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DESIGN AND SYNTHESIS OF NOVEL SUBSTITUTED 1,8-NAPHTHYRIDIN-2-YL-AMIDE DERIVATIVES AT AMBIENT TEMPERATURE AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT: A new series of substituted 1,8-naphthyridin-2-yl-amide derivatives have been successfully synthesized at ambient temperature by involving various substituted 3-phenyl-1,8-naphthyridin-2-amines with aryl benzoic acids **4** furnished compounds (**5a-l**) with good yields. The molecular structures of the newly synthesized compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral data as well as elemental analyses. All the newly synthesized compounds were evaluated for their in *vitro* antimicrobial activity. All these compounds exhibit good antibacterial and excellent antifungal activity. Among them, compound **5h, 5k** and **5g** showed remarkable inhibition of antimicrobial activity.

KEYWORDS: 1,8-naphthyridines, aryl benzoic acids, HATU, antimicrobial activity.

INTRODUCTION

1,8-Naphthyridine derivatives are significant class of heterocyclic compounds in medicinal chemistry. The 1,8-Naphthyridine ring system is a core structure in various synthetic pharmaceutical compounds exhibit interesting pharmacological activities include that anti-inflammatory[i], anti-tumor[ii], antibacterial[iii], ant-malarial [iv], anti-aggressive[v], anticancer[vi], antihypertensive[vii], anti-allergic[viii], anti-HIV[ix], gastric anti-secretary activities[x] and benzodiazepinereceptor activity [xi]. They were also used for the treatment of Alzheimer's disease [xii]. Some of the biological potent 1,8-naphthyridine derivatives are shown in **Fig.1**

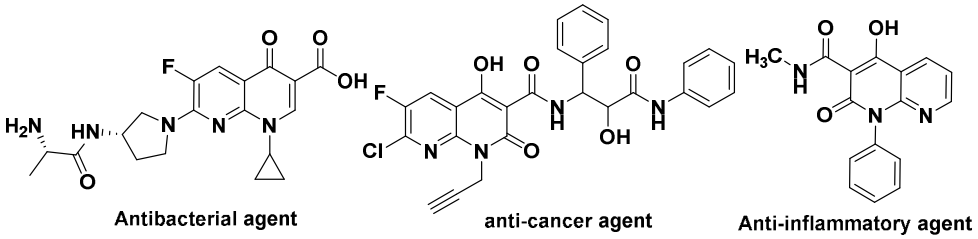


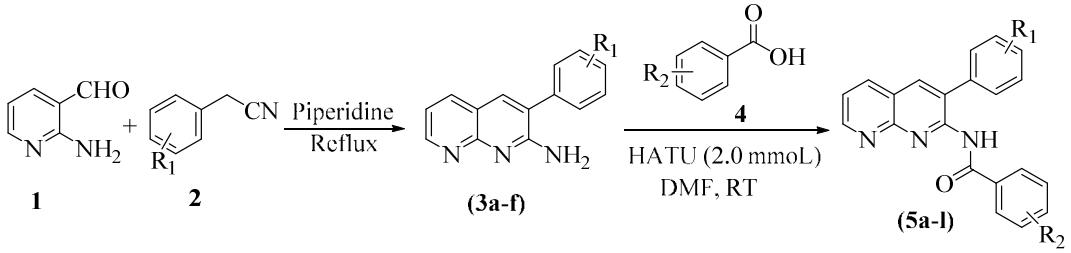
Fig. 1 Some of the bioactive 1,8-Naphthyridines

Amide bond construction is a basically very important reaction in organic synthesis and peptides and proteins play an important role in modern biology. Amide bonds are not limited to naturally occurring constituents and biological systems. They are present in vast group of

molecules like worldwide top selling "Atorvastatin" blocks the production of cholesterol[xiii]. This makes the necessary of amide function to synthetic organic researcher to synthesize amide bond containing heterocyclic compounds. Enthused by the above facts, we wish to synthesized amide bond containing substituted 1,8-naphthyridin-2-yl-amide derivatives at ambient temperature. In continuation, of our previous studies on the development eco-friendly methodology and biological active compounds [xiv-xvi] Here in, we report, synthesis and in *vitro* antibacterial and antifungal activities against various pathogenic strains and displayed promising inhibitory potential activities.

