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Design, synthesis, and antimicrobial evaluation of novel imidazo[1,2-*a*] [1,8] naphthyridine based thiazole and chromenone scaffolds

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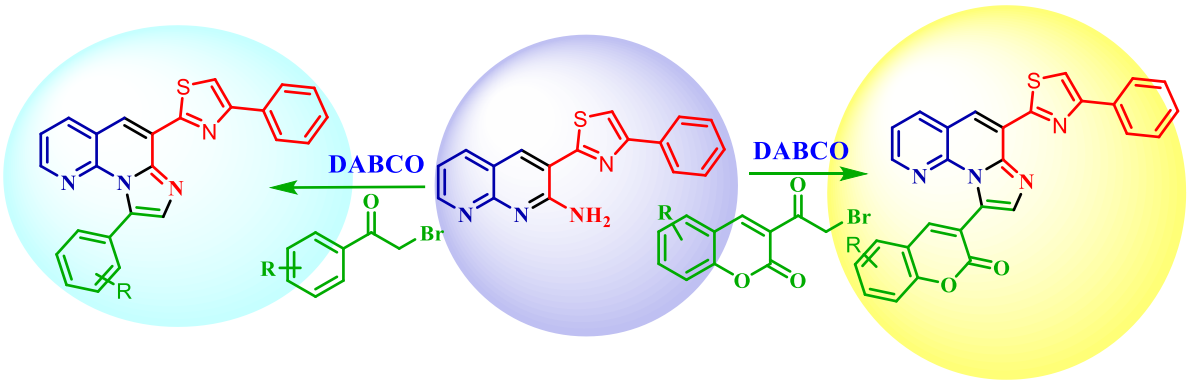
Abstract

A new library of 1,8-naphthyridine-based thiazole and chromene scaffolds was synthesized and confirmed through spectral analysis (^{1}H NMR, ^{13}NMR, and mass data). The microwave method has provided an efficient, rapid, and environmentally friendly approach to obtaining the target compounds with high yields in short reaction times. The synthesized derivatives were screened for their antimicrobial activity against pathogenic bacterial and fungal strains compared with the clinical reference drugs ampicillin and ketoconazole. The examined compounds showed significant to moderate antimicrobial activity. Among them, **5b** and **7c** exhibited the most potent antibacterial and antifungal activity against tested pathogenic cells compared with standard drugs.



Keywords: 1,8-naphthyridine, chromenone scaffolds, organic catalyst, antimicrobial activity.

Introduction

Antibacterial and antifungal resistance has become major global health threats, prompting the urgent necessity for developing novel antimicrobial agents with unique mechanisms of action. The World Health Organization has prioritized resistant pathogens, including *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Candida albicans*. These multidrug-resistant (MDR) microorganisms are responsible for many infections and deaths worldwide. The urgent need for novel and effective antimicrobial agents is critical, and researchers are increasingly turning to new molecular scaffolds. In today's world, antimicrobial resistance (AMR) plays a key role in public health, as it renders many existing antibiotics and antifungals ineffective against resistant pathogens. Substituted imidazo[1,2-*a*][1,8]naphthyridine derivatives combined with potent groups like thiazole and chromenones offer promising solutions targeting resistant bacteria and fungi.[1-3] Nitrogen-containing 1,8-naphthyridine heterocyclic compounds are a cornerstone in medicinal chemistry and drug discovery due to the wide range of beneficial biological activities, including anti-inflammatory,[4] antitumor,[5] anti-platelet,[6] and anti-allergic effects.[7] They also demonstrate significant antibacterial and antifungal properties,[8-9] as well as anti-malarial,[10] and anti-HIV activities.[11] Additionally, these compounds have been reported to inhibit key enzymes, such as p38 mitogen-activated protein kinase,[12] and show potent inhibition of protein kinase C isozymes.[13] Some of the biological significant 1,8-naphthyridine-based compounds that hold significant medicinal value shown in Figure 1.

