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Synthesis of new derivatives of 2-chloro-3-formyl-1,8-naphthyridine

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ABSTRACT

A simple and regioselective synthesis of 2-chloro-3-formyl-1,8-naphthyridine, through Vilsmeier-Haack cyclization of *N*-(pyridin-2-yl)acetamide has been reported. The reaction of 2-chloro-3-formyl-1,8-naphthyridine is also investigated and new series of 1,8-naphthyridine derivatives such as 3-chloro-4-(2-chloro-1,8-naphthyridine-3-yl)-1-(phenylamino)azetidin-2-one, 3-chloro-4-(2-chloro-1,8-naphthyridin-3yl)-1-((4-nitrophenyl) amino)-azetidin-2-one and 3-chloro-4-(2-chloro-1,8-naphthyridine-3-yl)-1-((2,4-dinitrophenyl) amino)-azetidin-2-one have been prepared. The formyl group in the 1,8-naphthyridine is subjected to further transformation into alkoxy carbonyl (NIS-K_2CO_3/alcohol) to afford 3-alkoxy carbonyl-1,8-naphthyridine and new hetero cyclic compounds such as oxadiazolo, thiadiazolo-thion and triazolo-thion have been prepared. The reaction between 2-chloro-3-formyl-1,8-naphthyridine and sodium sulphide in DMF produced 2-mercapto-3-formyl-1,8-naphthyridine. Some of the prepared compounds were found to have good biological activity against *Staphylococcus aureus* and *Staphylococcus epidermidis.*

1. Introduction

Naphthyridine or naphthyridone derivatives are great important because the 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substance, with various biological activities. Gemifloxacin is an antimicrobial which have naphthyridine skeleton [1]. It is known that substituted 1,8-naphthayridine series are potential drug for local anesthesia [2] and 1-2(2-florobenzyl-3-(2-tolyle)-1,8-naphthyridine-2(*H*)-one is used for treatment of memory disease [3]. Recently, quinolines and 1,8-naphthyridine are being exploited in cancer chemotherapy [4]. Various 1,8-naphthyridine derivatives have been reported to possess promising biological activities such as antibacterial [5], antimalarial [6] , anti-tumor [7], anti-inflammatory [8], and antihypertensive activities [9]. There are many methods used to prepare various types of 1,8-naphthyridine system involves consideration of 2-aminopyridine derivatives with carbonyl compounds containing an activated methylene group [7,10,11] or with β-ketoesters [12] or condensation of ethanolic 2-amino-3-formyl pyridine in the presence of piperidine base with active methylene compounds aldehydes, acyclic and cyclic ketone or diketones [13-15]. The Vilsmeier-Haack reagent has been proved to be averstile reagent capable of executing a large variety of synthetic transformations [16]. It finds applications in formylation [17], cyclohaloaddition [18], cyclisation [19] and ring annulations [20].

The aim of this work was to synthesized new 1,8-naphthyridine derivatives. In addition, we have obtained naphthyridine based azitidinone (**8**-**10**) and oxadiazole, thiadiazole, triazole (**15**, **16** and **17**) and studies the biological activity of some compounds (**16**, **17** and **18**).

2. Experimental

2.1. Instrumentation

Melting point were recorded on electro-thermal CIA9300 melting point apparatus and are uncorrected, ^{1}H NMR spectra were recorded on nucleic magnetic resinous model Ultra Shield 400 MHz, Bruker Co., Germany, using TMS as internal reference and DMSO-d_6 as solvent . IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, by using KBr discs.

2.2. Synthesis of 2-chloro-3-formyl-1,8-naphthyridine (1)

To solution of *N*-(pyridine-2-yl)acetamide (5 mmoles) in dry DMF (15 mL), at (0-5 °C) with stirring $POCl_3$ (60 mmoles) was added drop wise. The reaction mixture stirred at (80-90 °C) for 15 hr. The reaction mixture was poured into crushed ice, stirred for 30 min and the resulting solid filtered, washed well with water and dried and re-crystallized from ethyl alcohol to give pure compound **1** (Scheme 1).

