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COPPER (II) ACETATE CATALYSED SYNTHESIS OF NOVEL 6-(2-CHLORO-4-FLUOROPHENYL)-9-PHENYL-[1,2,4] TRIAZOLO[4,3-a][1,8]NAPHTHYRIDINE DERIVATIVES UNDER MICROWAVE IRRADIATION AND THEIR BIOLOGICAL AND MOLECULAR DOCKING STUDIES

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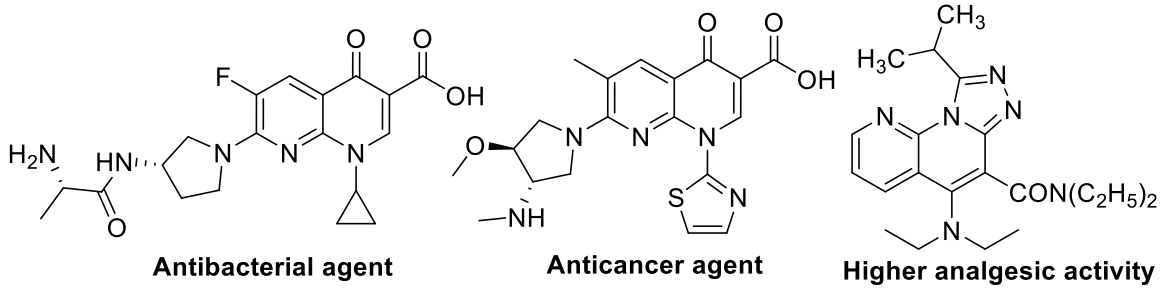
ABSTRACT;
An efficient, simple and eco-friendly synthetic route has been developed for the construction of 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine derivatives using $Cu(OAc)_2$ catalyst under microwave irradiation successfully accomplished (**7a–h**) with good yields (85–94%). The molecular structures of the compounds confirmed by IR, ^1H NMR, ^{13}C NMR and mass spectral data as well as elemental analyses studies. All synthesized compounds evaluated for their antimicrobial activity. Among them compounds **7c** and **7h** showed high antibacterial and antifungal activities. In silico studies have proved that compounds 7c and 7h have strong binding affinity.

KEYWORDS: [1,8]naphthyridines, $Cu(OAc)_2$, microwave irradiation, antimicrobial activity, molecular docking studies.

INTRODUCTION

Heterocyclic compounds containing 1,8-naphthyridine moiety are interesting as prospective biologically active substance and these are centre of attraction for the synthetic organic researcher and medicinal chemists because of the 1,8-naphthyridine group of products have gained special concentration of researchers on account of their demonstrating a variety of interesting biological activities that include anti-inflammatory[i], antibacterial[ii,iii] antioxidant[iv] anti-HIV[v] anti-allergic,[vi]anticancer,[vii]anti-malarial,[viii], anti-micobacterial activity.[ix] A number of other remarkable applications have also been reported in the literature, for example potent inhibition of protein kinase C isozymes,[x] discriminatory inhibition of p38 mitogen-activated proteinkinase,[xi] Acyl-CoA:cholesterolacyltransferase (ACAT) inhibitory activity[xii].
1,8-Naphthyridine derivatives have also exhibited potential applications in neurological disorders such as Alzheimer's disease[xiii]. In recent year microwave assisted organic reaction has emerged as new tool in organic synthesis and significant advantages include that remarkably accelerated the reaction rate and decrease reaction time and enhancement the yield..[xiv, xv] Some of the medicinally potent 1,8-naphthyridine derivatives are shown in **Fig 1**.