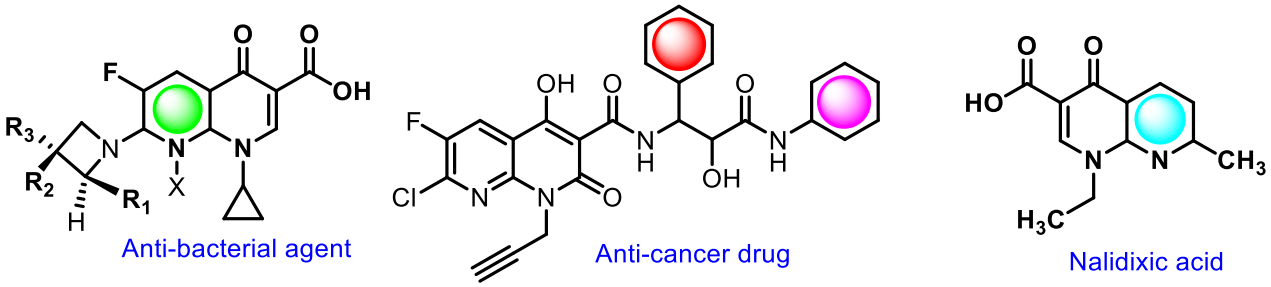
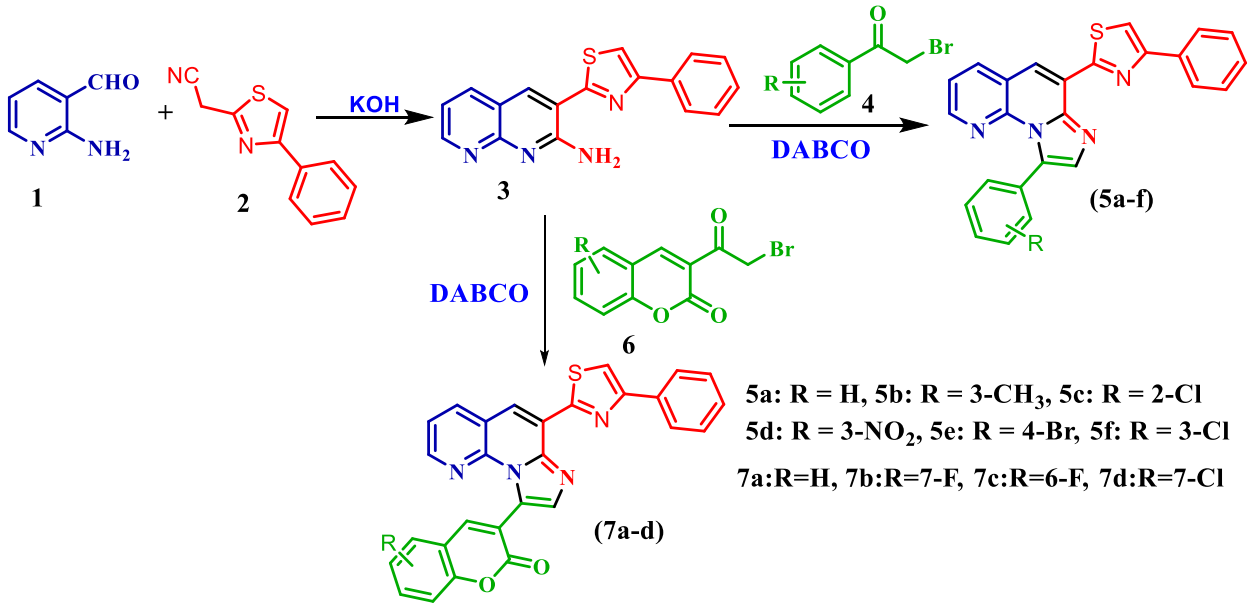


Figure 1. medicinally important 1,8-naphthyridine compounds with diverse pharmacological applications.

Microwave-assisted organic synthesis (MAOS) has become popular as a green chemistry approach due to its ability to improve reaction efficiency. This method offers advantages such as reduced reaction times, higher yields, and lower energy consumption than traditional methods. MAOS enhances reaction rates while ensuring selective product formation, aligning with sustainable chemistry goals and making it a valuable tool in both industry and laboratory.[14-16] Developing sustainable and environmentally friendly methods for synthesizing organic molecules has been a long-standing goal in chemistry. In this context, developing novel antimicrobial agents with enhanced potency and broad-spectrum activity has become a significant research focus in continuation of our previous studies on developing eco-friendly methodologies.[17] As part of this effort, we designed and synthesized a new series of imidazo[1,2-*a*][1,8]-naphthyridine-based thiazole and chromenone units (**5a**-**f**/**7a**-**d**) via a green and sustainable methodology. The antimicrobial properties of all synthesized products were examined, and all tested compounds exhibited remarkable activity. Among these, compounds **5b** and **7c** demonstrated highly potent antimicrobial activities.