RESULTS AND DISCUSSION

A general approach to synthesize the premeditated compounds is summarized in **Scheme 1**. The synthesis of substituted 1,8-naphthyridin-2-yl-amide derivatives involving by various substituted 3-phenyl-1,8-naphthyridin-2-amines (**3a-f**) with aryl benzoic acids (**4**) in the presence of HATU and DBU as a base in DMF at ambient temperature furnished **(5a-l)** compounds with good yields.



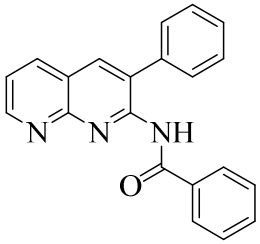
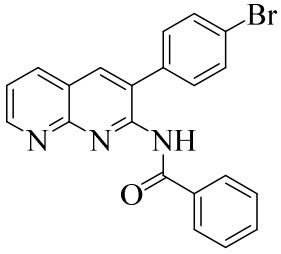
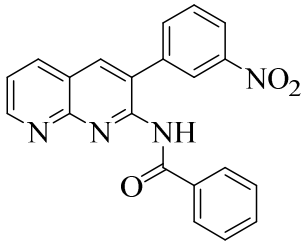
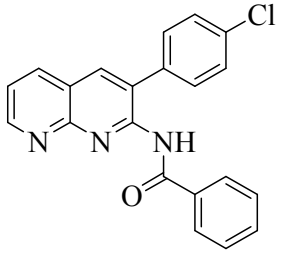
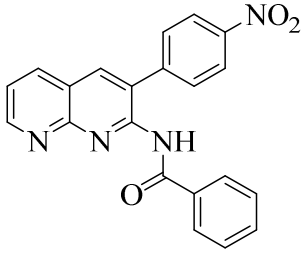
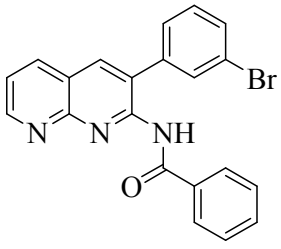
R_1=H, 4-Br, 3-NO_2, 4-Cl, 4-NO_2, 3-Br

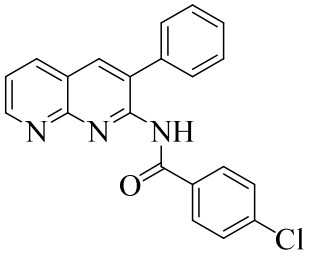
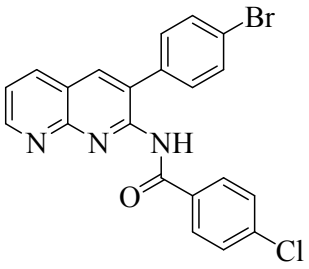
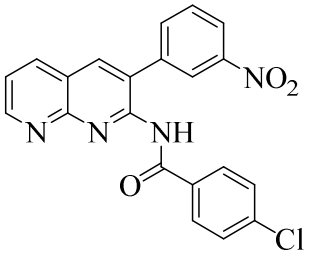
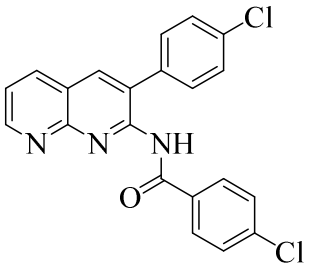
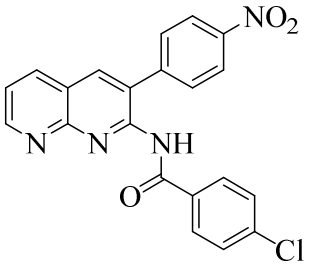
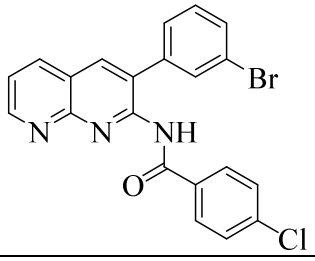
R_2= H, 4-Cl

Scheme 1 Synthesis of novel substituted 1,8-naphthyridin-2-yl-amide derivatives at room temperature.