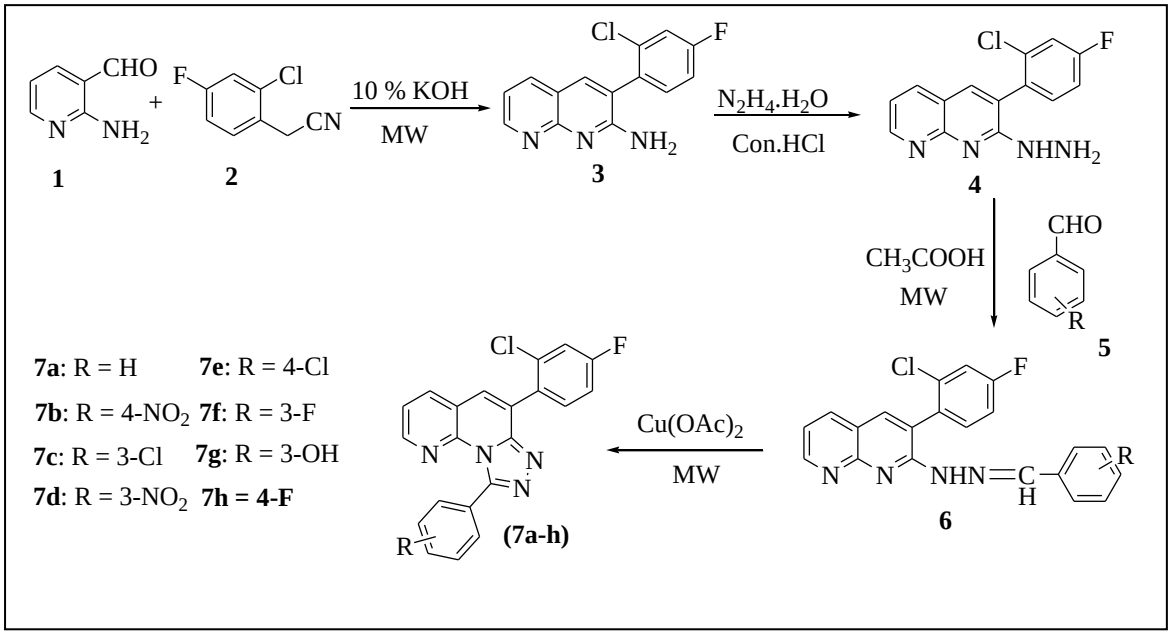


We have investigated a simple, convenient, and eco friendly process for the construction of 6-(2-chloro-4-fluorophen henyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridinederivatives. To the best of our knowle ere is no microwave method reported in the literature for these (7a-h) compounds using Copper (II) acetate catalyst under microwave irradiation.

RESULTS AND DISCUSSION

A representation for the formation of 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a] [1,8]naphthyridine derivatives **(7a-h)** catalyzed by $Cu(OAc)_2$ is shown in **Scheme 1.**. To develop eco-friendly methodology we have utilized cheap and non-toxicity of the reagent Copper (II) acetate $Cu(OAc)_2$ through microwave irradiation method. The experimental procedure for these reactions is remarkably simple, short reaction times and does not require the use of expensive
catalysts is significant improvement of this process.

Scheme1.$Cu(OAc)_2$ catalyzed synthesis of 6-(2-chloro-4-fluorophenyl)-9-phenyl-

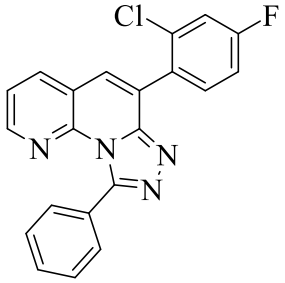
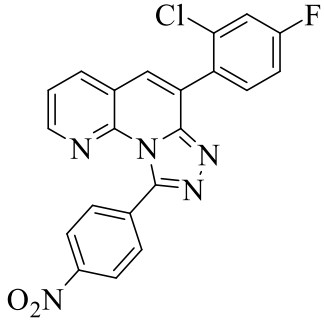
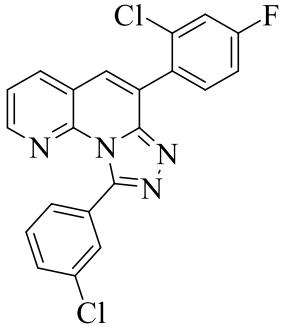
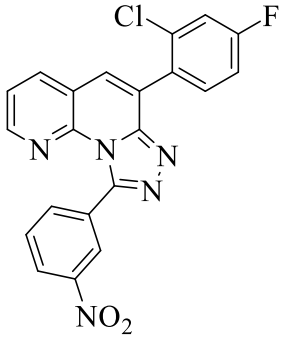


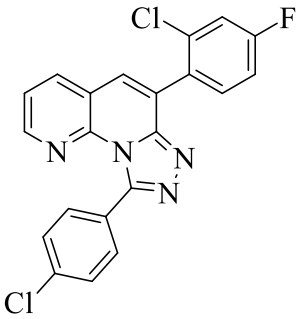
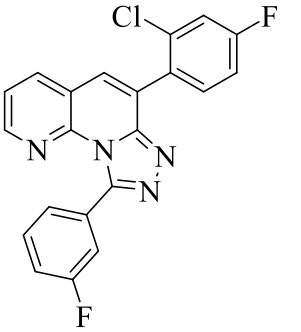
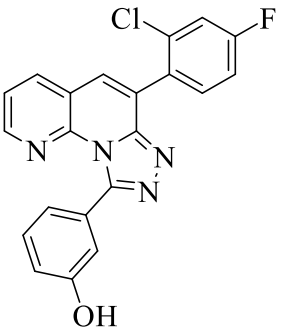
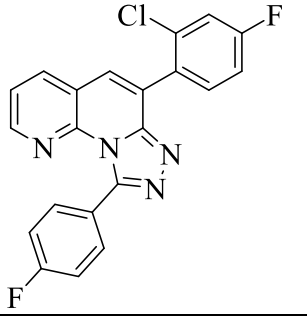
[1,2,4]triazolo[4,3-a][1,8]naphthyridine derivatives.