Results and Discussion

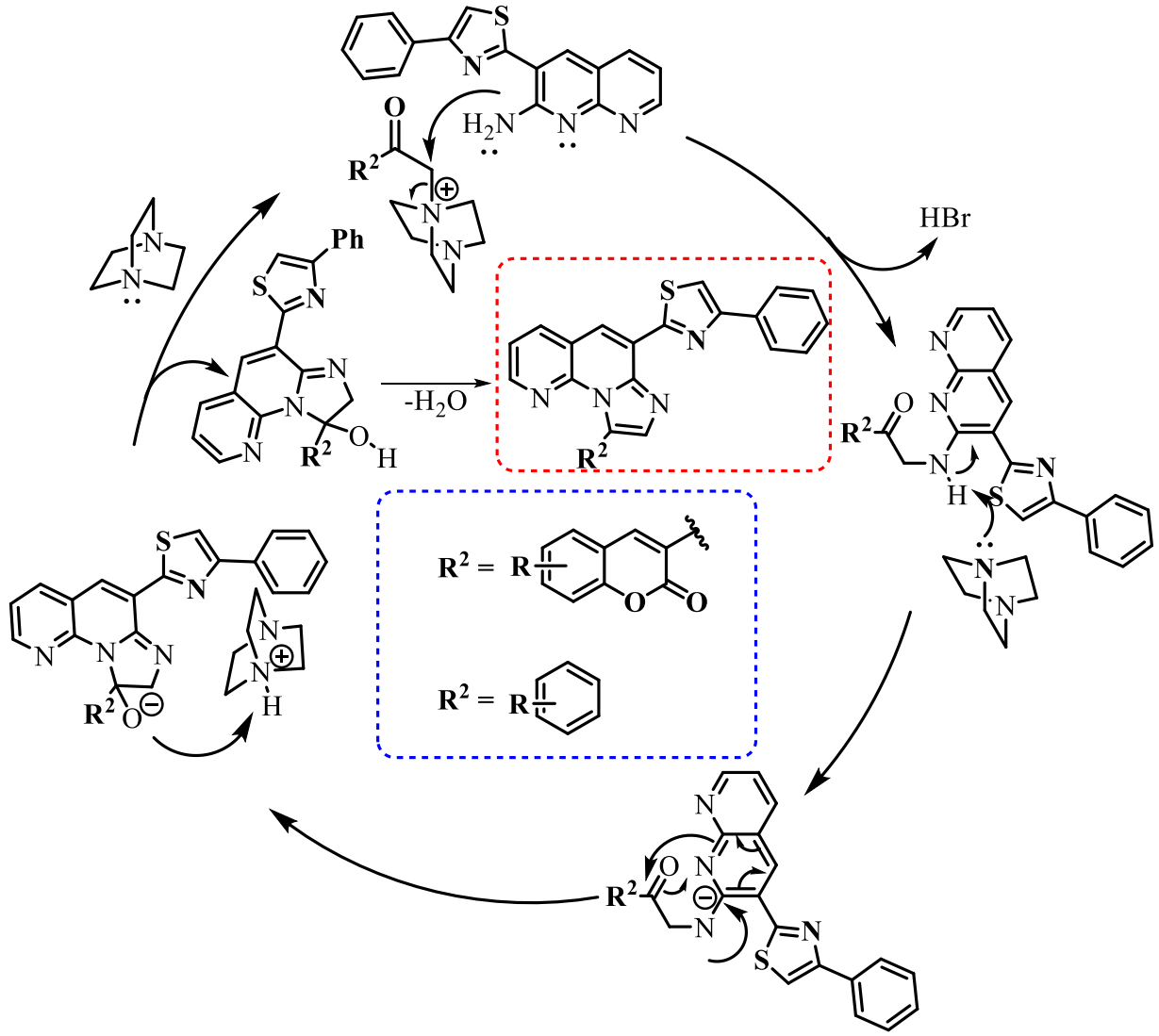
In this study, we developed fused [1,2-*a*][1,8]-naphthyridine-based thiazole and chromene scaffolds (**5a-f/7a-d**) in the presence of organic catalysts *via* intermolecular cyclization reactions under microwave irradiation as shown in Scheme 1. To diversify the synthesis, two types of α-bromo ketones were taken, using *in situ* generated salt, and metal-free synthesis of 4-phenyl-2-(9-arylimidazo[1,2-*a*][1,8]-naphthyridin-6-yl)thiazole and 3-(6-(4-phenylthiazol-2-yl)imidazo[1,2-*a*][1,8]-naphthyridin-9-yl)-2*H*-chromen-2-one derivatives were our central goal. The development of the reaction methodology began with a conventional reaction between an α-bromo-substituted ketone (1 equiv.) and DABCO (1 equiv.) in acetonitrile as the solvent, resulting in the in situ generation of the corresponding salt. This salt undergoes a substitution reaction in the presence of 3-(4-phenylthiazol-2-yl)-1,8-naphthyridin-2-amine **3**. Then, the product produced in the reaction underwent intermolecular cyclization with DABCO as base to make the targeted product with a 65% yield in 10-12 hours.



Scheme 1. Synthesis of novel fused naphthyridine (**5a-f/7a-d**) scaffolds.

After identifying the compound structure, we try to increase the reaction yield. To upscale the reaction yield, we studied the reaction with different solvents, like methanol, hexane, and ethyl acetate. However, the best yield was observed in the case of acetonitrile as a solvent. To improve the product yield and reduce the reaction time, we carried out the reaction using the microwave-irradiation method. This methodology drastically increased reaction yields to 85-95% and reduced the reaction time. Under these optimized reaction conditions in MW (132-146 °C), we synthesized novel (**5a-f/7a-d**) scaffolds. Initially, 2-aminonicotinaldehyde **1** and 2-(4-phenylthiazol-2-yl) acetonitrile **2** reacted in the presence of KOH afforded corresponding reaction intermediate 3-(4-phenylthiazol-2-yl)-1,8-naphthyridin-2-amine **3** was then it reacted with 2-bromo-1-phenylethan-1-one derivatives and 3-(2-bromoacetyl)-2H-chromen-2-one derivatives in the presence DABCO afforded substituted 1,8-naphthyridine derivatives (**5a-f**) and (**7a-d**) with excellent yields in short reaction times. The impact of various substituents on the reactivity and yield of the reaction was thoroughly investigated. We noticed that bromo-substituted reactant **5e** provided better results than fluro- and chloro-substituted reactants. However, the reaction was completed within 7-10 minutes with all the halogen-substituted substrates. Interestingly, substrates bearing a nitro substituent exhibited significantly short reaction times, with completion occurring

within 6-7 minutes. This increased rate is consistent with the strong electron-withdrawing nature of the nitro group, which enhances the electrophilicity of the reaction site, thereby facilitating a faster transformation. The nitro-substituted substrates maintained high reaction yields (92%) despite the shorter reaction time, indicating minimal side reactions and efficient conversion into the desired product.



