2024
11(2), 664

Chemical Biology
LETTERS

Synthesis and biological evaluation of 1,2,4-Triazolo[4,3-a][1,8] naphthyridines under Microwave condition

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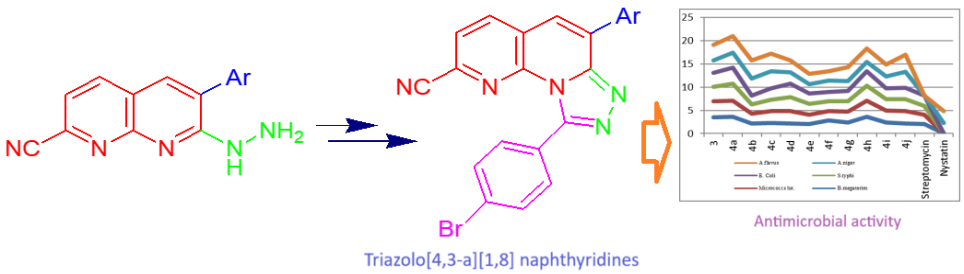
Submitted on: 11-Jan-2024, Accepted and Published on: 04-Apr-2024

Article

ABSTRACT



Synthesis of 9-(4-bromophenyl)-6 aryl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile (4a-j) from 7-(2-(4bromobenzylidene)hydrazinyl)-6-aryl-1,8-naphthyridine-2-carbonitrile (3) oxidized with chloramines-T in methanol under microwave irradiation is a straight forward and very efficient process. Very high yields and excellent purities of the products were achieved. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy are used to characterize the produced compounds. All synthesized compounds were tested for their antimicrobial efficacy and found moderately active against different types of bacterial and fungal strains in comparison with Streptomycin, Nystatin.

Keywords: Naphthyridines, Triazoles, Anti-Microbial activity, Microwave condition.

INTRODUCTION

The importance of 1,8-naphthyridines as heterocycles is now being recognized and their attention has been increasing at an impressive rate.[1] The discovery of new antibacterial agents sparked the initial phase of the 1,8-naphthyridines synthetic expand which has now expanded to include a broad range of functional compounds.[2] Many important synthetic techniques have been established for the production of 1,8-naphthyridine derivatives due to their vast scope.[3] Nowadays, the emphasis is on more efficient, more sustainable processes.[4-5] The biological and pharmacological effects of several 1,2,4-triazoles have been the focus of much investigation.[6]

The advantages of microwave-assisted organic synthesis which include faster reactions, higher yields, more selectivity for better final products.[7-9] Although there are a number of techniques for conducting microwave-induced reactions in solution with solvent free conditions, the most effective way to achieve consistent heating is with a homogenous mixture.[10-11] The synthetic utility of Chloramine-T (CAT) is significant, since it is a highly flexible oxidizing agent.[12] Considering this and our ongoing interest in using microwave irradiation for chemical processes involving 1,8-napthyridine derivatives.[13] There are several other 1,8-naphthyridine derivatives as drugs which have potential as antimycobacterial, anti-inflammatory, anticancer, anticonvulsant, cardiotonic, antiallergic, antiplatelet, gastric antisecretory and benzodiazepine receptor activities.[14-22] The synthesis of 1,2,4-triazolo[4,3-a][1,8] naphthyridines utilizing CAT in methanol under microwave irradiation is presented here in an efficient, practical, and convenient manner.[23]

EXPERIMENTAL SECTION

The data presented here are new, uncorrected melting points obtained using a Cintex melting point device. The compounds purity was verified by utilizing pre coated TLC plates (Merk, 60F-254). A Perkin-Elmer BX series FTIR spectrophotometer was used to record the infrared spectra (KBr) (ν_{max}: cm^{-1}). ^{1}H NMR spectra were captured using a Varian 400 MHz spectrometer in $CDCl_3$ solvent using TMS as the internal standard. The chemical shifts were measured in ppm. Mass spectra were recorded on SHIMADZU LCMS 2020 mass spectrometers. The elemental analyzer used for microanalysis was a Perkin-Elmer 240 CHN. An LG MG 556p, operating at 2450 MHz, was used as the microwave oven for the irradiation. As previously mentioned, the first compounds were synthesized in accordance with our procedures. The chemicals were purchased from Aldrich Chemical Company.