Optimization of the reaction conditions: Initially, for optimizing the reaction condition we have studied with various types of organic bases such as Pyridine, Et_3N, DABCO, DBU and DMAP in presence of HATU among them DBU is the most effective for this reaction giving 84% of yield. Remaining bases such as Pyridine, Et_3N, DABCO and DMAP were less effective gave 70%, 68%, 71% and 72 % yields, respectively. For increasing the yield of the reaction we have screened various solvents such as (CH_3OH, DCM, EtOH, DMF and DMA) to test their efficiency at RT among these DMF is giving better yields. The best optimized condition for this reaction HATU is a catalyst; DBU as a base and DMF solvent at room temperature. With this efficient transformation (HATU, 2 mmoL 760.40 mg, DBU, DMF, RT) we have successfully synthesized a new series of substituted 1,8-naphthyridin-2-yl-amide derivatives **(5a-l)** with good yields. The results are summarized in Table 1.We have screened systematic biological evaluation of in *vitro* antibacterial and anti fungal activity.

Table 1 Synthesis of 1,8-naphthyridin-2-yl-amide derivatives (5a-l) at ambient temperature.

Entry	Analog	Product	Time (h)	Yield (%)
1	**5a**		6	85
2	**5b**		5	86
3	**5c**		6.5	87
4	**5d**		6	85
5	**5e**		5	89
6	**5f**		6.5	88

7	**5g**		7	86
8	**5h**		6	84
9	**5i**		5.5	85
10	**5j**		7	87
11	**5k**		6.5	85
12	**5l**		6	88

ANTI MICROBIAL SCREENING

Anti-bacterial activity: All the newly synthesized compounds **(5a-l)** were screened for their in-*vitro* antibacterial activity against gram-positive bacteria (*Staphylococcus epidermidis*) and

gram-negative bacteria (*Escherichia coli*) using Amoxicillin as standard drug. Activity was resolute by the disc diffusion technique [xvii]. All these compounds exhibited superior activity against the all tested microorganisms. Among them compounds **5h, 5k** and **5g** demonstrate highest inhibition activity is shown in Table 1.

Anti-fungal activity: All these synthesized compounds **(5a-l)** were tested for their in-vitro antifungal activity against the two pathogenic fungal strains *Aspergillus niger* and *Aspergillus flavus* by agar well diffusion technique [xvii] compared with standard drug Griseofulvin and results are summarized in Table 1. All these tested compounds displayed moderate to high inhibition activity against the pathogenic fungal strains. Among them compounds **5h, 5k** and **5g** displayed highest inhibition activity.

Table.1 Antimicrobial activity data of the newly synthesized compounds (5a-l) at 250 µg/disk zone of inhibition in mm.

Compounds	*Bacterial strains*						*Fungal strains*					
	S. epidermidis (Conc.in µg/mL)			*E. coli* (Conc.in µg/mL)			*A. niger* (Conc.in µg/mL)			*A. flavus* (Conc.in µg/mL)		
	10	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**
5a	4	12	19	5	10	16	5	15	19	5	11	17
5b	6	14	18	5	12	17	5	13	18	8	14	19
5c	7	12	20	6	11	20	5	11	19	5	13	18
5d	5	13	16	6	12	19	6	12	19	6	11	18
5e	6	15	20	7	13	17	5	11	20	7	13	20
5f	4	13	16	5	12	17	5	13	17	6	11	15
5g	**6**	**12**	**20**	**5**	**11**	**18**	**6**	**19**	**18**	**6**	**12**	**19**
5h	**8**	**17**	**27**	**8**	**18**	**27**	**9**	**16**	**26**	**8**	**16**	**27**
5i	6	15	21	7	13	20	7	14	19	7	13	20
5j	5	14	18	6	12	19	6	12	19	6	11	18
5k	**7**	**15**	**26**	**7**	**18**	**25**	**7**	**14**	**25**	**6**	**15**	**26**
5l	5	14	19	6	11	15	6	10	18	5	12	19
Amoxicillin	**9**	**18**	**29**	**9**	**19**	**28**	-	-	-	-	-	-
Griseofulvin	-	-	-	-	-	-	**9**	**18**	**28**	**9**	**18**	**28**

EXPERIMENTAL

All the solvents and reagents were obtained from commercial sources and used as such unless noted otherwise. Melting points were determined in open capillaries using Buchi melting point apparatus and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography with F254 silica-gel precoated aluminum sheets using hexane/ethyl acetate (7/3) as eluent. The absorption spectral studies were conceded out by Ultraviolet-visible spectrophotometer. IR spectra were recorded on Perkin-Elmer 100S spectrophotometer using KBr pellet. NMR spectra were recorded on Bruker 400 MHz spectrometer using DMSO-d6 as solvent and TMS as an internal standard. Mass spectra (ESI) were recorded on a Jeo1 JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer.