Scheme 2. The proposed reaction pathway for the construction of fused 1,8-naphthyridines.

These observations highlight the dual role of electronic and steric effects in dictating the reaction rate and yield. While nitro substitution accelerates the process due to its strong electron-withdrawing effects, bromine substitution offers an optimal reactivity and product yield balance, making it the most effective halogen substituent under the given reaction conditions. A plausible reaction pathway for the construction of these compounds is shown in Scheme 2. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

Biological evaluations

Antimicrobial activity. The antibacterial and antifungal properties of each new compound were thoroughly investigated. Specifically, the antimicrobial efficacy of the synthesized molecules (**5a-f/7a-d**) was evaluated against a panel of pathogenic bacterial and fungal strains and compared with reference drugs Ampicillin and

Ketoconazole; activity was performed using the solution microdilution or broth microdilution method.[18] Synthesized products were assessed *in vitro* antibacterial activity against Gram (+) bacteria *Staphylococcus aureus, Bacillus subtilis,* and (-) bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and compared with clinical reference drug Ampicillin. All the compounds tested against two fungal strains*, Aspergillus niger and Candida albicans,* were used and evaluated with the reference drug Ketoconazole. Results are summarized in Table 1.

Table 1. The activity data of synthesized products (**5a-f/7a-d**) minimum inhibitory concentration (MIC) (µg/mL) against tested pathogenic strains

		Gram (+ve) bacteria		Gram (-ve) bacteria		Fungal strains	
S.NO	Molecules	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Candida albicans*
1	**5a**	153	138	142	156	141	148
2	**5b**	20.5	21	19.5	23	23.5	25.5
3	**5c**	41	38	34	36.5	32.5	37
4	**5d**	74	82.5	85.5	71	75	69
5	**5e**	106	122	109	118	107	125
6	**5f**	32	37	36	31.5	38	33
7	**7a**	131	126	124	127	125	121
8	**7b**	36	34.5	38.5	33.5	38	32.5
9	**7c**	20	21	21.5	22	23.5	26
10	**7d**	39	35	32	36	35	33.5
	Ampicillin	21	23	22	24	--	--
	Ketoconazole	--	--	--	--	25	27

The antimicrobial activities of the compounds were determined using standard *in vitro* assays, such as the minimum inhibitory concentration (MIC) determination values are given in Table-2 according to activity data, the compound (**5b**), 4-phenyl-2-(9-(*m*-tolyl)imidazo[1,2-*a*][1,8]naphthyridin-6-yl)thiazole, demonstrated outstanding activity against all the examined microorganisms, compound (**7c**), 6-fluoro-3-(6-(4-phenylthiazol-2-yl)imidazo[1,2-*a*][1,8]naphthyridin-9-yl)-2*H*-chromen-2-one also exhibited strong anti-microbial activity. The remaining compounds showed modest to activity. This study highlights their potential as antimicrobial agents. The bar graph represents the MIC values of compounds **5b**, **7c** shown in Figure 2 and minimum inhibitory concentration (MIC) values for the synthesized products against Gram-positive, Gram-negative, and fungal strains shown in Figure 3.

