Synthesis and antimicrobial activity of 2-cyclopropyl [1,8]naphthyridine-3-carboxylic acid (4-phenyl-2-thioxo-thiazol-3-yl)-amides, [1,3,5]triazine, [1,3,4]thiadiazole-2-thiol, [1,2,4]triazole-3-thiol and coumarin derivatives

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2-Cyclopropyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester 1 reacts with 99% hydrazine hydrate, to yield 2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid hydrazide 2, which further reacts with carbon disulphide in the presence of potassium hydroxide solution to yield compound 3. Compound 3 reacts with 99% hydrazine hydrate to offer 4-amino-5-(2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester 1 (Ref. 29) in the presence of piperidine in ethanol. In this work 2-amino-3-carboxaldehyde is valuable starting material for a wide variety of nitrogen containing heterocyclic compounds. Compound 1, when reacted with hydrazine hydrate gave the corresponding acid hydrazide 2 which reacted with CS\textsubscript{2} in the presence of EtOK to give potassium carbazate 3, which on treatment with hydrazine hydrate afforded compound 4 (Refs 30, 31).

The structure of the compounds were confirmed on the basis of their elemental analysis and spectral (IR, \textsuperscript{1}H NMR and MS) data. The synthetic approach is outlined in Scheme I.

Experimental Section

Chemicals and solvents are reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The \textsuperscript{1}H NMR spectra were recorded in the indicated solvent on a Varian 500 MHz spectrophotometer with TMS as internal standard. All chemical shifts (\textit{\delta}) were reported in ppm from internal TMS. Mass spectra were measured on a Joel JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Bruker-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using pre coated TLC plates (E. Merck Kieselgel 60 F254).

2-Cyclopropyl-[1,8]naphthyridine-3-carboxylic acid hydrazide, 2

To a solution of 2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester 1 (4.12 mmol) in ethanol (15 mL) was added 99% hydrazine hydrate (20.32 mmol) and refluxed for about 6 hr, under N\textsubscript{2} atmosphere, the reaction was monitored by TLC. After disappearance of starting material, reaction mass was cooled to RT, the ethanol was evaporated.

Keywords: 1,8-Naphthyridines, coumarin, triazole, microbial activity, glass slide humid chamber technique

In conjunction of our interest in the chemistry and biological activity of 1,8-naphthyridines and their derivatives\textsuperscript{1-21}, here we describe the synthesis and antimicrobial activity of 2-cyclopropyl [1,8]naphthyridine-3-carboxylic acid (4-phenyl-2-thioxo-thiazol-3-yl)-amides, [1,3,5]triazine, [1,3,4]thiadiazole-2-thiol, [1,2,4]triazole-3-thiol and coumarin derivatives. Recently, it was reported that the [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles and [1,2,4]triazolo-[3,4-b][1,3,4]thiadiazines possess antimicrobial activities\textsuperscript{22}. Also, 6-substituted 3-(1-adamantyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles have been evaluated for their antiviral activity\textsuperscript{23}. The[1,2,4]triazoles and [1,3,4]thiadiazoles are known for their broad-spectrum of biological activities and many other uses\textsuperscript{24-28}. The general synthetic procedure used in the preparation of these compounds involved the Friedlander condensation of 2-amino-pyridine-3-carbaldehyde with 3-cyclopropyl-3-oxo-propionic acid ethyl ester gives 2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester 1 (Ref. 29) in the presence of piperidine in ethanol. In this work 2-amino-3-carboxaldehyde is valuable starting material for a wide variety of nitrogen containing heterocyclic compounds. Compound 1, when reacted with hydrazine hydrate gave the corresponding acid hydrazide 2 which reacted with CS\textsubscript{2} in the presence of EtOK to give potassium carbazate 3, which on treatment with hydrazine hydrate afforded compound 4 (Refs 30, 31).

The structure of the compounds were confirmed on the basis of their elemental analysis and spectral (IR, \textsuperscript{1}H NMR and MS) data. The synthetic approach is outlined in Scheme I.