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URN:NBN:sciencein.cbl.2024.v11.664

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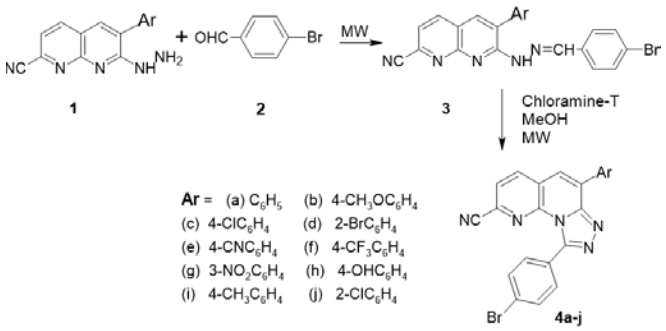

Scheme 1. Synthetic pathway to 1,8-naphthyridines.

General procedure for the synthesis of 7-(2-(4-bromobenzylidene)hydrazinyl)-6-aryl-1,8-naphthyridine-2-carbonitrile (3). A solution containing 20.0 mmol of 7-hydrazinyl-6-aryl-1,8-naphthyridine-2-carbonitrile (1), 20.0 mmol of 4-bromobenzaldehyde(2) and 5 drops of DMF was subjected to microwave irradiation at 400 watts at frequencies of 30 seconds for the specified duration. The reaction was cooled and treated with cold water once the TLC showed that the reaction was complete. We filtered off the solid by product, rinsed it with water and then re-crystallized it from ethanol. Yellowish solid, yield 81%, mp 172-174°C, IR (KBr): 3219 (NH), 2125 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 6.65 (m, 2H-ArH), 7.34 (m, 3H-ArH), 7.71 (m, 5H-ArH), 8.13 (s, 1H-ArH), 8.40 (s, 1H-ArH), 8.55 (s, 1H, ArH), 9.65 (m, 1H-NH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 117.23, 117.69, 118.36, 120.37, 123.99, 127.99, 128.30, 129.53, 132.45, 135.53, 136.23, 138.42, 142.79, 149.90, 151.07, 153.29. LCMS m/z: 427.04, Found: 427.09. Anal. Calcd: $C_{22}H_{14}BrN_5$; C, 61.70; H, 3.29; N, 16.35%. Found: C, 61.72; H, 3.30; N, 16.39%.

General procedure for the synthesis of 9-(4-bromophenyl)-6 aryl -[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile (4a-j). To a solution of suitable hydrazone 4 (20.0 mmol) in methanol (15 mL), add 20.0 mmol of Chloramine-T (CAT). The substance under reaction was exposed to a microwave that was set at 400 watts with 30s intervals during the period of time specified. The reaction mixture was cooled and processed with cold water after TLC verified complete conversion. The remaining solid was subsequently extracted using filtering, rinsed with water, and re-crystallized from ethanol.

9-(4-bromophenyl)-6-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile (4a). Yellowish solid, yield 90%, mp 208-210°C, IR (KBr): 2122 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.48 (m, 3H-ArH), 7.68 (m, 3H-ArH), 7.86 (m, 3H-ArH), 8.18 (s, 1H-ArH), 8.57 (d, *J*=1.1Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 118.09, 120.89, 123.54, 124.52, 127.50, 128.87, 129.83, 131.86, 131.65, 132.79, 133.20, 136.02, 142.33, 146.00, 151.48, 152.05. LCMS m/z: 425.03, Found: 425.72. Anal. Calcd: $C_{22}H_{12}BrN_5$; C, 61.97; H, 2.84; N, 16.43%. Found: C, 61.99; H, 2.86; N, 16.45%.

9-(4-bromophenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4b). Yellowish solid, yield 91%, mp 200-202°C, IR (KBr): 2122 (CN), 2870 (OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 3.91(s, 3H-OCH_3), 7.20 (m, 2H-ArH), 7.80 (m, 6H-ArH), 8.18 (s, 1H-ArH), 8.56 (d, *J*=7.1Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 56.04, 115.62, 118.09, 120.89, 123.54, 124.42, 128.82. 129.08, 131.16, 131.65, 132.79, 133.20, 142.33, 146.00, 151.48, 152.05, 159.63. LCMS m/z: 455.04, Found: 455.12. Anal. Calcd: $C_{23}H_{14}BrN_5O$; C, 60.54; H, 3.09; N, 15.35%. Found: C, 60.56; H, 3.11; N, 15.37%.

