



Synthesis, Characterization And Biological Studies of 1,6-Naphthyridine Derivatives

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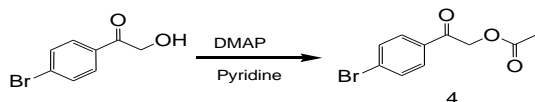
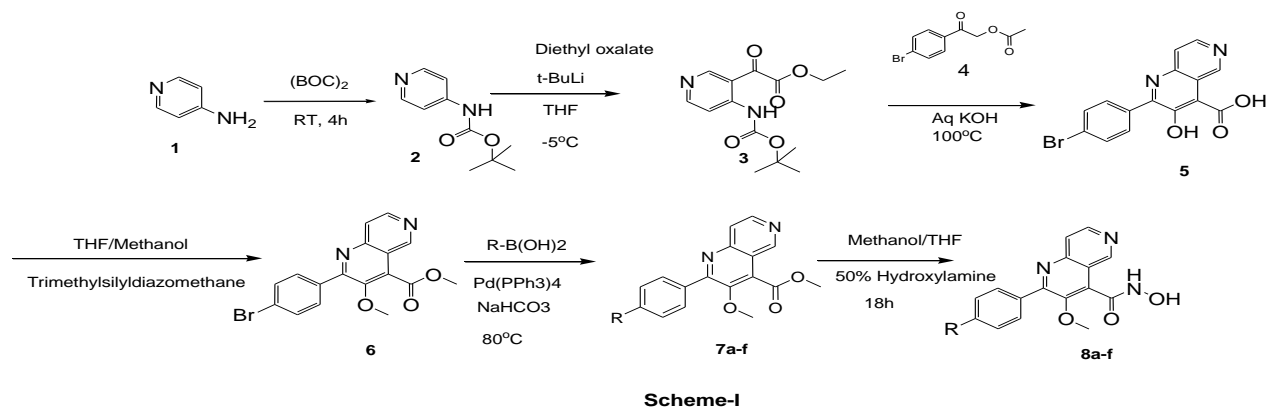
ABSTRACT

An effective way for the synthesis of 1,6 naphthyridines (7a-f , 8a-f) has been arrived from 4-amino pyridine and 2-(4-bromophenyl)-2-oxoethyl acetate(4) which underwent alkylation on substituted 4-amino pyridine to give the target compound(8a-f). All the synthesized compounds have been biologically screened for antibacterial and anti fungal activities.

Keywords: 6-naphthyridines, antibacterial activity, antifungal activity, alkylations.

INTRODUCTION

The synthesis of various derivatives of the heterocyclic compounds including the 1,6-naphthyridine moiety has been reported in relation with their pharmaceutical activity[1-7]. Several 1,6-naphthyridine have general antibacterial activity[8] and curative power in cardiac insufficiencies and infarction[9]. Many 1,6-naphthyridine compounds display excellent anticonvulsant activity[10], and a novel class of macrocyclic 1,6-naphthyridine are anti human cytomegalovirus[HCMV] inhibitors[11]. Derivatives bearing other substituents can exhibit potent antitumour activity, viz., topoisomerase I-targetting anticancer activity[12], and act as potent inhibitors of spleen tyrosine kinase(SYK) [13]. Also they have been used as antiviral agents inhibiting both the strand transfer process of HIV-I integrase and the viral replicaton in cells[14,15]. Prompted by the important medicinal applications of naphthyridines, herein we describe the synthesis and reactions of new 1,6- naphthyridine derivatives.

