF ₃ N ₃ O ₄ | 614.3 | 169 | 66 | 6.84 | 6.92 |
| 3f | 4-Br-C ₆ H ₄ - | C ₂₉ H ₂₃ BrF ₃ N ₃ O ₄ | 614.3 | 179 | 63 | 6.84 | 6.92 |
| 3g | 3-Cl-C ₆ H ₄ - | C ₂₉ H ₂₃ ClF ₃ N ₃ O ₄ | 570.1 | 153 | 58 | 7.37 | 7.31 |

| | | | | | | | |
|----|--|--|-------|-----|----|-------|-------|
| 3h | 4-Cl-C ₆ H ₄ - | C ₂₉ H ₂₃ ClF ₃ N ₃ O ₄ | 570.1 | 169 | 69 | 7.37 | 7.46 |
| 3i | 3-NO ₂ -C ₆ H ₄ - | C ₂₉ H ₂₃ F ₃ N ₄ O ₆ | 580.3 | 173 | 53 | 9.65 | 9.75 |
| 3j | 2-Thiophenyl- | C ₂₇ H ₂₂ F ₃ N ₃ O ₄ S | 541.2 | 158 | 65 | 7.76 | 7.84 |
| 3k | 2-Furanyl- | C ₂₇ H ₂₂ F ₃ N ₃ O ₅ | 525.3 | 133 | 61 | 8.00 | 8.10 |
| 3l | 2-Pyridinyl | C ₂₈ H ₂₃ F ₃ N ₄ O ₄ | 536.3 | 148 | 71 | 10.44 | 10.53 |

C. Antibacterial and antifungal activity

The newly synthesized compounds were screened for their antibacterial activity against Gram-positive (*S. aureus* ATCC 6538, *M. luteus* ATCC 9345), Gram negative (*E. coli* ATCC 4230, *S. typhi* ATCC 14028) bacteria, as described by the guidelines in NCCLS-approved standard document M7-A4, using the micro dilution broth procedure [17]. Ampicillin trihydrate was used as the reference antibacterial agent. The antifungal activities of the newly synthesized chemical compounds were tested against yeast strain (*C. albicans* ATCC 14053) according to the guidelines in NCCLS-approved standard document M27-A2, using the micro dilution broth procedure [18]. Fluconazole was used as the reference antifungal agent. The solutions of test compounds and reference drug were prepared by dissolving in DMSO at a concentration of 2560 µg/mL. The 2-fold dilutions of the compounds and the reference drug were prepared (1280, 640, 320, 160, 80, 40, 20, 10 µg/mL). Antibacterial activities of the newly synthesized chemical compounds were performed in Mueller-Hinton broth medium at a pH of 7.2 with an inoculum of $(1-2) \times 10^3$ cells/mL by the spectrophotometric method, and an aliquot of 100 µL solution was added to each tube of serial dilution. The chemical compounds-broth medium serial tube dilutions inoculated with each bacterium were incubated on a rotary shaker at 37°C for 18hrs at 150 rpm. The minimum inhibitory concentration (MIC) of each chemical compound was recorded as the lowest concentration of each chemical compound in the tubes with no growth (i.e., no turbidity) of inoculated bacteria. Minimum inhibitory concentration (MIC, µg/mL) was measured and compared with control; the MIC values of the compound screened are given in **Table 2**.