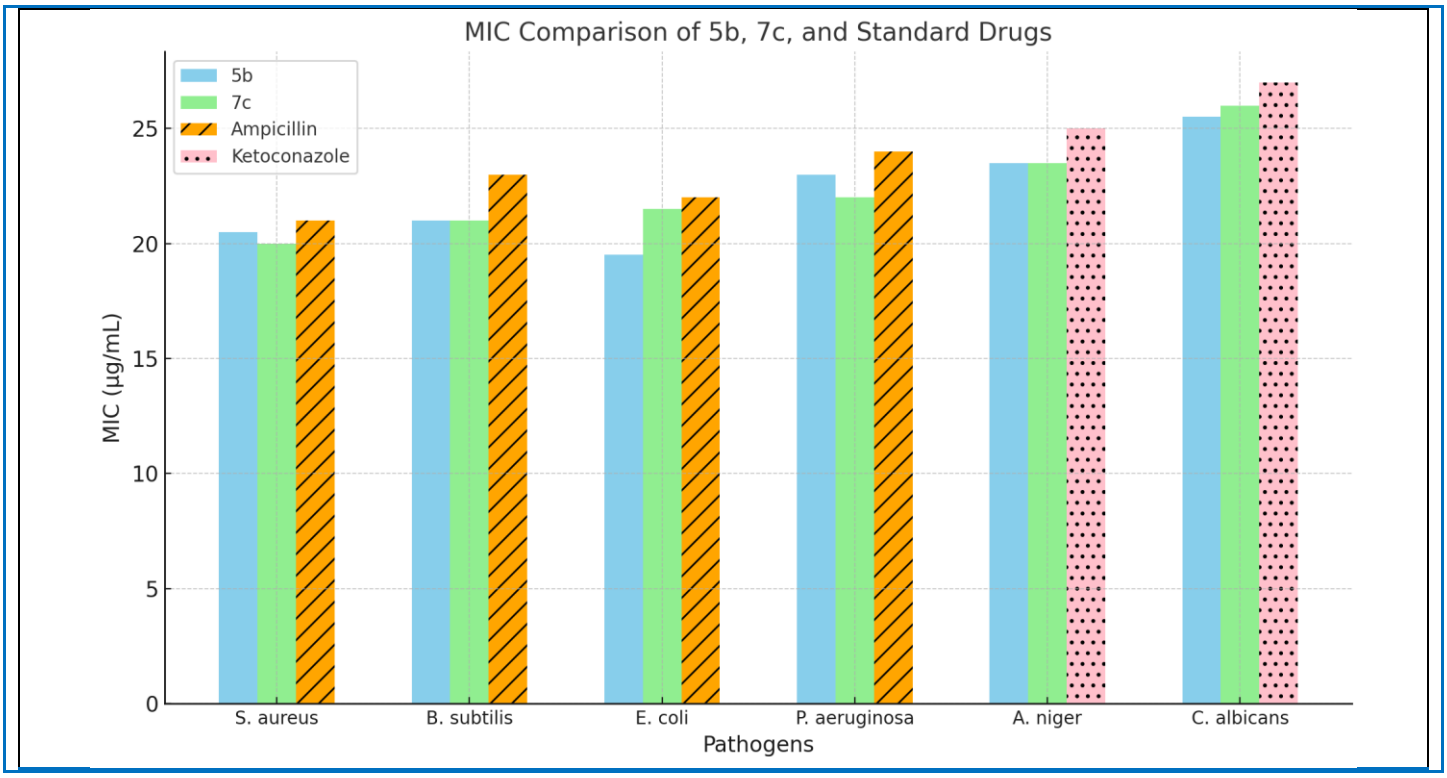


Figure 2. The bar graph represents the MIC values of compounds **5b**, **7c** and the standard drugs Ampicillin and Ketoconazole against the tested pathogens.

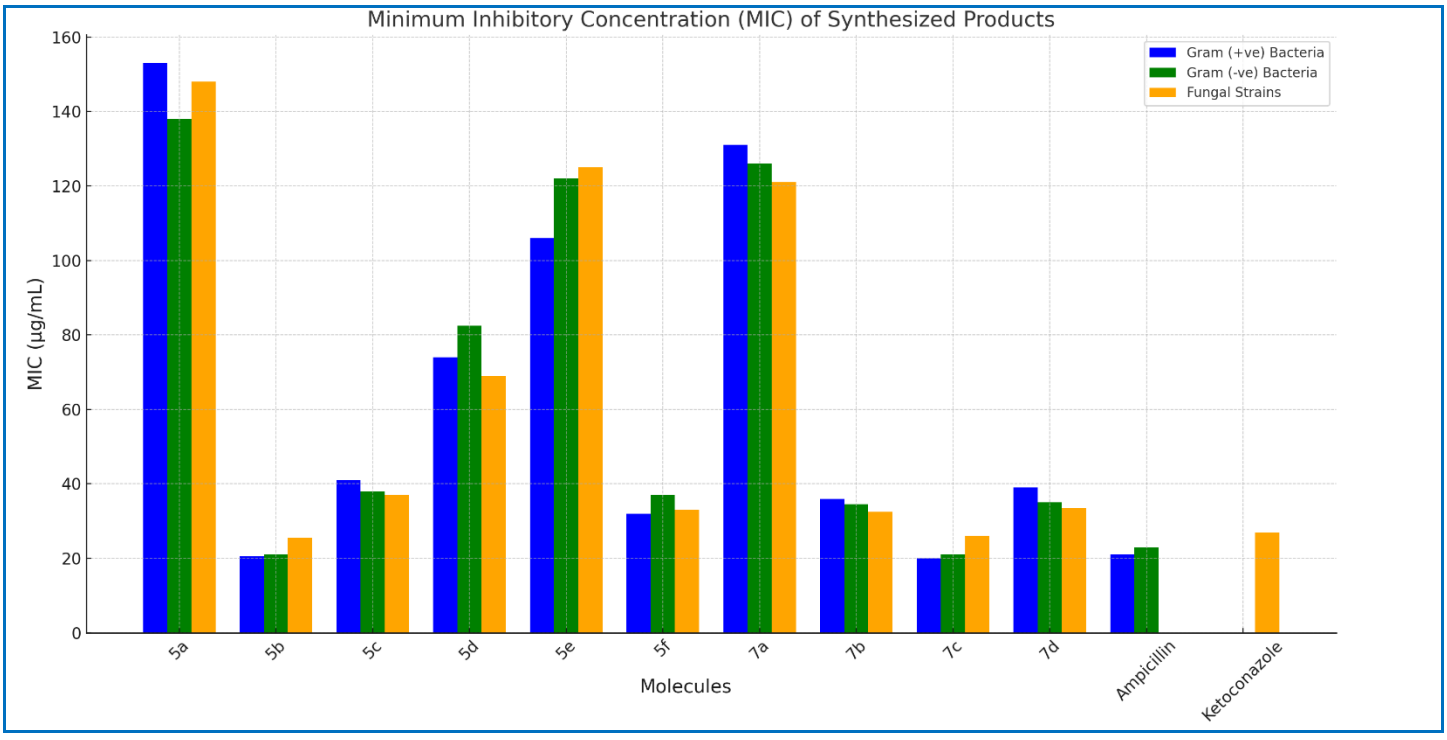


Figure 3. Graph illustrating the minimum inhibitory concentration (MIC) values for the synthesized products against Gram-positive, Gram-negative, and fungal strains.