Note
completely under reduced pressure. The reaction mass was co-distilled with ethanol twice, minimum amount of ethyl acetate was then added and the solid was filtered, recrystallized in ethyl acetate in hexane to provide 2 an off white solid with 95% yield. IR (KBr): 2250 (aliph. CH\_2), 1700 (CO, ester), 3110 (NH), 3231 cm\(^{-1}\) (NH); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 1.05 (q, 2H, \(J = 15\) Hz, CH\_2), 1.12 (q, 2H, \(J = 15\) Hz, CH\_2), 2.58 (m, 1H, CH), 4.62 (bs, 2H, NH\_2), 7.56 (t, 1H, \(J = 15\) Hz, CH), 8.32 (s, 1H, NH), 8.42 (d, 1H, \(J = 15\) Hz, CH), 9.02 (d, 1H, \(J = 15\) Hz, CH), 9.82 (s, 1H, CH); \(^13\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta\) 7.3 (2CH\_2), 138.2 (2CH), 142.3 (2CH), 165.4 (CO) MS: \(m/z\) 229 [M+].

N'-(2-Cyclopropyl-[1,8]naphthyridine-3-carbonyl)-hydrazinecarbodithioic acid potassium salt, 3

To a solution of 2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid hydrazide 2 (0.5 g, 2.19 mmol) in ethanol (5 mL), was added KOH solution (0.14 g, 2.63 mmol) in ethanol (2 mL). The resulting solution was treated with carbon disulphide (0.25 g, 3.28 mmol) and was stirred for about 16 hr at RT under N\(_2\) atmosphere, then diluted with diethyl ether (10 mL). The precipitated solid was filtered and washed with diethyl ether and dried in vacuo at 50°C, to offer light yellow solid (0.6 g), yield: 80%.

IR (KBr): 2250 (aliph. CH\_2), 1720 (CO, amide), 3125 (NH), 3231 cm\(^{-1}\) (NH); \(^1\)H NMR (500 MHz,
DMSO-d₆): δ 0.98-1.32 (m, 6H, J = 15 Hz, 2CH₂), 3.64-3.71 (m, 1H, J = 15 Hz, CH), 7.46-7.52 (m, 1H, CH), 8.56 (t, 1H, J = 15 Hz, CH), 8.72 (s, 1H, CH), 9.02 (d, 1H, J = 15 Hz, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 6.3 (2CH₃), 7.4 (CH), 126.3, 134.4 (CH), 135.6 (CH), 144.4 (CH), 146.1 (CH), 164.8 (CH), 168.3 (CO), 201 (CS); MS: m/z 343 [M⁺].

4-Amino-5-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-4H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl]-1,8 napthyridine, 4a

A solution of 2 N-(2-cyclopropyl-[1,8]naphthyridine-3-carbonyl)-hydrazinecarbothioic acid potassium salt 3 (0.5 g, 1.4 mmol) in water (5 mL) was treated with hydrazine hydrate 99% (0.23 g, 7.30 mmol), the resulting solution was refluxed for about 1 hr, the reaction mass was cooled and diluted with water (10 mL) and acidified with glacial acetic acid (1 mL). The precipitated solids was filtered, washed with cold water and recrystallised from ethanol, to yield off white solid (0.35 g, 84%).

IR (KBr): 2250 (aliph. CH₂), 1700 (CO ester), 3110 (NH), 3231 cm⁻¹ (aliph. CH₂); ¹H NMR (500 MHz, DMSO-d₆): δ 1.09-1.26 (m, 4H, J=15 Hz, 2CH₂), 2.12-2.32 (m, 1H, J = 15 Hz, CH), 2.58 (m, 1H, CH), 5.62 (s, 2H, NH₂), 7.56 (m, 1H, J = 15 Hz, CH), 8.42 (d, 1H, CH), 8.62 (s, 1H, J = 15 Hz, CH), 9.22 (s, 1H, CH), 14.15 (s, 1H,SH); ¹³C NMR (125 MHz, DMSO-d₆): δ 6.3 (2CH₃), 7.2 (CH), 122.2, 124.2, (2CH₂), 132.3, 133.2, 136.8 (3CH), 146.3, 148.2, 149.8, 162.8 (4CH); MS: m/z 285 [M⁺].

2-Cyclopropyl-3-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl]-1,8 napthyridine, 5a

To a solution of 4-amino-5-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-4H-[1,2,4]triazole-3-thiol 4, (0.2 g, 0.701 mmol) in ethanol (5 mL) was added 2-bromo-1-phenyl-ethanone (0.16 g, 0.842 mmol), and piperidine (0.89 g, 1.05 mmol), the resulting solution was heated at reflux for about 4 hr under N₂ atmosphere, reaction completion was monitored by TLC, then cooled to RT, ethanol was evaporated completely and recrystallised in methanol, the solid compound was filtered and dried to offer cream colour solid (0.19 g, 70%).