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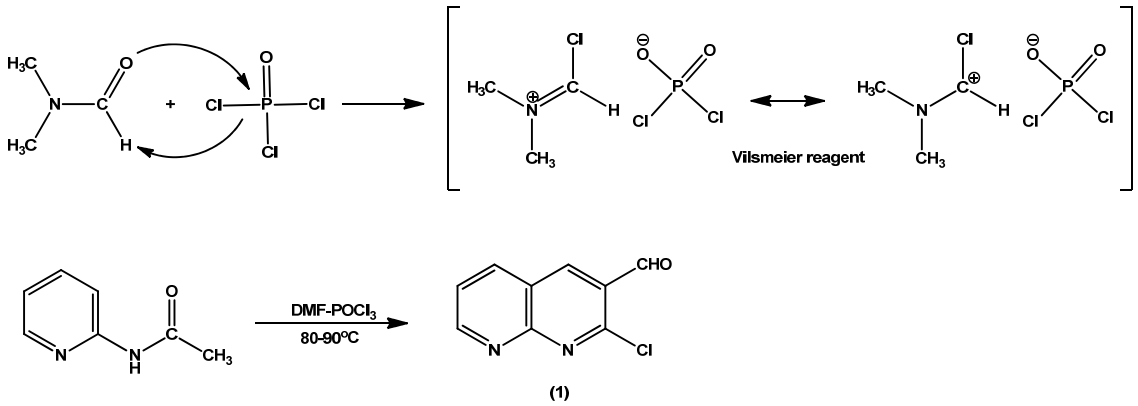


Scheme 1

Yield: 63%. Color: Pale yellow. M.p.: 165-157 °C. FT-IR (KBr, ν, cm^{-1}): 3055 (ArC-H), 2780 (C-H), 1720 (C=O), 1590 (C=N), 775 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.25 (t, 1H, C-6-H), 7.44 (d, 1H, C-5-H), 7.85 (s, 1H, C-4-H), 8.44 (m, 1H, C-7-H), 9.85 (s, 1H, CHO).

2.3. Synthesis of 2-mercapto-3-formyl-1,8-naphthyridine (2)

To a solution of compound **1** (1 mmole) in (5 mL) dry DMF, (1.5 mmole) of sodium sulphide was added and then the reaction mixture was stirred for 4 hr at room temperature. The reaction mixture was poured into 20 mL of crushed ice and acidified with acetic acid. The solid thus obtained was filtered and re-crystallized from ethyl alcohol to give pure compound **2** (Scheme 2). Yield: 67%. Color: Yellow powder. M.p.: 220-223 °C. FT-IR (KBr, ν, cm^{-1}): 3020 (ArC-H), 2792 (C-H), 1690 (C=O), 1595 (C=N), 1050 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.02 (s, 1H, S-H) 7.43 (t, 1H, C-6-H), 7.75 (d, 1H, C-5-H), 8.16 (s, 1H, C-4-H), 8.60 (m, 1H, C-7-H), 9.88 (s, 1H, CHO).

2.4. Synthesis of thioethers 3-formyl-2-methylthio-1,8-naphthyridine (3) and 3-formyl-2-benzylthio-1,8-naphthyridine (4)

To a solution of compound **1** (1 mmole) in 5 mL dry DMF, sodium sulphide (1.5 mmole) was added and stirred for 4 hr at room temperature, then the corresponding halo compound (methyl iodide or benzyl chloride) was added and stirred for another 1 hr and poured into ice-cooled water. The precipitate obtained was filtered dried and re-crystallized from ethanol to give pure compound **3** and **4** (Scheme 2).

3-Formyl-2-methylthio-1,8-naphthyridine (**3**): Yield: 81%. Color: Yellow. M.p.: 105-108 °C. FT-IR (KBr, ν, cm^{-1}): 3050 (ArC-H), 2775 (C-H), 1687 (C=O), 1590 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.86 (s, 3H, SCH_3), 7.44 (t, 1H, C-6-H), 7.75 (d, 1H, C-5-H), 8.18 (s, 1H, C-4-H), 8.64 (m, 1H, C-7-H), 9.86 (s, 1H, CHO).

3-Formyl-2-benzylthio-1,8-naphthyridine (**4**): Yield: 83%. Color: Brown powder. M.p.: 111-113 °C. FT-IR (KBr, ν, cm^{-1}): 3085 (ArC-H), 2780 (C-H), 1680 (C=O), 1585 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.6 (s, 2H, SCH_2), 7.1-7.4 (m, 5H Ar-H), 7.48 (t, 1H, C-6-H), 7.75 (d, 1H, C-5-H), 8.16 (s, 1H, C-4-H), 8.64 (m, 1H, C-7-H), 9.86 (s, 1H, CHO).

