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Microwave one-step synthesis and evaluation of antimicrobial activities of new fused [1,8]naphthyridine derivatives

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ABSTRACT

A simple and efficient procedure has been described for the synthesis of benzo[*g*]naphtho[*b*][1,8]naphthyrindes **3** by the condensation of 2-chloro-3-formylquinoline **1** with 1-naphthylamine **2** under microwave irradiation condition. The structures of the newly synthesized compounds were confirmed by analytical and spectral (IR, NMR, and Mass) data. All these compounds were evaluated for their *in vitro* growth-inhibitory activity against several microbes.

Keywords: Naphthylamine, Microwaves, Naphthyridines, Condensation, Anti-microbial activity.

INTRODUCTION

Recently there has been increased interest in the synthesis of 1,8-naphthyridine and their application in medicinal chemistry as quinoline bioisosteres.[1] 1,8-Naphthyridine derivatives represent one of the must active classes of compound possessing a wide spectrum of biological activities such as antibacterial,[2,3] antitumor,[4] antimalarial,[5] anti-inflammatory[6] and antihypertensive.[7] Traditionally, the cyclocondensation of aminopyridine with diethyl methoxy methlenemalonate (**EMME**) has provided entry into the naphthyridine core.[8] In order to prepare even, the simplest mono- and disubstituted 1,8-naphthyridines, it is necessary to subject the product derived from EMME synthesis, which is lengthy and low yielding series of transformation.[9] A simple way to the synthesis of naphthyridine is treatment of amino pyridine with α,β-unsaturated ketones or aldehydes.

Now a day, the quinoline derivatives are used as a convenient starting material for the synthesis of various fused naphthyridines[10,11] as they display characteristic properties in pharmacological and chemotherapeutic field. Recently, microwave induced rate acceleration technology has become a powerful tool in organic synthesis, because, the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction time.[12,13] By using this technique many organic reactions such as condensation,[14] cycloaddition,[15] Michael addition,[16] rearrangement[17] and miscellaneous reactions[18] have been carried out due to the reduction in reaction times, operational simplicity, cleaner reactions, easier work-up and better yield. In this paper, we report the synthesis of new ring fused [1,8]naphthyridines **3a-g** from 2-chloro-3 formylquinolines by condensing with 1-naphthylamine and all the compounds were characterized by IR, NMR, Mass spectral studies and elemental analysis. This series of compounds were then subjected to *in vitro* antibacterial and antifungal activities against some standard strains.

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MATERIALS AND METHODS

Melting points (mp) were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (Chemical shifts in δ, ppm).

Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Shimadzu GCMS-QP5050A (70 ev) mass spectrometer. For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used.

General Procedure for Synthesis of benzo[*g*]naphtho[*b*][1,8]naphthyridines: (3a-g)

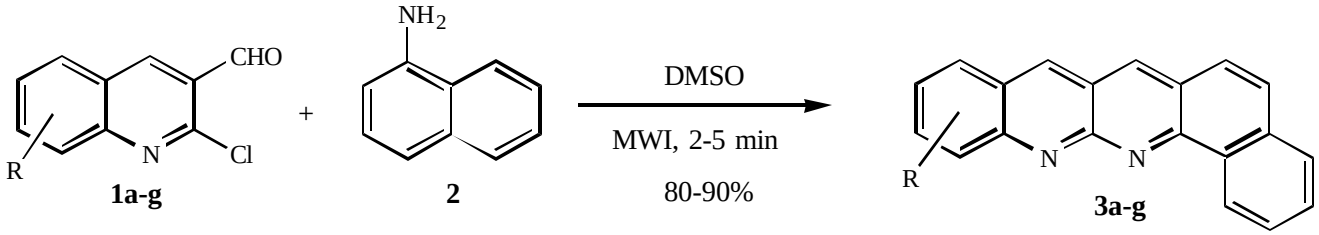
A mixture of respective 2-chloro-3-formylquinolines (**1a-g**) (0.001 mol), 1-naphthylamine (0.0012 mol) and DMSO (5 mL) was taken in a 100 mL beaker. The reaction mixture was irradiated in microwave oven at power 160 W for the specified time [**Table 1**]. TLC monitored the reaction at 30 s intervals. After completion of reaction, the mixture was allowed to cool. The solid separated was collected and purified by column chromatography using petroleum ether and ethyl acetate as an eluant.

Benzo[*g*]naphtho[*b*][1,8]naphthyridine 3a:

IR (KBr, cm^{-1}): 1612, 1571 (>C=N); ^{1}H NMR (DMSO-d_6): δ 7.16-8.42(m,10H,ArH),9.10(s,1H,C_8-H),9.22(s, 1H, C_7-H); Ms (m/z): 280; Anal. Calc. ($C_{20}H_{12}N_2$): C, 85.71, H, 4.32, N, 10.00; Found: 85.69, H, 4.31, N, 9.98.