IR (KBr): 2225 cm⁻¹ (aliph. CH₂); ¹H NMR (500 MHz, DMSO-d₆): δ 0.72 (m, 4H, J =15 Hz, CH₂), 1.30 (m, 1H, J = 15 Hz), 2.80 (s, 2H), 7.26-7.48 (m, 5H, J = 15 Hz, 4CH), 7.65-7.69 (m, 2H, J = 7.7 Hz), 8.32 (s, 1H, CH), 8.43 (d, 1H, CH), 9.32 (d, 1H, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 7.1, 8.2, 121.2, 124.4, 127.5, 126.2, 128.6, 129.3, 133.8, 139.2, 147.9, 151.2, 162.2, 165.8; MS: m/z 385 [M⁺].

Other compounds in the series were prepared similarly and their characterization data are recorded below.

2-Cyclopropyl-3-[6-(4-fluoro-phenyl)-7H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazin-3-yl]-1,8 napthyridine, 5b

Cream colour solid, (0.12 g, 50%), IR (KBr): 2220 cm⁻¹ (aliph. CH₂); ¹H NMR (500 MHz, DMSO-d₆): δ 0.69 (m, 4H, J =15 Hz, CH₂), 1.34 (m, 1H, J = 15 Hz), 2.84 (s, 2H), 7.36-7.48 (m, 5H, J = 15 Hz, 4CH), 7.65-7.68 (m, 2H, J = 7.7 Hz), 8.22 (s, 1H, CH), 8.43 (d, 1H,CH), 9.12 (d, 1H, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 7.2, 8.2, 121.4, 124.6, 127.6, 126.4, 128.2, 129.3, 133.8, 139.6, 147.9, 151.2, 162.8, 165.2; MS: m/z 403 [M⁺].

3-[6-(4-Chloro-phenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl]-2-cyclopropyl-1,8 napthyridine, 5c

Recrystallised in methanol, the solid compound was filtered and dried to offer cream colour solid (0.14 g, 55%), IR (KBr): 2225 cm⁻¹ (aliph. CH₂); ¹H NMR (500 MHz, DMSO-d₆): δ 1.21 (m, 4H, J = 15 Hz, CH₂), 1.44 (m, 1H, J = 15 Hz), 2.94 (s, 2H), 7.46-7.58 (m, 5H, J = 15 Hz, 4CH), 7.62-7.69 (m, 2H, J = 7.7 Hz), 8.24 (s, 1H, CH), 8.42 (d, 1H, CH), 9.21(d, 1H, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 7.1, 7.9, 123.4, 124.6, 128.6, 129.4,130.2, 131.3, 133.8, 139.6, 147.9, 153.2, 164.8, 167.2; MS: m/z 419 [M⁺].

2-Cyclopropyl-3-[6-(2,6-difluoro-phenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl]-1,8 napthyridine, 5d

Recrystallised in methanol, the solid compound was filtered and dried to offer cream colour solid (0.10 g, 40%), IR (KBr): 2215 cm⁻¹ (aliph. CH₂); ¹H NMR (500 MHz, DMSO-d₆): δ 1.25 (m, 4H, J =15 Hz, CH₂), 1.34 (m, 1H, J = 15 Hz), 2.91 (s, 2H), 7.36-7.48 (m, 3H, J = 15 Hz, 4CH), 7.52-7.59 (m, 2H, J = 7.7Hz), 8.14 (s, 1H, CH), 8.42 (d, 1H,CH), 9.21(d, 1H, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 7.3, 7.9, 121.4, 125.6, 128.6, 129.2, 130.6, 131.4, 133.8, 140.6, 145.9, 152.2, 164.8, 166.2; MS: m/z 421 [M⁺].

3-(2-Cyclopropyl-[1,8]naphthyridin-3-yl)-1,2,4 triazole[3,4-b][1,3,4]thiadiazine-6,7-dione, 6

To a solution of 4-amino-5-(2-cyclopropyl-[1,8]napthyridin-3-yl)-4H-[1,2,4]triazole-3-thiol 4 (0.2 g, 0.701 mmol) in DMF (10 mL) was added oxalyl
dichloride (0.10 g, 0.841 mmol), and triethyl amine (0.89 g, 1.05 mmol), the resulting solution was heated at 80°C for about 6 hr under N₂ atmosphere. The completion of the reaction was monitored by TLC, then cooled to RT, poured in crushed ice, the precipitated solid was filtered, dried and recrystallised in acetone, to offer light yellow solid (0.10 g, 42%).