2.5. Synthesis of 2-chloro-1,8-naphthyridine-3-carbaldehyde (phenyl hydrazone) (5)

To a solution of compound **1** (1 mmole) in ethanol (5 mL) was added with stirring phenyl hydrazine (2 mmole), and the mixture was refluxed for 4 hr. On cooling, the yellow precipitate was formed, filtered off, washed with ethanol and cold water, dried and re-crystallized from ethanol to give pure compound **5** (Scheme 2). Yield: 76%. Color: Yellow. M.p.: 223-225 °C. FT-IR (KBr, ν, cm^{-1}): 3340 (N-H), 3045 (ArC-H), 1625 (C=N), 745 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.23 (s, 1H, NH), 7.11-7.42 (5H, m, Ar-H), 7.48 (t, 1H, C-6-H), 7.83 (d, 1H, C-5-H), 9.14 (s, 1H, CH), 8.60 (s, 1H, C-4-H), 8.93 (m, 1H, C-7-H).

2.6. Synthesis of 2-chloro-1,8-naphthyridine-3-carbaldehyde (4-nitro phenyl hydrazone) (6)

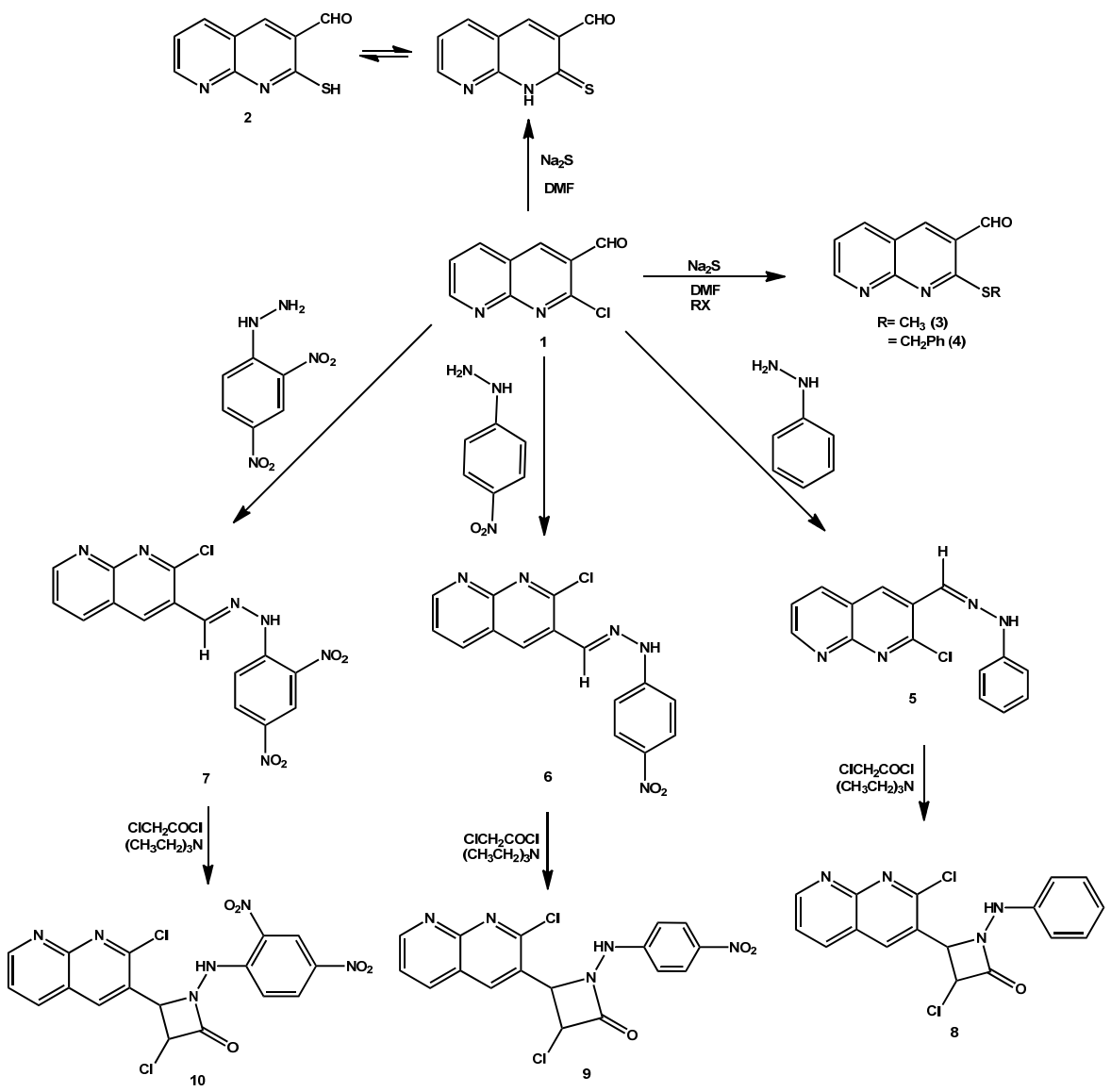
To a solution of compound **1** (1 mmole) in ethanol (5 mL) was added with stirring 4-nitro phenyl hydrazine (2 mmole), and refluxed for 4 hr on cooling the precipitate was formed dried and re-crystallized from ethanol to give pure compound **6** (Scheme 2). Yield: 85%. Color: Brown. M.p.: 228-230 °C. FT-IR (KBr, ν, cm^{-1}): 3335 (N-H), 3055 (ArC-H), 1605 (C=N), 1535, 1310 ($NO_{2Asym, Sym}$), 740 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.23 (s, 1H, NH), 7.11-7.41 (m, 4H, Ar-H), 7.48 (t, 1H, C-6-H), 7.81 (d, 1H, C-5-H), 9.14 (s, 1H, -CH), 8.61 (s, 1H, C-4-H), 8.90 (m, 1H, C-7-H).