| Id | Ar | Antibacterial Activity | | | | Antifungal Activity |
|----|---|------------------------|----------|--------|---------|---------------------|
| | | S.aureus | M.luteus | E.coli | S.typhi | C.albicans |
| 2a | C ₆ H ₅ - | 160 | 160 | 80 | 80 | 160 |
| 2b | 4-CH ₃ -C ₆ H ₄ - | 160 | 80 | 160 | 80 | 160 |
| 2c | 4-OCH ₃ -C ₆ H ₄ - | 80 | 80 | 160 | 80 | 80 |
| 2d | 4-OH-C ₆ H ₄ - | 40 | 20 | 80 | 80 | 80 |
| 2e | 4-Br-C ₆ H ₄ - | 40 | 80 | 40 | 20 | 160 |
| 2f | 4-Cl-C ₆ H ₄ - | 40 | 40 | 80 | 40 | 80 |
| 2g | 3-Cl-C ₆ H ₄ - | 20 | 20 | 80 | 40 | 80 |
| 2h | 3-Br-C ₆ H ₄ - | 80 | 80 | 40 | 20 | 160 |
| 2i | 3-NO ₂ -C ₆ H ₄ - | 20 | 40 | 80 | 40 | 80 |
| 2j | 2-Thiophenyl | 40 | 40 | 40 | 20 | 160 |
| 2k | 2-Furanyl | 80 | 40 | 80 | 40 | 160 |
| 2l | 2-Pyridinyl | 20 | 20 | 80 | 40 | 80 |
| 3a | C ₆ H ₅ - | 160 | 80 | 80 | 160 | 160 |
| 3b | 4-CH ₃ -C ₆ H ₄ - | 160 | 160 | 80 | 80 | 160 |
| 3c | 4-OCH ₃ -C ₆ H ₄ - | 80 | 80 | 160 | 80 | 80 |

| | | | | | | |
|----|--|----|----|----|----|-----|
| 3d | 4-OH-C ₆ H ₄ - | 20 | 20 | 80 | 40 | 80 |
| 3e | 4-Br-C ₆ H ₄ - | 20 | 20 | 80 | 80 | 160 |
| 3f | 4-Cl-C ₆ H ₄ - | 40 | 40 | 40 | 20 | 160 |
| 3g | 3-Cl-C ₆ H ₄ - | 40 | 20 | 80 | 80 | 80 |
| 3h | 3-Br-C ₆ H ₄ - | 80 | 80 | 80 | 40 | 80 |
| 3i | 3-NO ₂ -C ₆ H ₄ - | 40 | 80 | 40 | 20 | 160 |
| 3j | 2-Thiophenyl | 40 | 40 | 80 | 40 | 160 |
| 3k | 2-Furanyl | 20 | 40 | 40 | 20 | 160 |
| 3l | 2-Pyridinyl | 20 | 20 | 80 | 40 | 80 |
| | Ampiciline | 20 | 20 | 40 | 20 | - |
| | Fluconazole | - | - | - | - | 10 |

From the result of biological evaluation, it has been observed that the compounds exhibited interesting biological activity, however with a degree of variation. Most of the compounds tested were found to have comparable antibacterial and exhibit low antifungal activity. From the Table 1, it can be observed that compound 5g, 5l, 6d, 6e, 6l shows comparable activity against *S. aureus*, *M. luteus* and 2f, 2e, 2j, 3f, 3i, 3k shows comparable activity against *E. coli*, *S. thyphi*. The compounds 2d, 2j, 3f, 3g, 3k shows moderate activity against *S. aureus*, *M. luteus*. The compounds 2f, 2g, 2k, 2l, 3d, 3h, 3l were moderate active against *E. coli*, *S. thyphi*. and 5i, 6j shows moderate activity against *S. aureus*, *M. luteus*, *E. coli*. and *S. thyphi*. while all the synthesized compounds shows low antifungal activity against *C. albicans*. So result of all preliminary study indicated that the substituted 2-Amino-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-arylnicotinonitrile and 2-Methoxy-4-(3-methoxy-4-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)phenyl)-6-arylnicotinonitrile moiety represent a new class of pharmacophore for broad spectrum antibacterial activity.

III. CONCLUSION

In summary, we have synthesized a series of vanillin incorporated novel 3-Cyanopyridines derivatives. All the newly synthesized compounds were confirmed with spectroscopic data like ¹H-NMR, Mass, IR Spectra, elemental analysis and evaluated antibacterial and antifungal activity. The antibacterial study shows that 3-Cyanopyridines derivatives showed moderate activity with MICs between 20 and 80 µg/mL. The 3-Cyanopyridines showed low antifungal activity. The importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria, which could be helpful in designing more potent antibacterial agent for therapeutic use.

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