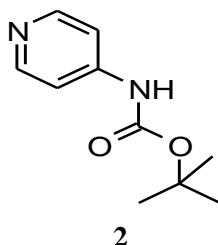


R	Phenyl boronic acid	4-Methoxy phenyl boronic acid	4-Methyl phenyl boronic acid	Pyridine-3-boronic acid	4-Propyl phenyl boronic acid	3-Methoxy phenyl boronic acid
7	a	b	c	d	e	f
8	a	b	c	d	e	f

MATERIALS AND METHODS

Thin layer chromatography was used to access the reaction and purity of products. Melting points were determined on a Boetius Microheating Table and Mettler-FP5 apparatus and are uncorrected. IR spectra were recorded in Shimadzu-8201-FT instrument in KBr pellets and only noteworthy absorption levels (reciprocal centimeter) are listed. ¹H NMR spectra were recorded on a AMX-400MHZ spectrometer in CDCl₃ Solution (chemical shifts in δ, ppm relative to TMS). Satisfactory microanalysis were obtained on carlo Erba 1106 and perkin Elmer models 240 CHN analyzer. Mass spectra were recorded on a Jeol-300 mass spectrometer.

Synthesis of tert-butyl pyridin-4-ylcarbamate (2):



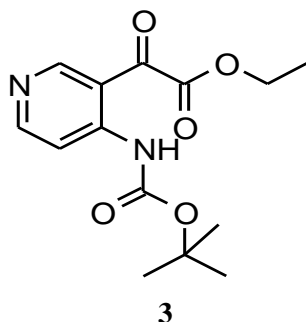
To a solution of 4-amino pyridine (5.0 g, 53.12 mmol) in THF (25 mL) at 0°C was added ditertiarybutyldicarbonate (15.20 mL, 63.74mmol) and stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the residue was triturated with n-hexane to get **tert-butyl pyridin-4-ylcarbamate** (8.6 g, 84.0%) as off-white solid.

LC-MS: $[M+1]^+$, 195.21

Mass: calculated for $C_{10}H_{14}N_2O_2$, 194.24.

1H NMR (400 MHz, δ ppm, $CDCl_3$): δ 8.44 (d, 2H), 7.31 (d, 2H), 6.88 (sb, 1H), 1.53 (s, 9H).

Synthesis of ethyl {4-[(*tert*-butoxycarbonyl) amino] pyridin-3-yl} (oxo)acetate(3):



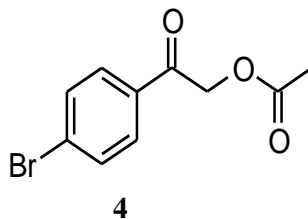
To a solution of **tert-butyl pyridin-4-ylcarbamate** (5.0 g, 25.75 mmol) in THF (50 ml) at -5 °C was added *t*-BuLi (16% in n-Hexane) (30.87 mL, 77.27 mmol) dropwise over a period of 30 min and stirred at the same temperature for 1.5 h and added diethyl oxalate (10.5 mL, 77.27 mmol) for 15 min. The reaction mixture was warm to room temperature and stirred for 2 h, quenched with cold water (20 mL) and evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethylacetate (50 mL x 2). The combined organic layer was washed with water (20 mL) and brine solution (20 mL), dried over anhydrous Mg_2SO_4 and evaporated the solvent to get crude compound. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 25% ethylacetate in pet ether as mobile phase to obtain **ethyl {4-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}(oxo)acetate** (3.2 g, 42.6%) as reddish brown oily liquid.

LC-MS: $[M+1]^+$ 295.8.

Mass: calculated for $C_{14}H_{18}N_2O_5$, 294.31.

1H NMR (400 MHz, δ ppm, $CDCl_3$): δ 10.47 (sb, 1H), 8.86 (s, 1H), 8.60 (d, 1H), 8.42 (d, 1H) 4.49 (q, 2H), 1.54 (s, 9H), 1.45 (t, 3H).

Synthesis of 2-(4-bromophenyl)-2-oxoethyl acetate (4):