The completion of the reaction was monitored by TLC, then cooled to RT, poured in crushed ice, the precipitated solid was filtered, dried and recrystallised in acetone, to offer light yellow solid (0.10 g, 42%).

To a solution of N’-(2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid potassium salt in glacial acetic acid (10 mL) was refluxed for about 2 hr, then cooled to RT and dissolved in ice-cold water (20 mL), on cooling a solid separated out which was filtered and dried to offer cream colour solid (0.21 g, 44%). IR (KBr): 2235 (aliph. CH), 1723 (CO, amide), 1755 (CS), 3125 cm⁻¹ (NH); ¹H NMR (500 MHz, DMSO-d₆): δ 7.1 (2CH₂), 8.01 (CH), 127.2, 128.4 (2CH), 143.5, 148.2 (2CH), 168.4 (CH); MS: m/z 43 (M⁺).

Other compounds in the series were prepared similarly and their characterization data are recorded below.

2-Cyclopropyl-[1,8]naphthyridine-3-carboxylic acid [4-(4-fluoro-phenyl)-2-thioxo-thiazol-3-yl]-amide, 8b

Recrystallised in methanol, the solid compound was filtered and dried to offer yellow solid (0.21 g, 44%). IR (KBr): 2215 (aliph. CH₂), 1723 (CO, amide), 1755 (CS), 3125 cm⁻¹ (NH); ¹H NMR (500 MHz, DMSO-d₆): δ 1.12 (m, 4H, J = 15 Hz, CH₂), 1.32 (m, 1H, J = 7.5 Hz, CH), 6.22 (s, 1H, CH), 7.26-7.46 (m, 5H, J = 15 Hz, 5CH), 8.12 (s, 1H, NH), 8.32 (d, 1H, CH), 8.42 (d, 1H, CH), 9.12 (d, 1H, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 7.1 (2CH₂), 8.01 (CH), 127.2, 128.4 (2CH), 143.5, 148.2 (2CH), 168.4 (CH); MS: m/z 43 (M⁺).

2-Cyclopropyl-[1,8]naphthyridine-3-carboxylic acid [4-(4-chloro-phenyl)-2-thioxo-thiazol-3-yl]-amide, 8c

Recrystallised in methanol, the solid compound was filtered and dried to offer cream colour solid (0.21 g, 44%). IR (KBr): 2215 (aliph. CH₂), 1723 (CO, amide), 1755 (CS), 3125 cm⁻¹ (NH); ¹H NMR (500 MHz, DMSO-d₆): δ 1.12 (m, 4H, J = 15 Hz, CH₂), 1.32 (m, 1H, J = 7.5 Hz, CH), 6.22 (s, 1H, CH), 7.26-7.46 (m, 5H, J = 15 Hz, 5CH), 8.12 (s, 1H, NH), 8.32 (d, 1H, CH), 8.42 (d, 1H, CH), 9.12 (d, 1H, CH); ¹³C NMR (125 MHz, DMSO-d₆): δ 7.1 (2CH₂), 8.01 (CH), 127.2, 128.4 (2CH), 143.5, 148.2 (2CH), 168.4 (CH); MS: m/z 43 (M⁺).

2-Cyclopropyl-[1,8]naphthyridine-3-carboxylic acid [4-(2,6-difluoro-phenyl)-2-thioxo-thiazol-3-yl]-amide, 8d

Recrystallised in methanol, the solid compound was filtered and dried to offer light yellow solid (0.21 g, 44%). IR (KBr): 2235 (aliph. CH₂), 1735 (CO, amide), 1765 (CS), 3135 cm⁻¹ (NH); ¹H NMR (500 MHz, DMSO-d₆): δ 1.12 (m, 4H, J = 15 Hz, CH₂), 1.22 (m, 1H, J = 7.5 Hz, CH), 6.26 (s, 1H,
CH), 7.28-7.46 (m, 3H, J = 15 Hz, 3CH), 8.24 (s, 1H, NH), 8.29 (d, 1H, CH), 8.42 (d, 1H, CH), 9.22 (d, 1H, CH), $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 7.1 (2CH$_2$), 8.01 (CH), 127.2, 128.2 (2CH), 131.3, 133.2 (2CH), 144.3, 146.2 (2CH), 167.4 (CH); MS: m/z 441 [M+].