General procedure for the synthesis of 3-phenyl-1,8-naphthyridin-2-amines (3a-f)

To take compound 2-amino-nicotinaldehyde **1** (1 mmol, 122.12 mg), Aryl acetonitrile **2** (1 mmol) and added catalytic amount of piperidine under reflux conditions 4-5 hours. After

completion of the reaction (monitored by the TLC) the reaction mixture was cooled to room temperature and the reaction was poured into cold water. The solid obtained was filtered, washed with water, and dried under vacuum to obtain the corresponding pure amide products (3a-f).

General procedure for the synthesis of 2-bromo-N-(3-Aryl-1,8-naphthyridin-2-yl)thiazole-4-carboxamide derivatives (5a-l)

To take compound 3-phenyl-1,8-naphthyridin-2-amine **3** (1.1 mmol), substituted aryl benzoic acid **4** (1 mmol), HATU (2 mmol, 760.40 mg) and added 0.5 mmoL DBU dissolved in DMF solvent and stirred 5-7 hours at ambient temperature. After completion of the reaction (monitored by the TLC) the reaction mixture was poured into cold water. The solid found was filtered, washed with water and recrystallized from methanol obtained corresponding pure products **(5a-l).**Yield of the products is 85-89%.

N-(3-phenyl-1,8-naphthyridin-2-yl)benzamide (5a)

Pale brown solid; M.p.: 175-176 °C; IR: 3381, 1653, 1548, 1157, 896 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.21 (s, 1H), 8.71 (m, 3H), 8.51 (s, 1H), 7.81-6.79 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 153.8, 149.7, 148.6, 143.8, 136.4, 135.3, 132.1, 130.5, 129.7, 129.5, 128.6, 127.3, 126.2, 120.5, 117.6, 114.7 ppm. ESI-MS: *m/z* 326.12 (100.0%) $[M+H]^{+1}$.

N-(3-(4-bromophenyl)-1,8-naphthyridin-2-yl)benzamide (5b)

Pale brown solid; M.p.: 263-264 °C; IR: 3372, 1676, 1568, 1162, 891 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.23 (s, 1H), 9.26 (s, 1H), 8.67 (d, J = 6.8 Hz, 2H), 8.56 (s, 1H), 7.89-7.58 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.4, 155.8, 148.5, 148.2, 143.8, 136.4, 135.3, 132.4, 131.5, 129.6, 129.3, 128.6, 127.4, 126.2, 120.5, 119.5, 115.4 ppm. ESI-MS: *m/z* 404.21 $[M+H]^{+1}$.

N-(3-(3-nitrophenyl)-1,8-naphthyridin-2-yl)benzamide (5c)

Pale block solid; M.p.: 143-144 °C; IR: 3383, 1714, 1660, 1521, 1192, 835 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 9.17 (s, 1H), 8.68 (d, J = 6.8 Hz, 2H), 7.98-7.67 (m, 10H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 158.4, 149.2, 148.8, 148.5, 136.7, 136.1, 131.4, 129.8, 129.4, 128.7, 127.6, 125.5, 124.6, 120.3, 117.7, 115.6 ppm. ESI-MS: *m/z* 371.11 $[M+H]^{+1}$.

N-(3-(4-chlorophenyl)-1,8-naphthyridin-2-yl)benzamide (5d)

Pale yellow solid; M.p.: 192-193 °C; IR: 3364, 1678, 1575, 1169, 876 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 9.43 s, 1H), 8.72 (m, 3H), 8.62 (d, J = 6.8 Hz, 2H), 7.87-7.63 (m, 7H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7, 154.8, 148.3, 147.7, 144.5, 136.4, 135.6, 131.7, 130.5, 129.6, 129.4, 128.9, 127.4, 126.2, 121.5, 118.7, 115.2 ppm. ESI-MS: *m/z* 360.08 $[M+H]^{+1}$.

N-(3-(4-nitrophenyl)-1,8-naphthyridin-2-yl)benzamide (5e)

Pale block solid; M.p.: 214-215 °C; IR: 3381, 1658, 1579, 1240, 833 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 9.19 (s, 1H), 8.51 (d, J = 6.8 Hz, 2H), 8.38-8.27 (m, 6H), 7.66 (m, 4H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.7, 153.3, 148.7, 146.3, 143.1, 136.8, 133.6, 132.6, 130.5, 129.7, 129.3, 128.8, 127.6, 126.4, 122.5, 119.6, 116.2 ppm. ESI-MS: *m/z* 371.11 (100.0%) $[M+H]^{+1}$.