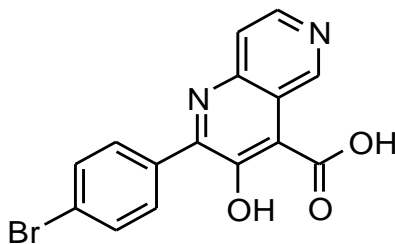
To a solution of 1-(4-Bromo-phenyl)-2-hydroxy-ethanone (4.0 g, 18.6 mmol) in dichloromethane (40 ml) at 0°C was added DMAP (0.22 g, 1.86 mmol), acetic anhydride (1.05 mL, 18.6 mmol) followed by pyridine (1.67 ml, 29.46 mmol). The reaction mixture was warm to room temperature and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and diluted with cold water (25 mL) and separated the organic layer. The aq. layer was extracted with dichloromethane (25 mL x 2) and the combined organic layer was washed with brine (25 mL), dried over anhydrous Mg_2SO_4 and evaporated the solvent to get crude compound. The crude compound was triturated with n-pentane and filtered to obtain **2-(4-bromophenyl)-2-oxoethyl acetate** (3.2 g, 68%) as white crystalline solid.

LC-MS: $[M, M-2]^+$ 255.0, 257.0.

Mass: calculated for C₁₀H₉BrO₃, 257.09.

¹H NMR (400 MHz, δ ppm, CDCl₃): δ 7.78 (d, 2H), 7.66 (d, 2H), 5.28 (s, 2H), 2.23 (s, 3H).

Synthesis of 2-(4-bromophenyl)-3-hydroxy-1,6-naphthyridine-4-carboxylic acid(5):



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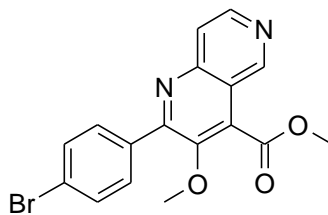
A mixture of ethyl {4-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}(oxo)acetate (2.0 g, 6.80 mmol) in 6M aq.KOH solution (10.0 mL) was heated at 100°C for 1 h and added a solution of 2-(4-bromophenyl)-2-oxoethyl acetate (2.09 g, 8.16mmol) in ethanol at the same temperature, dropwise carefully over a period of 30 min. After completion of addition the reaction mixture was stirred at the same temperature for 5 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and acidified with 2.0 M aq.HCl solution to pH -2.0 and filtered the precipitated solid, washed with water and dried under vacuum to obtain 2-(4-bromophenyl)-3-hydroxy-1,6-naphthyridine-4-carboxylic acid (1.8 g, 78.2%) as yellow solid.

Observed LC-MS: [M+2]⁺ 347.25.

Mass: calculated for C₁₅H₉N₂BrO₃, 345.15.

¹H NMR (400 MHz, δ ppm, DMSO-d₆): δ 10.61 (sb, 1H), 8.50 (d, 1H), 8.35 (d, 2H), 8.14 (d, 1H) 7.75 (d, 2H) 3.39 (sb, 1H).

Synthesis of methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate(6):



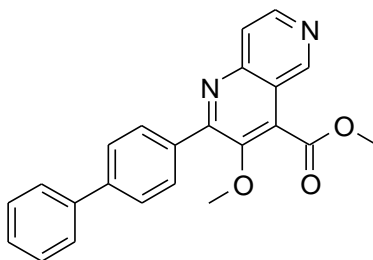
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To a suspension of 2-(4-bromophenyl)-3-hydroxy-1,6-naphthyridine-4-carboxylic acid (5.0 g, 14.49m mol) in 50 ml THF/ Methanol (1:1) at 0°C was added trimethylsilyl diazomethane (2.0 M solution in THF) (21.73 mL, 43.47 mmol) for 15 min and stirred at room temperature for 4 h. The excess diazomethane was quenched with acetic acid and the solvent was removed under reduced pressure to get crude product. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 20% ethylacetate in pet ether as mobile phase to get methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate (1.2 g, 22.2%) as yellowish brown solid.

Observed LC-MS: [M+2]⁺ 375.21.

Mass: calculated for C₁₇H₁₃N₂O₃Br, 373.21.

¹H NMR (400 MHz, δ ppm, CDCl₃): δ 9.22 (d, 1H), 8.76 (d, 1H), 7.98 (d, 2H), 7.96 (d, 1H), 7.68 (d, 2H), 4.14 (s, 3H) 3.66 (s, 3H).