2.7. Synthesis of 2-chloro-1,8-caphthyridine-3-carbaldehyde (2,4-dinitro phenyl hydrazone) (7)

To a solution of compound **1** (1 mmole) in ethanol (5 mL) was added with stirring 2,4-dinitro-phenyl hydrazine (2 mmole), and refluxed for 4 hr on cooling the precipitate was formed dried and re-crystallized from ethanol to give pure compound **7** (Scheme 2). Yield: 78%. Color: Orange. M.p.: 235-236 °C. FT-IR (KBr, ν, cm^{-1}): 3324 (N-H), 3100 (ArC-H), 1595 (C=N), 1565, 1385 ($NO_{2Asym, Sym}$), 740 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.01-7.42 (m, 3H, Ar-H), 6.23 (s, 1H, NH), 7.48 (t, 1H, C-6-H), 7.78 (d, 1H, C-5-H), 9.02 (s, 1H, CH), 8.41 (s, 1H, C-4-H), 8.82 (m, 1H, C-7-H).

2.8. Synthesis of 3-chloro-4-(2-chloro-1,8-naphthyridine-3-yl)-1-(phenylamino)azetidin-2-one (8)

The compound 5 (0.01 mole) was dissolved in dry DMF (20 mL) and triethylamine (0.02 mole) was added to it. Chloroacetyle chloride (0.02 mole) was added drop wise for a period of 30 min. The reaction mixture was refluxed for 6 hr. then poured into crushed ice, the resulting solid was filtered washed with cold water and re-crystallized from ethyl acetate to give pure compound **8** (Scheme 2). Yield: 65%. Color: Yellow. M.p.: 251-253 °C. FT-IR (KBr, ν, cm^{-1}): 3344 (N-H), 3025 (ArC-H), 1665 (C=O), 1575 (C=N), 755 (C-Cl).