Table 1.Synthesis of Compounds 3a-g from 1a-g under microwaves

Compound	Time (min)	Yield (%)	mp °C
3a	3	84	194
3b	2	90	172
3c	4	86	210
3d	3	88	196
3e	4	85	191
3f	5	80	202
3g	4	82	242



3a: R = H, **3b**: R = 10-CH_3 **3c**: R = 12-CH_3 **3d**: 10-OCH_3

3e: R = 12-OCH_3 **3f**: R = 10-Cl **3g**: R = 10-Br

Scheme 1

Table 2: *In vitro* antimicrobial activity of 3a-g (µg/disc) by disc diffusion assay

Microorganisms	Diameter of zone of inhibition in mm (mg/disc)															
	3a		3b		3c		3d		3e		3f		3g		A	B
	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	500	1000	5	10
Escherichia coli (NCIM 2065) [a]	9	12	7	10	7	9	7	9	7	10	9	11	8	10	23	NT
Pseudomonas aeruginosa (NCIM 2200) [a]	7	9	-	8	-	9	7	10	7	10	7	12	8	10	22	NT
Klebsiella aerogenes (NCIM 2239) [a]	-	-	-	-	7	9	7	10	-	-	-	-	7	10	24	NT
Salmonella typhimurium (NCIM 2501) [a]	-	-	7	8	-	-	7	8	-	-	10	12	8	10	21	NT
Bacillus subtilis (NCIM 2063) [a]	-	8	-	7	-	8	7	10	7	9	9	11	7	9	24	NT
Bacillus cereus (NCIM 2155) [a]	9	10	9	13	10	12	10	13	7	9	8	10	7	9	19	NT
Vibrio fischeri (NCIM 2154) [a]	-	-	-	-	-	-	-	-	8	10	-	-	-	-	27	NT
Corynebacterium rubrum (NCIM 2252) [a]	-	-	-	-	-	-	-	-	-	-	9	10	7	9	25	NT
Staphylococcus albus (NCIM 2178) [a]	-	-	-	-	-	-	-	-	-	9	7	10	7	10	21	NT
Proteus vulgaris (NCIM 2027) [a]	-	-	-	-	-	-	-	-	8	9	-	-	-	-	19	NT
Aspergillus niger (NCIM 1196) [b]	-	-	-	-	-	-	-	-	-	-	8	10	8	10	NT	16
Aspergillus flavus (NCIM 535) [b]	10	13	9	10	7	9	-	10	9	13	9	11	9	12	NT	16
Rhodotorula rubra (NCIM 3174) [b]	9	12	7	10	7	11	-	8	8	10	7	10	-	8	NT	17
Aspergillus fumigatus (NCIM 902) [b]	-	-	-	-	-	-	-	-	-	-	-	-	9	10	NT	18
Aspergillus parasiticus (NCIM 904) [b]	-	8	9	12	7	9	8	10	8	9	9	11	8	10	NT	18
Penicillium chrysogenum (NCIM 707) [b]	-	-	-	-	-	-	-	-	-	8	-	-	-	-	NT	21
Lipomyces lipofera (NCIM 3252) [b]	-	-	-	-	-	-	-	-	-	-	8	11	9	10	NT	18
Trichoderma viridie (NCIM 1195) [b]	9	10	11	14	10	13	8	10	9	11	9	10	8	11	NT	19

[a] *bacteria* [b] *fungi ;* ***A*** *= Ofloxacin,* ***B*** *= Clotrimazole, - No inhibition, NT- Not Tested*

Table 3: Minimum Inhibitory Concentration values of 3a-g (µg/ml) against the microorganisms tested in broth dilution assay