9-(4-bromophenyl)-6-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4c). Yellowish solid, yield 90%, mp 205-207°C, IR (KBr): 2122 (CN), 800 (C-Cl) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.49 (m, 2H-ArH), 7.56 (m, 2H-ArH), 7.75 (s, 4H-ArH), 8.21 (s, 1H-ArH), 8.59 (d, *J*=8.4Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 118.09, 120.89, 123.54, 124.42, 128.87. 129.68, 131.16, 131.16, 131.65, 132.79, 133.28, 134.33, 142.33, 146.01, 151.48, 152.05. LCMS m/z: 458.99, Found: 458.20. Anal. Calcd: $C_{22}H_{11}BrN_5$; C, 57.35; H, 2.41; N, 15.20%. Found: C, 57.36; H, 2.45; N, 15.25%.

6-(2-bromophenyl)-9-(4-bromophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4d). Yellowish solid, yield 91%, mp 208-210°C, IR (KBr): 2122 (CN), 670 (C-Br) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.23 (m, 2H-ArH), 7.76 (m, 5H-ArH), 8.19 (s, 2H-ArH), 8.70 (s, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 118.09, 120.87, 121.53, 123.54, 124.19, 127.08, 128.87, 129.75, 130.39, 130.84, 131.65, 132.79, 133.20, 133.83, 140.97, 142.33, 146.50, 151.01, 152.05. LCMS m/z: 502.94, Found: 502.26. Anal. Calcd: $C_{22}H_{11}Br_2N_5$; C, 52.31; H, 2.19; N, 13.86%. Found: C, 52.35; H, 2.22; N, 13.89%.

9-(4-bromophenyl)-6-(4-cyanophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4e). Yellowish solid, yield 89%, mp 206-208°C, IR (KBr): 2122 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.50 (m, 2H-ArH), 8.05 (m, 5H-ArH), 8.21 (s, 2H-ArH), 8.61 (d, *J*=1.9Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 111.22, 118.09, 119.12, 120.89, 123.54, 124.52, 127.92, 128.95, 129.46, 131.43, 131.65, 132.89, 133.20, 140.53, 142.33, 146.00, 151.48, 152.05. LCMS m/z: 450.02, Found: 450.90. Anal. Calcd: $C_{23}H_{11}BrN_6$; C, 61.21; H, 2.46; N, 18.62%. Found: C, 61.23; H, 2.49; N, 18.65%.

9-(4-bromophenyl)-6-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4f). Yellowish solid, yield 91%, mp 208-210°C, IR (KBr): 2122 (CN) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.82 (m, 3H-ArH), 7.91 (m, 4H-ArH), 8.21 (s, 2H-ArH), 8.62 (d, *J*=2.8Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 118.09, 120.89, 123.54, 124.44, 127.94, 128.47, 128.87, 131.16, 131.65, 132.79, 133.20, 138.20, 138.14, 142.33, 146.00, 151.48, 152.05. LCMS m/z: 493.01, Found: 493.10. Anal. Calcd: $C_{23}H_{11}BrF_3N_5$; C, 55.89; H, 2.24; N, 14.17%. Found: C, 55.90; H, 2.26; N, 14.26%.

9-(4-bromophenyl)-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4g). Yellowish solid, yield 88%, mp 210-212°C, IR (KBr): 2122 (CN), 2250 (C-Br) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.65 (m, 4H-ArH), 7.70 (m, 1H-ArH), 8.14 (d, *J*=4.43Hz, 2H-ArH), 8.25 (s, 1H-ArH), 8.62 (d, *J*=2.7Hz, 3H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 118.09, 120.06, 120.89, 123.54, 124.15, 125.28, 128.87, 130.91, 131.68, 132.79, 133.20, 133.94, 138.59, 142.33, 144.87, 146.00, 151.48, 152.05. LCMS m/z: 470.01, Found: 470.20. Anal. Calcd:

$C_{22}H_{11}BrN_6O_2$; C, 56.07; H, 2.35; N, 17.83%. Found: C, 56.10; H, 2.39; N, 17.85%.