Scheme 2

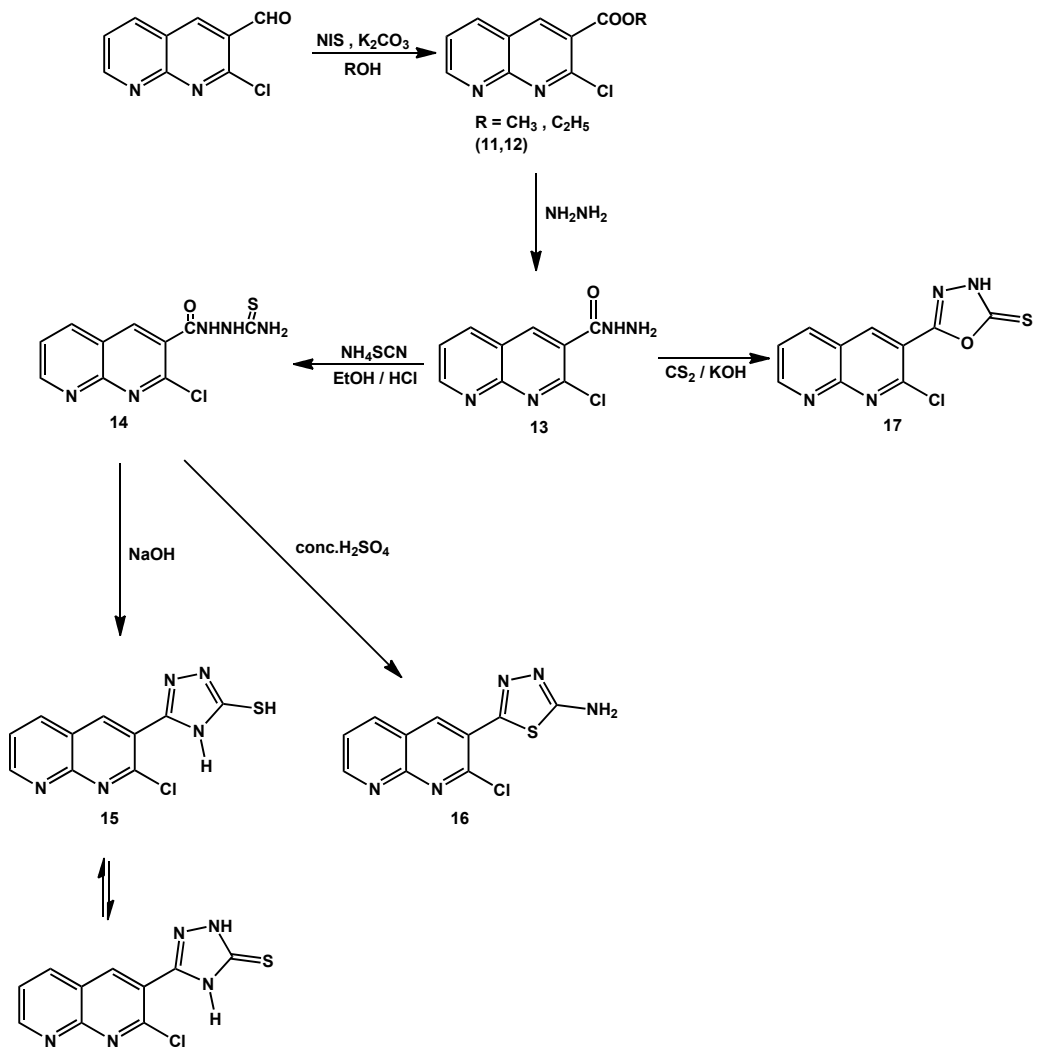
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.15 (s, 1H, NH), 5.82 (d, 1H, CH-Cl), 6.95 (d, 1H, CH-N), 7.20-7.35 (m, 5H, Ar-H), 7.41 (t, 1H, C-6-H), 7.85 (d, 1H, C-5-H), 8.56 (s, 1H, C-4-H), 8.78 (m, 1H, C-7-H).

2.9. Synthesis of 3-chloro-4-(2-chloro-1,8-naphthyridin-3yl)-1-((4-nitrophenyl) amino)-azetidin-2-one (9)

The compound **6** (0.01 mole) was dissolved in dry DMF (20 mL) and triethylamine (0.02 mole) was added to it. Chloroacetyle chloride (0.02 mole) was added drop wise for a period of 30 min. The reaction mixture was refluxed for 6 hr. The reaction mixture was poured into crushed ice, the resulting solid was filtered washed well with cold water and re-crystallized from ethyl acetate to give pure compound **9** (Scheme 2). Yield: 63%. Color: Yellow. M.p.: 236-237 °C. FT-IR (KBr, ν, cm^{-1}): 3440 (N-H), 3050 (ArC-H), 1665 (C=O), 1545 (C=N), 1555, 1370 ($NO_{2Asym, Sym}$), 765 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.84 (d, 1H, CH-Cl), 6.23 (s, 1H, NH), 6.92 (m, 1H, CH-N), 7.15-7.33 (m, 4H, Ar-H), 7.48 (t, 1H, C-6-H), 7.80 (d, 1H, C-5-H), 8.52 (d, 1H, C-4-H), 8.72 (m, 1H, C-7-H).