Conclusions

A simple and proficient green synthetic methodology has been developed for a new series of (**5a-f/7a-d**) derivatives under the microwave method that obtained excellent yields. This methodology has the advantage of high purity yields in short reaction times, high selectivity, a clean reaction profile, and no by-products. The newly synthesized compounds were characterized using spectroscopic techniques, including ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. Furthermore, all the synthesized products were screened for their antibacterial and fungal activities. The synthesized compounds **(5a-f/7a-d)** demonstrated promising antibacterial and antifungal activities against various pathogenic microbial pathogenic strains. Compounds **5b** and **7c** displayed the highest antimicrobial activity. The findings highlight the potential of these molecules as effective antimicrobial agents.

Experimental Section

General. All reagents and chemicals were procured from Aldrich, and all commercially obtained chemicals were used as they were received without further purification. The reaction progress was monitored by TLC using hexane/ethyl acetate (7:3) as eluent. NMR spectral data was taken from Bruker 500 MHz spectrometer. Mass spectra (ESI) were recorded on a Jeo1 JMSD-300 spectrometer. Elemental analyses were accomplished on a Carlo Erba EA 1108 automatic elemental analyzer and a Buchi melting point apparatus was used to measure melting points.

Antimicrobial activity method. The current study evaluated antimicrobial activity using the minimum inhibitory concentration (MIC) method.[18] Serial twofold compound dilutions were prepared in 2% DMSO, with concentrations ranging from 1000 µg/mL-15.62 µg/mL. These solutions were added to each well of a 96-well plate. A 100 µL inoculum was introduced into each well. Nalidixic acid was used as a positive control for bacterial strains, and Clotrimazole was used as a control for fungal strains. The plates were incubated at 28 °C for 48 to 72 hours for fungal assays, while bacterial assays were incubated at 37 °C for 24 hours. The MIC for fungi was determined to be the lowest concentration of the compound, where no fungal growth was visible after the incubation period. For bacterial tests, 5 µL of the broth from each well was plated on sterile MHA plates and incubated at the appropriate temperature. The MIC for bacteria was identified as the lowest concentration at which no visible bacterial growth appeared on the agar plate.

Typical procedure for the construction of 3-(3,5-bis(trifluoromethyl)phenyl)-1,8-naphthyridin-2-amine (**3**)
2-aminonicotinaldehyde **1** (1 mmol, 122 mg) and 2-(4-phenylthiazol-2-yl) acetonitrile 2 (1 mmol, 200 mg) were taken, and 10% KOH 10 drops were added portion-wise, then irradiated in a microwave oven at 400 W at 60 s intervals specific time (4-6 mins). After completion of the reaction, the product was separated by column chromatography, using 20% EtOAc/hexane as eluent to afford a 85% yield.

General synthetic procedure for the preparation of 4-phenyl-2-(9-phenylimidazo[1,2-*a*] [1,8]naphthyridin-6-yl)thiazole derivative (5a–f)
To 3-(3,5-bis(trifluoromethyl)phenyl)-1,8-naphthyridin-2-amine **3** (1 mmol, 357 mg), 2-bromo-1-phenylethan-1-one derivative **4** (1 mmol) was added and then reaction mixture, 1.2 equiv. of DABCO. The resulting reaction mixture was irradiated in a microwave oven at (400 W) specific time (7-10 minutes). After completion of the reaction, the crude reaction mixture was concentrated under vacuum and purified by (silica gel) column chromatography using solvent 10–15% (ethyl acetate and hexane) as eluents to form the desired corresponding target products with excellent yield 85-95%.

General procedure for the synthesis of 3-(6-(4-phenylthiazol-2-yl) imidazo[1,2-*a*][1,8]naphthyridin-9-yl)-2-chromen-2-one derivatives (7a–d)

To the compound 3-(3,5-bis(trifluoromethyl)phenyl)-1,8-naphthyridin-2-amine **3** (1 mmol, 357 mg), 3-(2-bromoacetyl)-2H-chromen-2-one **6** (1 mmol) was added. In that reaction mixture, 1.2 equiv. of DABCO base was added. Then, the resulting reaction mixture was irradiated in a microwave oven at (400 W) specific time (7-11 minutes). After completion of the reaction, the crude reaction mixture was concentrated under vacuum and purified by (silica gel) column chromatography using solvent 10–15% (ethyl acetate and hexane) as eluents to form the desired corresponding target products with excellent yield 87-95%**.**

4-phenyl-2-(9-phenylimidazo[1,2-a] [1,8] naphthyridin-6-yl) thiazole (5a)

Pale yellow solid, (352 mg, 87%); Mp 217-218 °C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.96 (d, J= 7.6 Hz, 1H), 9.58 (d, J= 7.6 Hz, 1H), 8.95 (s, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.53 (d, J= 7.6 Hz, 2H), 7.43-7.26 (m, 4H), 7.20- 7.08 (m, 5H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 165.32, 164.59, 161.76, 158.15, 157.08, 154.23, 153.09, 152.37, 150.59, 147.02, 143.08, 138.43, 137.35, 136.29, 133.08, 132.70, 130.19, 126.21, 124.41, 122.98, 121.56, 118.70, 117.62, 113.67, 109.76; MS: 404.3154 [M$^+$]. Anal. calc. for $C_{25}H_{16}N_4S$: C, 74.24; H, 3.99; N, 13.85; found: C, 74.29; H, 4.12; N, 13.87.