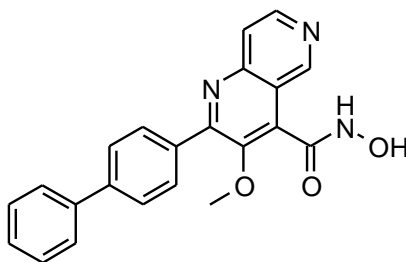
Synthesis of methyl 2-(biphenyl-4-yl)-3-methoxy-1,6-naphthyridine-4-carboxylate (7a):**7a**

To an argon purged solution of **methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate** (0.25 g, 0.67 mmol) and phenylboronic acid (0.08 g, 0.67 mmol) in 10 mL of 1, 2-dimethoxyethane was added Pd (PPh₃)₄ (0.038 g, 0.03 mmol) at room temperature and the reaction mixture was purged with argon for 10 min. NaHCO₃ (0.11 g, 1.34mmol) dissolved in 3.0 mL of water and again purged argon for 15 min. The reaction mixture was heated under argon atmosphere at 80°C for 4 h. The solvent was evaporated under reduced pressure and the residue was diluted with water (20 mL) and extracted with ethylacetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Mg₂SO₄ and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 12% ethylacetate in chloroform as mobile phase to obtain **methyl 2-(biphenyl-4-yl)-3-methoxy-1,6-naphthyridine-4-carboxylate** (0.125 g, 52.0%) as brown solid.

Observed LC-MS: [M+1]⁺ 371.29.

Mass: calculated for C₂₃H₁₈N₂O₃ 370.41.

¹H NMR (400 MHz, δ ppm, CDCl₃): δ 9.45 (s, 1H), 8.85 (d, 1H), 8.18-8.12 (m, 4H), 8.05 (d, 1H) 7.78 (d, 2H) 7.69 (d, 2H) 7.49-7.40 (m, 8H) 4.10 (s, 3H) 3.72 (s, 3H).

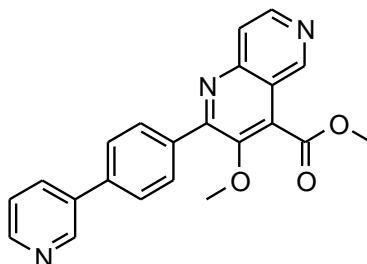
Synthesis of 2-(biphenyl-4-yl)-N-hydroxy-3-methoxy-1,6-naphthyridine-4-carboxamide(8a):**8a**

To a solution of **methyl 2-(biphenyl-4-yl)-3-methoxy-1,6-naphthyridine-4-carboxylate** (0.12 g, 0.32 mmol) in methanol /THF (1:1) was added aqueous 50% hydroxylamine (1.2 mL) followed by catalytic amount of KCN (~1 mg) and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was quenched with aqueous 10% citric acid solution (~2 mL) and stirred for 15 min, diluted with water (10 mL) and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed brine solution (10 mL), dried over Mg₂SO₄ and evaporated the solvent under reduced pressure to get crude compound. The crude compound was purified by preparative HPLC to obtain **2-(biphenyl-4-yl)-N-hydroxy-3-methoxy-1,6-naphthyridine-4-carboxamide** (20 mg, 16%) as pale yellow solid.

Observed LC-MS: [M+1]⁺ 372.3.

Mass: calculated for C₂₂H₁₇N₃O₃, 371.40.

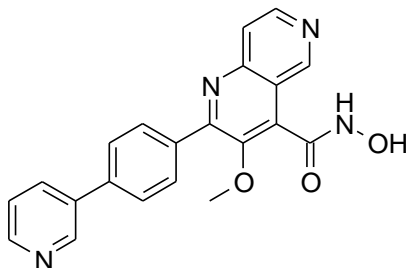
¹H NMR (400 MHz, δ ppm, DMSO-d₆): δ 11.41 (sb, 1H) 9.65 (sb, 1H) 9.18 (s, 1H), 8.75 (d, 1H), 8.13 (d, 2H), 7.99 (d, 2H), 7.89 (d, 2H) 7.79 (d, 2H), 7.52 (t, 2H), 7.43 (t, 1H) 3.73 (s, 3H).