Microorganisms	3a	3b	3c	3d	3e	3f	3g
Escherichia coli (NCIM 2065) [a]	31.2	62.5	125	125	62.5	31.2	62.5
Pseudomonas aeruginosa (NCIM 2200) [a]	125	125	125	62.5	62.5	62.5	62.5
Klebsiella aerogenes (NCIM 2239) [a]	-	-	125	62.5	-	-	62.5
Salmonella typhimurium (NCIM 2501) [a]	-	125	-	125	-	31.2	62.5
Bacillus subtilis (NCIM 2063) [a]	125	125	125	62.5	125	62.5	125
Bacillus cereus (NCIM 2155) [a]	62.5	15.6	31.2	15.6	62.5	62.5	62.5
Vibrio fischeri (NCIM 2154) [a]	-	-	-	-	62.5	-	-
Corynebacterium rubrum (NCIM 2252) [a]	-	-	-	-	-	62.5	125
Staphylococcus albus (NCIM 2178) [a]	-	-	-	-	62.5	62.5	62.5
Proteus vulgaris (NCIM 2027) [a]		-	-	-	125	-	-
Aspergillus niger (NCIM 1196) [b]	-	-	-	-	-	62.5	62.5
Aspergillus flavus (NCIM 535) [b]	15.6	62.5	62.5	62.5	15.6	31.2	31.2
Rhodotorula rubra (NCIM 3174) [b]	31.2	62.5	31.2	125	62.5	62.5	125
Aspergillus fumigatus (NCIM 902) [b]	-	-	-	-	-	-	125
Aspergillus parasiticus (NCIM 904) [b]	125	31.2	62.5	31.2	125	31.2	62.5
Penicillium chrysogenum (NCIM 707) [b]	-	-	-	-	125	-	-
Lipomyces lipofera (NCIM 3252) [b]	-	-	-	-	-	62.5	62.5
Trichoderma viridie (NCIM 1195) [b]	62.5	7.8	15.6	62.5	31.2	62.5	31.2

[a] *bacteria* [b] *fungi; - Not Tested*

10-Methyl-benzo[*g*]naphtho[*b*][1,8]naphthyridine 3b:

IR (KBr, cm^{-1}): 1612, 1570 (>C=N); ^1H NMR (DMSO-d_6): δ 2.58 (s, 3H, C_{10}-CH_3), 7.16-8.96 (m, 9H, Ar-H), 9.11 (s, 1H, C_8-H), 9.26 (s, 1H, C_7-H); Ms (m/z): 294; Anal. Calc. ($C_{21}H_{14}N_2$): C, 85.71, H, 4.80, N, 9.52; Found: C, 85.70, H, 4.78, N, 9.50.

12-Methyl-benzo[*g*]naphtho[*b*][1,8]naphthyridine 3c:

IR (KBr, cm^{-1}): 1613, 1575 (>C=N); ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H, C_{12}-CH_3), 7.20-8.45 (m, 9H, Ar-H), 9.08 (s, 1H, C_8-H), 9.20 (s, 1H, C_7-H); Ms (m/z): 294; Anal. Calc. ($C_{21}H_{14}N_2$): C, 85.71, H, 4.80, N, 9.52; Found; C, 85.71, H, 4.77, N, 9.51.

10-Methoxy-benzo[*g*]naphtho[*b*][1,8]naphthyridine 3d:

IR (KBr, cm^{-1}): 1614, 1570 (>C=N); ^1H NMR (DMSO-d_6): δ 3.96 (s, 3H, C_{10}-OCH_3), 7.30-8.65 (m, 7H, Ar-H), 8.96 (s, 1H, C_9-H), 8.99 (d, 1H, C_6-H), 9.15 (s, 1H, C_8-H), 9.24 (s, 1H, C_7-H); Ms (m/z): 310; Anal. Calc. ($C_{21}H_{14}N_2O$): C, 81.29, H, 4.55, N, 9.03; Found: C, 81.26, H, 4.53, N, 9.01.

12-Methoxy-benzo[*g*]naphtho[*b*][1,8]naphthyridine 3e:

IR (KBr, cm^{-1}): 1612, 1570 (>C=N); ^1H NMR (DMSO-d_6): δ 3.90 (s, 3H, C_{12}-OCH_3), 7.36-8.65 (m, 7H, Ar-H), 8.90 (d, 1H, C_9-H), 8.99 (d, 1H, C_6-H), 9.05 (s, 1H, C_8-H), 9.11 (s, 1H, C_7-H); Ms (m/z): 310; Anal. Calc. ($C_{21}H_{14}N_2O$): C, 81.29, H, 4.55, N, 9.03; Found: C, 81.28, H, 4.52, N, 9.02.

10-Chloro-benzo[*g*]naphtho[*b*][1,8]naphthyridine 3f:

IR (KBr, cm^{-1}): 1612, 1568 (>C=N); ^1H NMR (DMSO-d_6): δ 7.30-8.72 (m, 9H, Ar-H), 9.07 (s, 1H, C_8-H), 9.21 (s, 1H, C_7-H);Ms (m/z): 314; Anal. Calc. ($C_{20}H_{11}N_2Cl$): C, 76.43, H, 3.53, N, 8.91; Found: C, 76.40, H, 3.53, N, 8.89.

10-Bromo-benzo[*g*]naphtho[*b*][1,8]naphthyridine 3g:

IR (KBr, cm^{-1}):1610, 1567 (>C=N); ^1H NMR (DMSO-d_6): δ 7.10-8.64 (m, 9H, Ar-H), 9.08 (s, 1H, C_8-H), 9.29 (s, 1H, C_7-H); Ms (m/z): 359; Anal. Calc. ($C_{20}H_{11}N_2Br$): C, 66.87, H, 3.08, N, 7.80; Found: C, 66.87, H, 3.09, N, 7.77.