2.10. Synthesis of 3-chloro-4-(2-chloro-1,8-naphthyridine-3-yl)-1-((2,4-dinitrophenyl) amino)-azetidin-2-one (10)

The compound **7** (0.01 mole) was dissolved in dry DMF (20 mL) and triethylamine (0.02 mole) was added to it. Chloroacetyle chloride (0.02 mole) was added drop wise for a period of 30 min. The reaction mixture was refluxed for 6 hr. The reaction mixture was poured into crushed ice, the resulting solid was filtered washed well with cold water and re-crystallized from ethyl acetate to give pure compound **10** (Scheme 2). Yield: 89%. Color: Yellow. M.p.: 222-225 °C. FT-IR (KBr, ν, cm^{-1}): 3445 (N-H), 3035 (ArC-H), 1665 (C=O), 1510 (C=N), 1565, 1340 ($NO_{2Asym, Sym}$), 745 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.88 (d, 1H, CH-Cl), 6.04 (s, 1H, NH), 6.92 (m, 1H, C-7-H), 7.13-7.33 (m, 3H, Ar-H), 7.40 (t, 1H, C-6-H), 7.80 (d, 1H, C-5-H), 8.52 (s, 1H, C-4-H), 8.72 (m, 1H, C-7-H).



Scheme 3

2.11. Conversion to methyl and ethyl ester derivatives: Synthesis of 2-chloro-3-(methoxy or ethoxy)carbonyl-1,8-naphthyridine (11,12)

To a solution of compound **1** (1 mmole) in methanol or ethanol (10 mL) were added NIS (*N*-iodo succimide) (2.5 mmole) and potassium carbonate (2.5 mmole). The resultant dark mixture was stirred in dark for 6 hr. The reaction mixture was then diluted with 5-6 mL of water and sodium thiosulphite (0.5 g) was added to destroy any remaining NIS or hypoiodite species and the solid product filtered, dried and re-crystallized from ethanol to give pure compound **11** and **12** (Scheme 3).

2-Chloro-3-methoxycarbonyl-1,8-naphthyridine (**11**): Yield: 81%. Color: Pale yellow. M.p.: 82-84 °C. FT-IR (KBr, ν, cm^{-1}): 3045 (ArC-H), 1735 (C=O), 1595 (C=N), 760 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.15 (s, 3H, OCH_3), 7.28 (t, 1H, C-6-H), 7.48 (d, 1H, C-5-H), 7.88 (s, 1H, C-4-H), 8.40 (m, 1H, C-7-H).

2-Chloro-3-ethoxycarbonyl-1,8-naphthyridine (**12**): Yield: 76%. Color: Pale yellow. M.p.: 96-98 °C. FT-IR (KBr, ν, cm^{-1}): 3285 (NH), 3060 (ArC-H), 1730 (C=O), 1595 (C=N), 760 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.48 (s, 3H, CH_3), 4.4 (q, 2H, OCH_2), 7.28 (t, 1H, C-6-H), 7.46 (d, 1H, C-5-H), 7.86 (s, 1H, C-4-H), 8.41 (m, 1H, C-7-H).

2.12. Synthesis of 2-chloro-1,8-naphthyridine-3-hydrazide (13)

To a solution of compound **11** (0.04 mole) in ethanol, hydrazine hydrate (0.2 mole) was added and the reaction mixture was stirred for 6 hr in temperature below 100 °C. The solvent was evaporated to half under reduced pressure. The precipitate was cooled and collected by filtration then re-crystallized from ethanol to give pure compound **13** (Scheme 3). Yield: 68%. Color: Brown. M.p.: 256-257 °C. FT-IR (KBr, ν, cm^{-1}): 3315 (NH), 3100 (ArC-H), 1650 (C=O), 1585 (C=N), 755 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.25 (s, 2H, NH_2), 7.35 (t, 1H, C-6-H), 7.48 (d, 1H, C-5-H), 8.15 (s, 1H, C-4-H), 8.47 (m, 1H, C-7-H), 10.78 (s, 1H, CO-NH).

2.13. Synthesis of 2[(2-chloro-1,8-naphthyridin-3-yl) carbonyl] hydrazine carbothioamide (14)

A mixture of hydrazide (**13**) (0.02 mole) ammonium thiocyanate (4.56 g, 0.06 mole), hydrochloric acid (8 mL) in absolute ethanol (50 mL) was refluxed for 20 hr. The solvent was evaporated under reduced pressure and the residue poured on crushed ice with stirring. The solid formed filtered and re-crystallized from ethanol to give pure compound **14**

(Scheme 3). Yield: 55%. Color: Brown. M.p.: 222-225 °C. FT-IR (KBr, ν, cm^{-1}): 3385 (NH), 3035 (ArC-H), 1660 (C=O), 1595 (C=N), 1225 (C=S), 755 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.20 (s, 2H, NH_2), 7.45 (t, 1H, C-6-H), 7.78 (d, 1H, C-5-H), 7.83 (s, 1H, C-4-H), 8.44 (m, 1H, C-7-H), 9.52 (s, 1H, NHCS), 10.78 (s, 1H, CO-NH).