N-(3-(3-bromophenyl)-1,8-naphthyridin-2-yl)benzamide (5f)

Pale brown solid; M.p.: 186-187°C; IR: 3352, 1720, 1524, 1194 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.21 (s, 1H), 9.31 (s, 1H), 8.03 (s, 1H), 7.94-7.79(m, 9H), 6.98(s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3, 154.8, 148.7, 148.3, 143.8, 137.4, 135.3, 132.1, 131.4, 129.8, 129.2, 128.6, 128.1, 127.4, 126.2, 120.5, 119.7, 115.3 ppm. ESI-MS: *m/z* 404.17 $[M+H]^{+1}$.

4-chloro-N-(3-phenyl-1,8-naphthyridin-2-yl)benzamide (5g)
Pale yellow solid; M.p.: 244-245 °C; IR: 3368, 1657, 1152, 895 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 8.71 (d, J = 7.2 Hz, 2H), 8.56 (m, 2H), 7.81-6.79 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 160.8, 152.2, 143.8, 136.7, 135.3, 132.1, 130.5, 129.9, 129.5, 128.4, 127.8, 126.5, 121.3, 115.3 ppm. ESI-MS: *m/z* 360.14 (100.0%) $[M+H]^{+1}$.
N-(3-(4-bromophenyl)-1,8-naphthyridin-2-yl)-4-chlorobenzamide (5h)
Pale yellow solid; M.p.: 291-293 °C; IR: 3365, 1647, 1541, 1159, 887 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H), 8.75 (s, 1H), 8.42 (m, 2H), 7.79-6.7.29 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 160.3, 151.3, 142.6, 135.4, 135.3, 130.7, 129.7, 128.3, 127.2, 126.1, 121.6, 114.7 ppm. ESI-MS: *m/z* 439.16 (100.0%) $[M+H]^{+2}$.
4-chloro-N-(3-(3-nitrophenyl)-1,8-naphthyridin-2-yl)benzamide (5i)
White solid; M.p.: 207-208 °C; IR: 3357, 1649, 1557, 1148, 893 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.63 (m, 3H), 8.56 (s, 1H), 7.56-6.79 (m, 8H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 160.4, 151.4, 142.5, 136.6, 134.7, 132.4, 129.7, 129.3, 128.5, 127.3, 126.2, 122.3, 114.8 ppm. ESI-MS: *m/z* 405.23 (100.0%) $[M+H]^{+1}$.
4-chloro-N-(3-(4-chlorophenyl)-1,8-naphthyridin-2-yl)benzamide (5j)
Pale yellow solid; M.p.: 183-184 °C; IR: 3372, 1655, 1552, 887 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.24 (s, 1H), 8.63 (d, J = 7.8 Hz, 2H), 8.38 (m, 3H), 7.59-6.92 (m, 7H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 161.3, 153.2, 137.5, 134.6, 132.4, 129.6, 129.3, 128.5, 127.6, 126.2, 114.6 ppm. ESI-MS: *m/z* 394.37 (100.0%) $[M+H]^{+1}$.
4-chloro-N-(3-(4-nitrophenyl)-1,8-naphthyridin-2-yl)benzamide (5k)
Pale yellow solid; M.p.: 226-227 °C; IR: 3372, 1649, 1556, 1159, 885 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1H), 8.71 (s, 1H), 8.37 (d, J = 7.2 Hz, 2H), 7.72-7.04 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 160.4, 151.2, 136.5, 132.7, 130.8, 129.5, 129.1, 128.3, 127.6, 121.3, 114.5 ppm. ESI-MS: *m/z* 405.42 (100.0%) $[M+H]^{+1}$.
N-(3-(3-bromophenyl)-1,8-naphthyridin-2-yl)-4-chlorobenzamide (5l)
Pale yellow solid; M.p: 254-255 °C; IR: 3373, 1646, 1547, 892 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.22 (s, 1H), 8.67 (d, J = 7.6 Hz, 2H), 8.28 (s, 1H), 7.76-7.21 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 160.3, 151.4, 141.5, 135.8, 132.3, 130.8, 129.7, 129.4, 128.5, 127.4, 121.6, 115.8 ppm. ESI-MS: *m/z* 439.39 (100.0%) $[M+H]^{+2}$.

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