4-phenyl-2-(9-(m-tolyl) imidazo[1,2-a] [1,8] naphthyridin-6-yl) thiazole (5b)

White solid, (385 mg, 92%); Mp 221-223°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.57 (d, J= 8.0 Hz, 1H), 8.93 (d, J= 7.6 Hz, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.85 (s, 1H), 7.65-7.59 (m, 2H), 7.43-7.26 (m, 4H), 720-7.10 (m, 4H), 3.95 (s, 3H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 164.96, 164.59, 160.68, 158.88, 152.73, 147.02, 146.66, 145.58, 143.78, 140.58, 139.15, 136.29, 135.57, 133.79, 131.64, 130.93, 127.70, 125.49, 124.06, 122.27, 119.75, 117.62, 114.40, 112.26, 110.83, 21.83; MS: 418.0243 [M$^+$]. Anal. calc. for $C_{26}H_{18}N_4S$: C, 74.62; H, 4.34; N, 13.39; found: C, 74.56; H, 4.38; N, 13.32.

2-(9-(2-chlorophenyl) imidazo[1,2-a] [1,8] naphthyridin-6-yl)-4-phenylthiazole (5c)

Light brown solid, (390 mg, 89%); Mp 198-199 °C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.20 (d, J= 7.8 Hz, 1H), 8.93 (d, J= 7.6 Hz, 1H), 8.73 (s, 1H), 8.40 (s, 1H), 8.01 (s, 1H), 7.68-7.59 (m, 3H), 7.43-7.35 (m, 3H), 7.26- 7.12 (m, 4H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 167.82, 165.32, 163.17, 157.84, 156.38, 152.02, 150.94, 148.08, 146.66, 145.58, 141.29, 138.06, 136.65, 134.50, 133.43, 131.64, 130.57, 129.14, 128.43, 127.70, 125.49, 124.77, 122.27, 120.49, 117.62; MS: 438.2326 [M$^+$]. Anal. calc. for $C_{25}H_{15}ClN_4S$: C, 68.41; H, 3.44; N, 12.76; found: C, 68.45; H, 3.47; N, 12.81.

2-(9-(3-nitrophenyl) imidazo[1,2-a] [1,8] naphthyridin-6-yl)-4-phenylthiazole (5d)

Yellow solid, (413 mg, 92 %); Mp 181-182°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.63 (d, J= 7.8 Hz, 1H), 9.20 (d, J= 8.0 Hz, 1H), 8.95 (s, 1H), 8.73 (s, 1H), 8.47 (d, 2H), 8.21 (d, J= 7.6 Hz, 2H), 8.18-8.11 (m, 4H), 8.01-7.91 (m, 3H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 165.67, 161.76, 160.68, 157.84, 155.31, 154.95, 150.59, 147.37, 145.22, 143.08, 141.29, 138.06, 136.65, 135.57, 134.50, 132.70, 129.50, 128.43, 126.21, 125.86, 123.70, 118.35, 116.91, 114.76, 112.59; MS: 449.0946 [M+1]. Anal. calc. for $C_{25}H_{15}N_5O_2S$: C, 66.80; H, 3.36; N, 15.58; found: C, 66.86; H, 3.42; N, 15.63.

2-(9-(4-bromophenyl) imidazo[1,2-a] [1,8] naphthyridin-6-yl)-4-phenylthiazole (5e)

Pale brown solid, (458 mg, 95%); Mp 206-207°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.87 (s, 1H), 9.32 (d, J= 7.8 Hz, 1H), 8.98 (s, 1H), 8.54 (s, 1H), 8.40 (s, 1H), 8.21-8.10 (m, 7.2 Hz, 2H), 8.09-7.74 (m, 4H), 7.64-7.31 (m, 4H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 165.67, 163.54, 160.68, 157.08, 155.67, 154.59, 153.44, 152.02, 150.94, 147.02, 143.45, 138.78, 137.35, 135.22, 133.43, 130.57, 126.21, 124.06, 121.92, 119.07, 118.70, 116.56, 115.84, 111.89, 109.40; MS: 482.3014 [M+1]. Anal. calc. for $C_{25}H_{15}BrN_4S$: C, 62.12; H, 3.13; N, 11.59; found: C, 62.18; H, 3.16; N, 11.64.

2-(9-(3-chlorophenyl) imidazo[1,2-a] [1,8] naphthyridin-6-yl)-4-phenylthiazole (5f)

Pale yellow solid, (385 mg, 88%); Mp 190-191°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.92 (d, J= 7.4 Hz, 1H), 9.56 (d, J= 7.8 Hz, 1H), 9.18 (s, 1H), 8.89 (s, 1H), 8.53 (s, 1H), 7.98-7.91 (d, 2H), 7.81-7.78 (d, 2H), 7.43- 7.39 (d, 2H), 7.14-7.03 (m, 4H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 164.59, 160.30, 157.84, 155.31, 153.09, 152.73, 150.25, 148.08, 146.66, 145.94, 141.29, 138.43, 136.65, 135.93, 131.28, 130.93, 129.50, 128.78, 127.70, 122.63, 117.26, 115.46, 112.26, 110.83, 108.69; MS: 438.0706 [M$^+$]. Anal. calc. for $C_{25}H_{15}ClN_4S$: C, 68.41; H, 3.44; N, 12.76; found: C, 68.49; H, 3.51; N, 12.89.