2.14. Synthesis of 5-(2-chloro-1,8-naphthyridin-3-yl)-4H-1,2,4-triazole-3-thiol (15)

To ethanolic solution of compound **14** (1.0 mmole), sodium hydroxide (0.056 g, 1.0 mmole) in 5 mL water was added and stirred for 6 hr at (90 °C). The solution was filtered, the solution was then neutralized with dilute hydrochloric acid. The solid product was filtered off and crystallized from ethanol to give pure compound **15** (Scheme 3). Yield: 87%. Color: Brown. M.p.: 225-227 °C. FT-IR (KBr, ν, cm^{-1}): 3350 (NH), 3038 (ArC-H), 1605 (C=N), 1015 (C=S), 750 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.21 (s, 1H, N-H), 7.45 (t, 1H, C-6-H), 7.86 (d, 1H, C-5-H), 8.45 (s, 1H, C-4-H), 8.84 (m, 1H, C-7-H), 13.68 (s, 1H, SH).

2.15. Synthesis of 5-(2-chloro-1,8-naphthyridin-3-yl)-1,3,4-thiadiazol-2-amine (16)

To a stirred solution of compound **14** (1.0mole) in (50 mL) ethanol, concentrated sulfuric acid (6 mL) was added and refluxed for 6 hr at (90 °C). The solution was poured onto ice water, ammonia was added until basic, a precipitate was obtained which was filtered and crystallized from ethanol to give pure compound **16** (Scheme 3). Yield: 92%. Color: Brown. M.p.: 202-205 °C. FT-IR (KBr, ν, cm^{-1}): 3450 (NH), 3040 (ArC-H), 1610 (C=N), 765 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.5 (s, 2H, NH_2), 7.45 (t, 1H, C-6-H), 7.85 (d, 1H, C-5-H), 8.45 (s, 1H, C-4-H), 8.85 (m, 1H, C-7-H).

2.16. Synthesis of 5-(2-chloro-1,8-naphthyridin-3-yl)-1,3,4-oxadiazole-2(3H)-thione (17)

To ethanolic solution of hydrazide (**13**) (1.0 mmole) potassium hydroxide (0.056 g, 1.0 mmole) and carbon disulfide (2 mmole) was added. The mixture was heated under reflux until the hydrogen sulfide evolution ceased. The solvent was then removed, water added and the solution was filtered off. The filtrate was acidified with diluted hydrochloride acid. The precipitate formed was collected washed with water and crystallized from ethanol to give pure compound **17** (Scheme 3). Yield: 90%. Color: Yellow. M.p.: 196-198 °C. FT-IR (KBr, ν, cm^{-1}): 3382, 3220 (NH), 3050 (ArC-H), 1605 (C=N), 1050 (C=S), 755 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.40 (t, 1H, C-6-H), 7.6 (s, 1H, NH), 7.80 (d, 1H, C-5-H), 8.40 (s, 1H, C-4-H), 8.82 (m, 1H, C-7-H).

3. Result and discussion

3.1. Synthesis

The starting material 2-chloro-3-formyl-1,8-naphthyridine (**1**) was synthesized by the reaction of *N*-(pyridine-2-yl) acetamide with DMF-$POCl_3$ at 80-90 °C. The Vilsmeier cyclization of *N*-(pyridine-2-yl)acetamide was carried out by adding $POCl_3$ to substrate in DMF at 0-5 °C followed by heating to 90 °C [21] (Scheme 1)

The structure of compound **1** could be matched with their spectral data. The IR spectrum of compound **1** showed a band for carbonyl group at 1720 cm^{-1} and band at 2780 cm^{-1} for νCH, and the ^{1}H NMR spectrum indicated the presence of aldehyde proton at δ 9.85 ppm.

Treatment of compound **1** with sodium sulphide afford 2-mercapto-3-formyl-1,8-naphthyridine (**2**) [22] (Scheme 2). The IR spectra showed a sharp and strong absorption at 1690 cm^{-1} for carbonyl group and strong absorption at 1050 cm^{-1} for C=S and absence of absorption 775 cm^{-1} for C-Cl. The ^{1}H NMR spectrum indicated the presence of aldehydic proton at δ 9.88 ppm.

The reaction of compound **1** with Na_2S/DMF followed by reaction with alkyl halide afforded thioethers **3** and **4**. The ^{1}H NMR spectra of compound **3** shows a singlet at δ 2.86 ppm for S-CH_3, and compound **4** shows singlet at δ 4.6 ppm for S-CH_2- and multiplets at δ 7.1-7.4 ppm for Ar-H.