N-(2-Cyclopropyl-[1,8]naphthyridine-3-carbonyl)-guanidine, 9

To a solution of 2-cyclopropyl-[1,8]naphthyridine-3-carboxylic acid ethyl ester 1 (0.5 g, 2.06 mmol) in ethanol (5 mL), was added guanidine hydrochloride (0.29 g, 3.09 mmol), the resulting solution was heated to offer reddish colour solid (0.21 g, 24%). IR (KBr): 2215 (aliph. CH), 1735 (CO, amide), 3120 (NH), 3235 cm$^{-1}$ (2CH), 144.2 (2CH), 167.4 (CH); MS: m/z 341 [M+].

4-(2-Cyclopropyl-[1,8]naphthyridin-3-yl)-6-(4-nitro-phenyl)-[1,3,5]triazin-2-ylamine, 10c

Recrystalised in acetone, the solid compound was filtered and dried to offer reddish colour solid (0.13 g, 21%). IR (KBr): 2235 (aliph. CH$_2$), 3245 cm$^{-1}$ (NH$_2$); $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.35 (m, 4H, J = 15 Hz, CH$_2$), 1.46 (m, 1H, J = 7.5 Hz, CH), 4.36 (bs, 2H, NH$_2$), 7.46-7.58 (m, 4H, J = 15 Hz, 4CH), 8.29 (d, 1H, CH), 8.62 (d, 1H, CH), 9.34 (d, 1H, CH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 7.2 (2CH$_2$), 8.23 (CH), 121.2, 123.2 (2CH), 125.3, 132.2 (2CH), 144.3, 149.2 (2CH), 167.4 (CH); MS: m/z 386 [M+].

4-(2-Cyclopropyl-[1,8]naphthyridin-3-yl)-6-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-[1,3,5]triazin-2-ylamine, 10a

To a solution of N-(2-cyclopropyl-[1,8]naphthyridin-3-carbonyl)-guanidine 9 (0.5 g, 1.71 mmol) in ethanol (10 mL), was added benzonitrile (0.26 g, 2.56 mmol), the resulting solution was heated to offer reddish colour solid (0.21 g, 24%). IR (KBr): 2225 (aliph. CH$_2$), 3231 cm$^{-1}$ (NH$_2$); $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.05 (m, 4H, J = 15 Hz, CH$_2$), 1.24 (m, 1H, J = 7.5 Hz, CH), 4.16 (bs, 2H, NH$_2$), 7.46-7.53 (m, 5H, J = 15 Hz, 5CH), 8.19 (d, 1H, CH), 8.36 (d, 1H, CH), 9.14 (d, 1H, CH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 7.2 (2CH$_2$), 8.13 (CH), 123.2, 126.2 (2CH), 129.3, 131.2 (2CH), 142.3, 145.2 (2CH), 169.4 (CH); MS : m/z 341 [M+].

4-(4-Chloro-phenyl)-6-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-[1,3,5]triazin-2-ylamine, 10b

Recrystalised in acetone, the solid compound was filtered and dried to offer reddish colour solid (0.21 g, 24%). IR (KBr): 2215 (aliph. CH$_2$), 3235 cm$^{-1}$ (NH$_2$); $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.25 (m, 4H, J = 15 Hz, CH$_2$), 1.44 (m, 1H, J = 7.5 Hz, CH), 4.46 (bs, 2H, NH$_2$), 7.56-7.63 (m, 4H, J = 15 Hz, 4CH), 8.29 (d, 1H, CH), 8.62 (d, 1H, CH), 9.34 (d, 1H, CH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 7.2 (2CH$_2$), 8.23 (CH), 121.2, 123.2 (2CH), 126.3, 130.2 (2CH), 141.3, 144.2 (2CH), 167.4 (CH); MS: m/z 444 [M+].

4-(4-Bromo-phenyl)-6-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-[1,3,5]triazin-2-ylamine, 10d

Recrystalised in acetone, the solid compound was filtered and dried to offer reddish colour solid (0.24 g, 28%). IR (KBr): 2215 (aliph. CH$_2$), 3235 cm$^{-1}$ (NH$_2$); $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.25 (m, 4H, J = 15 Hz, CH$_2$), 1.44 (m, 1H, J = 7.5 Hz, CH), 4.46 (bs, 2H, NH$_2$), 7.56-7.63 (m, 4H, J = 15 Hz, 4CH), 8.29 (d, 1H, CH), 8.62 (d, 1H, CH), 9.34 (d, 1H, CH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 7.2 (2CH$_2$), 8.23 (CH), 121.2, 123.2 (2CH), 126.3, 130.2 (2CH), 141.3, 144.2 (2CH), 167.4 (CH); MS: m/z 420 [M+].