Synthesis of methyl 3-methoxy-2-[4-(pyridin-3-yl)phenyl]-1,6-naphthyridine-4-carboxylate (7b):**7b**

To an argon purged solution of **methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate** (0.25 g, 0.67 mmol) and 3-pyridinyl boronic acid (0.08 g, 0.67 mmol) in 10 mL of 1, 2-dimethoxyethane was added Pd (PPh₃)₄ (0.038 g, 0.03 mmol) followed by NaHCO₃ (0.11 g, 1.34 mmol, in 3.0 mL of water). The reaction mixture was heated under nitrogen atmosphere at 80°C for 4 h. The solvent was evaporated to dryness and the residue was diluted with water (20 mL) and extracted with ethylacetate (50 mL x 2). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Mg₂SO₄ and evaporated to get the crude compound. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 25% ethylacetate in chloroform as mobile phase to obtain **methyl 3-methoxy-2-[4-(pyridin-3-yl)phenyl]-1,6-naphthyridine-4-carboxylate** (0.11 g, 45 %) as yellow brown solid.

Observed LC-MS: [M+1]⁺, 372.29.

Mass: calculated for C₂₂H₁₇N₃O₃, 371.

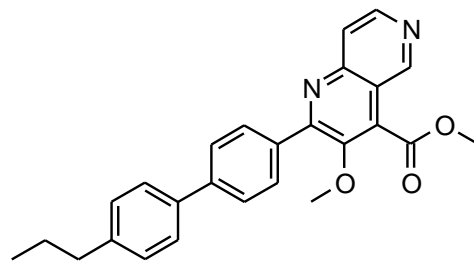
Synthesis of N-hydroxy-3-methoxy-2-[4-(pyridin-3-yl)phenyl]-1,6-naphthyridine-4-carboxamide(8b):**8b**

To a solution of **methyl 3-methoxy-2-[4-(pyridin-3-yl)phenyl]-1,6-naphthyridine-4-carboxylate** (0.1 g, 0.26 mmol) in 2 ml methanol/THF (1:1) was added aqueous 50% hydroxylamine (1.0 mL) followed by catalytic amount of KCN (~1 mg) and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was quenched with aqueous 10% citric acid solution (~2 mL) and stirred for 15 min, diluted with water (10 ml) and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Mg₂SO₄ and evaporated the solvent to get crude compound. The crude compound was purified by preparative HPLC to get **N-hydroxy-3-methoxy-2-[4-(pyridin-3-yl)phenyl]-1,6-naphthyridine-4-carboxamide** (20 mg, 20%) as pale yellow solid.

Observed LC-MS: [M-1]⁻ 371.32.

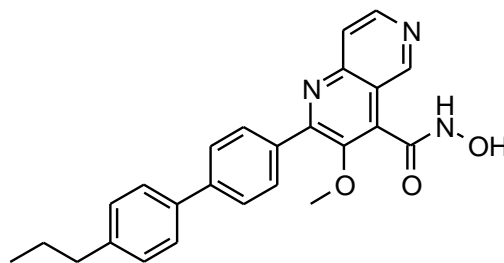
Mass: calculated for C₂₁H₁₆N₄O₃, 372.39.

¹H NMR (400 MHz, δ ppm, DMSO-d₆): δ 11.41 (sb, 1H) 9.64 (sb, 1H) 9.18 (s, 1H), 9.02 (d, 2H) 8.75 (d, 1H), 8.63 (d, 1H), 8.22 (d, 1H), 8.15 (d, 2H) 7.99-7.95 (m, 3H), 7.56-7.53 (m, 1H), 3.74 (s, 3H).