9-(4-bromophenyl)-6-(4-hydroxyphenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4h). Yellowish solid, yield 91%, mp 208-210°C, IR (KBr): 2122 (CN), 3300 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 3.93 (s, 1H-OH), 7.07 (m, 2H-ArH), 7.58 (m, 4H-ArH), 7.77 (m, 2H-ArH), 8.18 (s, 1H, ArH), 8.54 (d, *J*=1.3Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 116.36, 118.09, 120.89, 123.54, 124.42, 129.20, 131.16, 131.65, 132.79, 133.20, 142.33, 146.00, 151.48, 152.05, 156.77. LCMS m/z: 441.02, Found: 441.50. Anal. Calcd: $C_{22}H_{12}BrN_5O$; C, 59.75; H, 2.73; N, 15.84%. Found: C, 59.79; H, 2.77; N, 15.86%.

9-(4-bromophenyl)-6-p-tolyl-[1,2,4]triazolo[4,3-a][1,8] naphthyridine-2-carbonitrile(4i). Yellowish solid, yield 90%, mp 206-208°C, IR (KBr): 2122 (CN), 1420 (CH_3) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 2.45 (s, 3H-CH_3), 7.39 (m, 2H-ArH), 7.58 (m, 3H-ArH), 7.60 (m, 3H-ArH), 8.18 (s, 1H-ArH), 8.56 (d, *J*=3.3Hz, 2H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 21.13, 118.09, 120.89, 123.54, 124.42, 128.98, 130.31, 131.16, 131.65, 132.79, 133.20, 136.05, 137.35, 142.33, 146.50, 151.48, 152.05. LCMS m/z: 439.04, Found: 439.45. Anal. Calcd: $C_{23}H_{14}BrN_5$; C, 62.74; H, 3.20; N, 15.91%. Found: C, 62.76; H, 3.24; N, 15.93%.

9-(4-bromophenyl)-6-(2-chlorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile(4j). Yellowish solid, yield 90%, mp 206-208°C, IR (KBr): 2122 (CN), 850 (C-Cl) cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ ppm: 7.29 (m, 2H-CH_3), 7.49 (m, 3H-ArH), 7.78 (m, 3H-ArH), 8.22 (d, *J*=3.9Hz, 2H-ArH), 8.53 (s, 1H-ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ ppm: 118.09, 120.89, 123.54, 125.62, 126.92, 128.96, 130.06, 130.48, 130.90, 131.65, 132.89, 133.20, 135.74, 142.33, 146.00, 151.01, 152.25. LCMS m/z: 458.99, Found: 458.50. Anal. Calcd: $C_{22}H_{11}BrClN_5$; C, 57.35; H, 2.41; N, 15.20%. Found: C, 57.38; H, 2.45; N, 15.24%.

RESULTS AND DISCUSSION

The corresponding 7-(2-(4-bromobenzylidene)hydrazinyl)-6-aryl-1,8-naphthyridine-2-carbonitrile(3) were obtained in good yields by condensation of 7-hydrazinyl-6-aryl-1,8-naphthyridine-2-carbonitrile (1) with 4-bromobenzaldehyde (2) in the presence of a catalytic quantity of DMF under microwave irradiation.

The 9-(4-bromophenyl)-6 aryl - [1,2,4]triazolo[4,3-a][1,8]naphthyridine-2-carbonitrile (4a-j) were produced by the oxidative cyclization of hydrazones (3) with Chloramine-T (CAT) in methanol when treated by microwave irradiation. An efficient and clean oxidative transformation has been achieved. This experiment has a relatively simple procedure. There were no undesirable byproducts formed during the high yield process. In addition, this method yielded more pure products and further purification was usually unnecessary. It is worth noting that when conducted under conventional conditions in an oil-bath preheated to 110°C (the temperature measured at the end of the microwave experiment) this oxidative reaction only proceeds to a minor extent (5-8% in 3.5-4.5 minutes). This confirms the rate enhancement that occurs during microwave heating (Scheme 1). Analytical and spectroscopic data (IR, ^1H NMR, ^{13}C NMR, Elemental analysis and Mass spectroscopy) were used to determine the structures of compounds 3 and 4.