3-(6-(4-phenylthiazol-2-yl) imidazo[1,2-a] [1,8] naphthyridin-9-yl)-2H-chromen-2-one (7a)

White solid, (411 mg, 87%), Mp 235-236°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.59 (d, J= 7.8 Hz, 1H), 9.35 (d, J= 7.8 Hz, 1H), 9.18 (s, 1H), 8.82 (s, 1H), 8.27-8.18 (m, 2H), 8.01-7.98 (m, 3H), 7.62-7.53 (m, 3H), 7.49-7.23 (m, 4H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 166.75, 165.67, 164.24, 162.10, 160.68, 157.84, 155.31, 154.23, 152.02, 151.66, 150.94, 148.81, 147.02, 145.22, 143.08, 138.78, 137.70, 136.29, 134.15, 132.70, 130.57, 127.36, 123.34, 122.63, 120.49, 117.98, 115.46, 111.54; MS: 472.0994 [M$^+$]. Anal. calc. for $C_{28}H_{16}N_4O_2S$: C, 71.17; H, 3.41; N, 11.86; found: C, 71.27; H, 3.49; N, 11.95.

7-fluoro-3-(6-(4-phenylthiazol-2-yl) imidazo[1,2-a] [1,8] naphthyridin-9-yl)-2H-chromen-2-one (7b)

Light yellow solid, (406 mg, 83%); Mp 241-242°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.59 (d J= 7.8 Hz, 1H), 9.20 (d, J= 7.8 Hz, 1H), 8.79 (s, 1H), 8.56 (s, 1H), 8.37-27 (m, 3H), 7.78-7.56 (m, 4H), 7.53-7.32 (m, 4H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 167.46, 164.96, 162.10, 156.38, 154.95, 153.44, 152.73, 150.25, 147.37, 146.28, 145.22, 141.66, 138.78, 137.01, 134.50, 132.70, 131.28, 130.19, 129.14, 128.43, 127.36, 123.70, 121.92, 120.49, 117.98, 116.56, 115.12, 112.97; MS: 490.2140 [M$^+$]. Anal. calc. for $C_{28}H_{15}FN_4O_2S$: C, 68.56; H, 3.08; N, 11.42; found: C, 68.61; H, 3.18; N, 11.49.

6-fluoro-3-(6-(4-phenylthiazol-2-yl) imidazo[1,2-a] [1,8] naphthyridin-9-yl)-2H-chromen-2-one (7c)

White solid, (417 mg, 85%); Mp 238-239°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.60 (d, J= 7.8 Hz, 1H), 9.23 (s, 1H), 8.77 (s, 1H), 8.58 (s, 1H), 8.24-8.19 (d, J= 7.4 Hz, 2H), 7.76-7.53 (m, 4H), 7.49-7.31 (m, 5H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 166.03, 165.32, 160.68, 157.08, 155.67, 153.81, 152.37, 150.59, 148.08, 145.94, 144.86, 142.01, 140.18, 139.86, 134.88, 132.70, 130.19, 129.85, 128.06, 126.21, 125.49, 124.41, 122.98, 119.40, 118.35, 114.40, 111.54, 109.04; MS: 490.0900 [M$^+$]. Anal. calc. for $C_{28}H_{15}FN_4O_2S$: C, 68.56; H, 3.08; N, 11.42; found: C, 68.62; H, 3.20; N, 11.51.

7-chloro-3-(6-(4-phenylthiazol-2-yl) imidazo[1,2-a] [1,8] naphthyridin-9-yl)-2H-chromen-2-one (7d)

Yellow solid, (446 mg, 88%); Mp 253-254°C; ^{1}H NMR (500 MHz, DMSO-d_6); δ(ppm) 9.87 (d, J= 7.8 Hz, 1H), 9.46 (d, J= 7.8 Hz, 1H), 8.84 (s, 1H), 8.21 (s, 1H), 8.11-8.03 (m, 7.4Hz, 2H), 7.76-7.61 (m, 4H), 7.43- 7.09 (m, 5H); ^{13}C NMR (125 MHz; DMSO-d_6), δ, ppm: 166.62, 165.50, 162.85, 160.98, 156.47, 154.95, 152.69, 150.37, 148.11, 146.60, 145.47, 143.95, 141.70, 138.69, 136.80, 135.68, 133.04, 131.15, 130.39, 129.28, 128.51, 127.01, 122.88, 119.40, 118.28, 114.52, 113.01, 112.26.; MS: 506.2822 [M$^+$]. Anal. calc. for $C_{28}H_{15}ClN_4O_2S$: C, 66.34; H, 2.98; N, 11.05; found: C, 66.37; H, 3.05; N, 11.18.

Supplementary Material

Copies of ^{1}H NMR spectra of compounds **5a-d**, **5f** and **7a, b**, and ^{13}C NMR spectra of compounds **5a-f** and **7a-d** are available in the supplementary material file associated with this manuscript.

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