Synthesis of methyl 3-methoxy-2-(4'-propylbiphenyl-4-yl)-1,6-naphthyridine-4-carboxylate (7c):**7c**

To an argon purged solution of **methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate** (0.25 g, 0.67 mmol) and 4-propylphenylboronic acid (0.12 g, 0.73 mmol) in 10 mL of 1, 2-dimethoxyethane was added Pd (PPh₃)₄ (0.038 g, 0.03 mmol) at room temperature and the reaction mixture was purged with argon for 10 min. Then added NaHCO₃ (0.112 g, 1.340mmol) in 1.0 mL of water and the reaction mixture was again purged for 15 min. The reaction mixture was heated under nitrogen atmosphere at 80°C for 1.5 h. The solvent was evaporated to dryness under reduced pressure and the residue was diluted with water (25 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Mg₂SO₄ and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) and 20% ethyl acetate in pet ether as mobile phase to obtain **methyl 3-methoxy-2-(4'-propylbiphenyl-4-yl)-1,6-naphthyridine-4-carboxylate** (0.13 g) as brown solid.

¹H NMR (400 MHz, δ ppm DMSO-d₆): δ 9.23 (s, 1H), 8.77 (d, 1H), 8.16 (d, 2H) 7.97 (d, 1H), 7.77 (d, 2H), 7.61 (d, 2H), 7.31 (d, 2H), 4.15 (s, 3H), 3.69 (s, 3H), 2.67 (t, 3H), 1.74 (m, 2H), 0.99(t, 3H).

Synthesis of N-hydroxy-3-methoxy-2-(4'-propylbiphenyl-4-yl)-1,6-naphthyridine-4-carboxamide (8c):**8c**

To a solution of **methyl 3-methoxy-2-(4'-propylbiphenyl-4-yl)-1,6-naphthyridine-4-carboxylate** (0.12 g, 0.29 mmol) in 3 ml methanol/THF (1:1) was added aqueous 50% hydroxylamine (1.0 mL) followed by catalytic amount of KCN (~1 mg) and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was quenched with aqueous 10% citric acid solution (~2 mL) and stirred for 15 min, diluted with water (10 mL) and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine solution (10 mL), dried over Mg₂SO₄ and evaporated the solvent to get the crude compound. The crude compound was purified by preparative TLC to get **N-hydroxy-3-methoxy-2-(4'-propylbiphenyl-4-yl)-1,6-naphthyridine-4-carboxamide** (15 mg) as pale yellow solid .

LC-MS: [M+1]⁺ , 414.28.

Mass: calculated for C₂₅H₂₃N₃O₃, 413.48

¹H NMR (400 MHz, δ ppm, DMSO-d₆): δ 11.39 (sb, 1H), 9.64 (sb, 1H), 9.17 (s, 1H), 8.72 (d, 1H), 8.09 (d, 2H), 7.98 (d, 1H), 7.88 (d, 2H), 7.71 (d, 2H), 7.34 (d, 2H), 3.73 (s, 3H), 2.62 (m, 2H), 1.65 (m, 2H), 0.95 (t, 3H).