To prepare Schiff base (**5**, **6** and **7**), the compound **1** was treated with phenyl hydrazine or substituted phenyl hydrazine. The IR spectrum of compounds showed the absence of absorption at 1720 cm^{-1} for νC=O and showed absorption between 3340, 3335 and 3324 cm^{-1} for NH groups, respectively. The ^{1}H NMR spectrum of compounds (**5**, **6** and **7**) exhibited no peak corresponding to aldehydic proton instead it shows signals at δ 7.3, 6.2 and 7.2 ppm for NH, respectively.

The substituted Schiff base (**5**, **6** and **7**) was also reacted with chloro acetyl chloride in the presence of triethylamine to give azetidin-2-one derivatives (**8**, **9** and **10**). The formation of compounds were supported spectroscopically by showing the absence of CH=N proton at δ 9.02-9.14 ppm in the ^{1}H NMR spectra and presence of strong absorption at 1665 cm^{-1} in the IR for νC=O in the azetidine rings.

The formyl group in 1,8-naphthyridine (**1**) was oxidized to esters (**11** and **12**) in good yield by using NIS-K_2CO_3 in CH_3OH/C_2H_5OH at room temperature (Scheme 3). The IR spectrum of compounds **11** and **12** showed a sharp strong absorption at 1735 and 1730 cm^{-1} due to the presence of ester function in the structures, respectively. The ^{1}H NMR spectra substantiated the results of the IR analysis. The characteristic signals of an ester moiety confirm the presence of an ester group in the structure as singlet at δ 4.15 ppm for O-CH_3 for compound **11** and as quartet and triplet for CH_2 and CH_3 at δ 4.4 and 1.48 ppm, respectively, for compound **12**.

Then compound **11** was reacted with hydrazine hydrate in ethanol at reflux temperature to obtain 2-chloro-1,8-naphthyridine-3-hydrazide. The IR spectrum of compound **13** showed the absence of ester stretching frequency instead it gave a band at 1650 cm^{-1} for carbonyl group and band at 3315 cm^{-1} for NH group. ^{1}H NMR spectrum of compound **13** exhibited no peak corresponding to ester instead it shows signals at δ 10.78 ppm and at δ 5.25 ppm for CONH and NH_2 of hydrazide, respectively.

Thiosemicarbazide (**14**) was synthesized from reaction of compound **13** with ammonium thiocyanate. The ^{1}H NMR showed two characteristic singlet for CSNH and CONH at δ 9.52 and 10.78 ppm, respectively. The IR spectrum supported these results and showed band at 1660 and 1225 cm^{-1} for C=O and C=S group, respectively.

Compound **15** and **16** was synthesized from the cyclization of thiosemicarbazide (**14**) in basic and acidic medium. The ^{1}H NMR is characterized by the disappearance of thiosemicarbazide signals.

The reaction of compound **3** with carbon disulfide in alcoholic potassium hydroxide affords oxadiazolo (**17**) (Scheme 3).

3.2. Biological studies

The biological studies of compounds (**15**, **16** and **17**) were assayed for antibacterial activity against two representative Gram-positive organisms such as *Staphylococcus aureus*, *Staphylococcus epidermidis* and two Gram-negative organism such as *Escherichia coli* and *Proteus vulgaris* by broth dilution method. Ciprofloxacin was used as standard for comparison of antibacterial activities. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 hr at 35 °C.

The results showed that these compounds (**15**, **16** and **17**) have a good activity against (*Staphylococcus aureus* and *Staphylococcus epidermidis*) Table 1.

Table 1. Antibacterial activity data of compound **15**, **16**, and **17**.

Compound		Zone of inhibition in mm			
		Staphylococcus aureus	*Staphylococcus epidermidis*	*Escherichia coli*	*Proteus vulgaris*
		10 mg/disk	10 mg/disk	10 mg/disk	10 mg/disk
15		26	24	12	10
16		23	22	11	10
17		18	22	13	10
Control	Ciprofloxacin, 5 mg/disk	-	-	15	14
	Chloramphenicol, 30 mg/disk	17	16	14	-

4. Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of some new 1,8-naphthyridine derivatives and characterized by spectral studies. The newly synthesized compounds (**15**, **16** and **17**) were evaluated for antibacterial activities. The results obtained indicated that these compounds have a good activity against (*Staphylococcus aureus* and *Staphylococcus epidermidis*).

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