Here, we present a practical, efficient, mild, and economical synthetic method for the synthesis of novel[1,8]naphthyridine-2-carbonitrile analogs, which has garnered considerable attention recently. Furthermore, The compound known as [1,8]naphthyridine-2-carbonitrile derivatives has displayed intriguing antimicrobial properties comparable to Streptomycin and Nystatin. Therefore, 1,8-naphthyridines moiety was to incorporated during the optimization process.

The advantages of this process include its high yields, non-toxicity of the reagent, low operating costs, fast reaction time and pure products of hybridized heterocycles.[24,25] The procedure is affordable and economical.

Antimicrobial studies:

In order to determine all of the compounds had antimicrobial properties the agar cup method was used to test them against a variety of bacterial (*Bacillus megaterium*, *Micrococcus luteus*, *Salmonella typhi, and Escherichia coli*) and fungus strains (*Aspergillus niger*, *Aspergillus flavus*) were examined (Figure 1). We measured the growth-inhibiting zone in millimeters (Table 1). The substance was dissolved using dimethyl sulfoxide (DMSO). The compound (3) and (4a, 4h) were shown to have high levels of activity against *Escherichia coli*, *S. typhi*, *Micrococcus lut*, and *B. megaterium*, whereas remaining all were found to have moderate levels of activity. When tested against strains of fungi, (**4b, 4c**) showed highest activity.

The antibacterial activity of all of the substances was promising when tested against streptomycin. There was a wide range of antifungal efficacy when tested against Nystatin. This research conclusions might be used to other bio evaluations.

Table 1: Antimicrobial activities of compounds.

Antibacterial activity					**Antifungal activity**	
Gram +*ve* bacteria			**Gram–*ve* bacteria**			
Code	***B. megaterim***	***Microccs lut.***	***S. typhi***	***E. Coli***	***A. niger***	***A. flavus***
3	3.5	3.4	3.2	3.0	2.6	3.4
4a	3.6	3.5	3.6	3.5	3.2	3.6
4b	2.2	2.1	2.0	1.9	3.6	3.9
4c	2.3	2.5	2.5	2.4	3.7	3.8
4d	2.2	2.6	3.0	2.9	2.5	2.6
4e	2.0	2.1	2.3	2.2	2.0	2.2
4f	2.8	2.0	2.1	2.0	2.5	2.0
4g	2.4	2.3	2.3	2.2	2.1	3.0
4h	3.6	3.5	3.2	3.1	2.0	2.9
4i	2.4	2.5	2.5	2.3	2.6	2.5
4j	2.2	2.6	2.6	2.5	3.4	3.7
Streptomycin	2.0	2.0	2.0	2.2	-	-
Nystatin	-	-	-	-	2.3	2.5

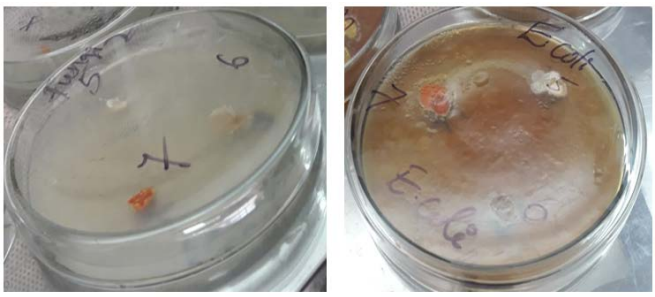

Figure 1: Representative images for antimicrobial activity of synthesised compounds.

CONCLUSION

In this study 6 aryl-[1,2,4]triazolo[4,3-a][1,8]naphthyridines were prepared. Newly synthesized compounds (4a-j) were tested for their antibacterial activity against four common pathogens. Most of the synthesized compounds were very effective in inhibiting growth of both Gram-positive and Gram-negative bacteria and both types of bacteria and fungi. Therefore, the present study would be very useful in the search for effective novel antimicrobial medications. The significant advantages of this procedure are operational simplicity, short reaction time, pure products, inexpensive, and non-toxicity of the reagent and high yields.

ACKNOWLEDGMENT

The authors express their gratitude to the Director of the Indian Institute of Chemical Technology in Hyderabad. Chaitanya Deemed to be the University's Principal, Hanumakonda, for providing Spectral data and biological activity.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no financial or academic conflict of interest that might have influenced publication of this work.

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