4-(3-Chloro-phenyl)-6-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-[1,3,5]triazin-2-ylamine, 10e

Recrystalised in acetone, the solid compound was filtered and dried to offer reddish colour solid (0.21 g, 24%). IR (KBr): 2215 (aliph. CH$_2$), 3235 cm$^{-1}$ (NH$_2$); $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.25 (m, 4H, J = 15 Hz, CH$_2$), 1.44 (m, 1H, J = 7.5 Hz, CH), 4.46 (bs, 2H, NH$_2$), 7.56-7.63 (m, 4H, J = 15 Hz, 4CH), 8.29 (d, 1H, CH), 8.62 (d, 1H, CH), 9.34 (d, 1H, CH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 7.2 (2CH$_2$), 8.23 (CH), 121.2, 123.2 (2CH), 126.3, 130.2 (2CH), 141.3, 144.2 (2CH), 167.4 (CH); MS: m/z 420 [M+].
The ethanol was evaporated completely and co-distilled with toluene twice and recrystallised in ethylacetate in hexane (3:1) to provide 2-cyclopropyl-[1,8]naphthyridine-3-carbonyl acid hydrazide\(^2\) as off white solid in 90% yield, which on treatment with carbon disulphide in aq. potassium hydroxide solution to provide N-(2-cyclopropyl-[1,8]naphthyridine-3-carbonyl)-hydrazine carbodiimide in presence of 10% HCl by refluxing at 180\(^\circ\)C to provide intermediate 5, which on reaction with substituted salicilaldehydes to yield 4-(2-cyclopropyl-[1,8]naphthyridin-3-yl)-6-phenyl-[1,3,5]triazin-2-ylamine (10a-e). Further continuation of our work, intermediate 2 with diethyl malonate refluxing in ethanol to offer intermediate 6, which on reaction with substituted salicylaldehydes to provide coumarins (6). Further continuation of our work intermediate 1 reacts with guanidine hydrochloride in presence of 10% HCl by refluxing at 180\(^\circ\)C to provide intermediate 7, which on reaction with aromatic nitriles by refluxing at 180\(^\circ\)C to offered cyclised product 8.

### Antimicrobial activity

The 1,8-naphthyridine derivatives were evaluated in vitro for their antimicrobial activity against *S. aureus*, *E. coli*, *Klebsiella pneumonia*, *Salmonella paratyphi A*, *Salmonella paratyphi B* and *Micrococcus luteus* bacteria, using the cup diffusion technique\(^1,10,15,16\). The compounds were dissolved in DMSO at a concentration of 1 mg/mL. Sterile nutrient agar (Oxoid) was incubated with the organisms tested. Each 100
mL of the medium received 1 mL of 24 hr broth culture and 3 drops of the test compounds were placed separately in cups (8 mm diameter) cut in the agar. The plates were incubated at 37°C for 24 hr, DMSO as a blank showed no inhibition zone. A solution of 0.1% of penicillin G or streptomycin sulphate in DMSO was used as the standard for Gram-positive and Gram-negative bacteria, respectively. The resulting inhibition zone diameters (I.Z) were measured in mm. For compounds, which exhibited reasonable inhibition zones (≥ 20 mm), the MIC was determined. The organisms tested were grown in suitable broth media for 24 hr at 37°C.

The new 1,8-naphthyridine derivatives were evaluated in vitro for their antibacterial activity against *S. aureus*, *Klebsiella pneumonia*, *E. coli*, *Salmonella paratyphi A*, *Salmonella paratyphi B*, *Micrococcus luteus* as Gram-positive bacteria and Gram-negative bacteria. Furthermore, the MIC values in µg/mL were calculated using the cup diffusion technique for compounds which exhibited reasonable inhibition zones (≥ 20 mm). The results of the biological evaluation indicate that all the compounds tested were moderately active than the reference standards. Compounds 5a-d and 6, 7, 8d possessed good activity with an MIC value of 15-17 and compounds 8a, b, c, e, 10a, b, c, d possessed moderate activity with MIC values from 10 to 15 and compounds 3, 4 showed reasonable activity, and some compounds showed poor activity while others were found to be inactive (Table II).

On the basis of these results the 1,8-naphthyridine derivatives were found to be more active against *S. aureus* and *E. coli* than *Klebsiella pneumonia*.

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