RESULTS AND DISCUSSION

4-amino pyridine was N-protected using BOC anhydride to afford N-Protected amino pyridine(2) which was confirmed by ^1H NMR technique where we can see the presence of tertiary butyl peak at 1.53 δ ppm and obtained with an yield of 84.0% as off white solid. Further the molecule was confirmed by LC-MS which shows ionization molecular ion peak at 195.21. To this solution of tert-butyl pyridin-4-ylcarbamate (2) in THF (50 ml) at -5°C was added *t*-BuLi (16% in n-Hexane) dropwise over a period of 30 min and stirred at the same temperature for 1.5 h in order to generate a carbanion which on further reacted with di ethyl oxalate to yield ethyl {4-[(*tert*-butoxycarbonyl) amino] pyridin-3-yl} (oxo)acetate (3). The product obtained was confirmed by ^1H NMR where a triplet corresponding to O-CH₂ protons was observed. Furthermore an LC-MS characterization shows a peak at $[\text{M}+1]^+$ 295.8 corresponding to our target product (3) of the stage. Compound 3 obtained was treated with 2-(4-bromophenyl)-2-oxoethyl acetate (4) in 6M aq.KOH solution which resulted to give 2-(4-bromophenyl)-3-hydroxy-1,6-naphthyridine-4-carboxylic acid (5). The reaction residue after rotoevaporation was diluted with water and acidified with 2.0 M aq.HCl solution to pH -2.0 and filtered the precipitated solid, washed with water and dried under vacuum to obtain 2-(4-bromophenyl)-3-hydroxy-1,6-naphthyridine-4-carboxylic acid (5) as yellow solid with an yield of 78.2%. The acid obtained was treated with trimethylsilyl diazomethane (2.0 M solution in THF) for 15 min and stirred at room temperature for 4 h. The excess diazomethane was quenched with acetic acid and the solvent was removed under reduced pressure to get crude product. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 20% ethylacetate in pet ether as mobile phase to get methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate as yellowish brown solid which corresponds to an yield of 22.2%. The compound(6) obtained was confirmed based on ^1H NMR and Mass spectral analysis. To the solution of methyl 2-(4-bromophenyl)-3-methoxy-1,6-naphthyridine-4-carboxylate (6) and phenylboronic acid in 10 mL of 1, 2-dimethoxyethane was added Pd (PPh₃)₄ (0.038 g, 0.03 mmol) at room temperature and the reaction mixture was purged with argon for 10 min. The reaction mixture was heated under argon atmosphere at 80°C for 4 h. Once coupling of the reaction was confirmed then the solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with ethylacetate. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 12% ethylacetate in chloroform as mobile phase to obtain methyl 2-(biphenyl-4-yl)-3-methoxy-1,6-naphthyridine-4-carboxylate (7a) as brown solid With an yield of 52.0%. The compound obtained was confirmed by Mass spectral analysis using LC-MS which is complying with the molecular weight of the desire product. To this solution of compound 7a in methanol / THF (1:1) was added aqueous 50% hydroxylamine (1.2 mL) followed by catalytic amount of KCN (~1 mg) and the resulting solution was stirred at room temperature for 18 h. TLC showed conversion of ester to hydroxyl amine derivative which was quenched with aqueous 10% citric acid solution, diluted with water (10 mL) and extracted with ethyl acetate. The combined organic layer was washed brine solution, dried over Mg₂SO₄ and evaporated the solvent under reduced pressure to get crude compound. The crude compound was purified by preparative HPLC to obtain 2-(biphenyl-4-yl)-*N*-hydroxy-3-methoxy-1,6-naphthyridine-4-carboxamide as pale yellow solid. The desired compound was confirmed by 1H NMR spectroscopy and further clarified by mass spectral analysis using LC-MS. (Observed LC-MS: $[\text{M}+1]^+$ 372.3., Mass: calculated for C₂₂H₁₇N₃O₃, 371.40). The reaction procedures were extended to its derivatives (b-f) and products were confirmed by their spectral and Analytical data.

APPLICATIONS

Antimicrobial activities: All the synthesised compounds were screened for their antibacterial activities against *Salmonella typhii*, *Escherichia coli* and *Aeromonas Hydrophilla* by using the disc diffusion method [16-22]. Bacteria were cultured in nutrient agar medium and used as inoculum for study. *Streptomycin* was used as standard. All the compounds exhibited moderate activity against *Salmonella typhii* and *Escherichia coli*. The activity towards *Aeromonas hydrophilla* was found to be very low. According to the study, the toxicity increases with the increase in the concentration of test solution containing new compounds. All the

compounds were less active than streptomycin. The variation in effectiveness of different compounds against different organisms depend either on impermeability of cells of the microbes or diffusion in the ribosomes of the microbial cells.

The compounds were also screened for their invitro antifungal activities against *Fusarium oxysporum* and *Alternaria macrospora*. The fungi were cultured in Czapek-Dox medium and used as inoculum for study. The inhibitory activities were compared with the commercial fungicide *carbendazim* tested under similar conditions. The percentage inhibition after the incubation for five and seven days, were calculated by using the Abott formula.

$$\% \text{ Inhibition} = (C-T) \times 100/C$$

From the Results obtained, compounds were found toxic to both the test fungi at various concentrations. Their activity decreases with dilution and their toxicity towards both the species was as effective as standard *carbendazim*.

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