Antimicrobial activity

All the synthesized compounds were screened for their antibacterial and antifungal activities. For preliminary screening, the antimicrobial tests were carried out by disc-diffusion method.[19] One hundred µL of suspension containing 10^8 CFU/mL of bacteria, 10^6 CFU/mL of fungi were spread on Mueller-Hinton agar medium (MHA) and Sabouraud's dextrose agar (SDA) medium respectively. The discs (6 mm in diameter), impregnated with 10 µl of the test compounds (500 µg/disc and 1000 µg/disc) at the concentration of 50 mg/mL and 100mg/mL were placed on the inoculated agar. Negative controls were prepared using the same solvent (DMSO) employed to dissolve the test compounds. Ofloxacin (5 µg/disc) and Clotrimazole (10 µg/disc) were used as positive reference standard to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37^0C for 24 hr and 27^0C for 72 hr for bacteria and fungi strains respectively. Antimicrobial activity was evaluated by measuring the diameter of zone of inhibition against test organisms.

Minimum inhibitory concentration (MIC) of the compounds was also estimated by broth dilution assay[20] for the microorganisms, which were determined as sensitive to the compounds in disc-diffusion assay. Nutrient broth (NB) and Sabouraud's dextrose broth (SDB) were used to estimate the MIC values of the test compounds against bacteria and fungi respectively. A two fold serial dilution of test compounds were followed with 1mL of sterile broth in test tubes to provide various concentration ranges from 3.9-1000 µg/mL of the test compounds. Ten µl of the test organism was added to each tube and incubated at 37° C for 24 hr and 27° C for 72 hr for bacteria and fungi strains respectively. The highest dilution of the test compound completely inhibiting the test organism was considered as MIC value of the test compound respectively.

RESULTS AND DISCUSSION

2-Chloro-3-formylquinoline **1a** was treated with 1-naphthylamine in presence of dimethylsulphoxide as catalyst under microwaves at power 160 W for 3 min. After completion of the reaction (monitored by TLC) the mixture was allowed to cool slowly. The separated solid **3a** was further purified by column chromatography (silica gel, petroleum ether-ethyl acetate; yield 84%; mp-194°C). The IR spectrum exhibited the absence of carbonyl peak at 1680 cm^{-1} which indicated the loss of aldehyde group due to condensation and showed the presence of two absorption bands at 1612, 1571 cm^{-1} due to two >C=N groups. The ^1H NMR spectrum revealed two sharp singlets at δ 9.10 and 9.22 for C_8- and C_7-protons respectively. All other ten aromatic protons resonance exhibited their absorption between δ 7.16-8.42 as an unresolved multiplet. The mass spectrum indicated the molecular ion peak at m/z 280 and other fragment ion peaks at m/z 251, 227, 185, 154, 140 and 127. All the above spectral data supported the structure of **3a** as benzo[*g*]naphtho[*b*][1,8]naphthyridine [**Scheme 1**]. Similar series of compounds (**3b-g**) were prepared using **1b-g** as starting substrates [**Table 1**].

The in vitro antibacterial and antifungal activities of all the newly synthesised compounds (**3a-g**) were carried out against ten bacteria and eight fungi strains [**Table 2**]. Investigation of antibacterial activity revealed that the compounds **3a-g** exhibited promising activity against four organisms such as *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis and Bacillus cereus*, whereas compounds **3e**, **3f**, and **3g**, showed the moderate activity against other bacteria like *Klebsiella aerogenes*, *Salmonella typhimurium*, *Vibrio fischeri*, *Corynebacterium rubrum*, *Staphylococcus albus* and *Proteus vulgaris*. These compounds showed moderate to good fungal activity against *Aspergillus flavus*, *Rhodotorula rubra*, *Aspergillus parasiticus* and *Trichoderma viridie*, especially compounds **3b** and **3c** exhibited significant activity against *Trichoderma viridie*. But these compounds showed no activity on the other fungi like *Aspergillus niger*, *Aspergillus fumigatus*, *Penicillium chrysogenum* and *Lipomyces lopofera*. Minimum inhibitory concentration (MIC) of the compounds was also estimated by broth dilution assay method. The results of the MIC values of the compounds are listed in **Table 3**. The MIC values of the compounds range between 7.8 and 125 µg/mL in most of the cases.

In conclusion, we have demonstrated the synthesis of newer derivatives of benzo[*g*]-naphtho[*b*][1,8]naphthyridines in a single step by microwave assisted method. The main advantages of this method are shorter reaction time and higher yield of the product.

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