The reaction proceeds *via* Friedlander condensation of 2-aminonicotinaldehyde **1** with appropriate active methylene compound 2-(2-chloro-4-fluorophenyl)acetonitrile **2** in the presence of 10% KOH without any solvent under MW irradiation yielded 3-(2-chloro-4-fluorophenyl)-1,8-naphthyridin-2-amine **3**. Then compound **3** reacted with hydrazine hydrate in the presence of catalytic amount of Conc. HCl obtained 3-(2-chloro-4-fluorophenyl)-2-hydrazinyl-1,8-naphthyridine derivative **4.** In the presence of acetic acid various aromatic aldehydes reacted with compound **4** formed the corresponding compounds (E)-2-(2-

benzylidenehydrazinyl)-3-(2-chloro-4-fluorophenyl)-1,8-naphthyridines (**6a-h),** then in the presence of $Cu(OAc)_2$ **Copper (II) Acetate** intramolecular cyclization occured and formed the 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a] [1,8]naphthyridine derivatives (**7a-h)** with good yields in short reaction time.

Table 1 Synthesisof 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine derivatives **(7a-h).**

Entry	**Analog**	**Aldehyde**	**Products**	**Time (m)**	**Yield[a] (%)**
1	**7a**	Benzaldehyde		3	87
2	**7b**	4-Nitrobenzaldehyde		3.5	85
3	**7c**	3-Chlorobenzaldehyde		2.5	82
4	**7d**	3-Nitrobenzaldehyde		4	88

5	**7e**	4-Chlorobenzaldehyde		3.5	81
6	**7f**	3-Flurobenzaldehyde		2.5	84
7	**7g**	3-Hydroxybenzaldehyde		4	87
8	**7h**	4-Flurobenzaldehyde		3.5	94

[a]Isolated yields after purification

The reaction proceeds proficiently with very good yields in microwave condition and the reaction is clean and devoid of any by products. The products were formed with an elevated quantity of purity by this method. All the newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral data as well as elemental analyses studies.
The reaction proceeds efficiently in very good yields in mortar and pestle grinding and the reaction is clean and devoid of any by-products.

BIOLOGICAL ACTIVITIES (ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES)
Antibacterial activity: All these newly synthesized products (**7a–h)** were evaluated for their *in vitro* antibacterial activity against the Gram-positive bacteria *S. Epidermidis*and Gram-negative bacteria *Escherichia coli* at three diverse concentrations using standard reference

drug Amoxicillin. The products activity was tested by agar well diffusion procedure according to the developed earlier method[xvi]. All compounds displayed high inhibition activity, particularly
7c and **7h** demonstrated the highest antibacterial activity against all the tested strains (Table 2).

Antifungal activity: All the synthesized products (**7a–h)** were screened for their antifungal activity against two pathogenic fungal strains *Aspergillusniger* and *Candida metapsilosis* using standard reference drug Grieseofulvin. Activity was tested by using the disc diffusion technique [xvii]. All the compounds revealed high inhibition activity against the pathogenic fungal strains. Compounds **7c** and **7h** exhibited the highest antifungal activity (Table 2).

Table 2 Antimicrobial activity screening data of the synthesized products (**7a–h)**

Compounds	Bacterial strains						Fungal strains					
	S. epidermidis(conc.in μg/mL)			*E. coli* (conc.in μg/mL)			*A. niger* (conc.in μg/mL)			*C.Metapsilosis* (conc. in μg/mL)		
	10	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**
7a	3	4	7	3	5	9	5	7	11	5	9	12
7b	5	6	10	4	6	7	6	8	11	7	11	12
7c	**7**	**9**	**14**	**8**	**11**	**15**	**8**	**11**	**12**	**9**	**12**	**15**
7d	4	6	8	4	8	10	6	9	10	6	9	12
7e	6	8	9	5	9	11	5	8	12	7	10	11
7f	4	9	12	6	9	12	7	9	11	6	11	12
7g	5	8	9	5	8	10	6	9	12	6	9	11
7h	**7**	**11**	**16**	**9**	**12**	**14**	**9**	**12**	**15**	**9**	**12**	**16**
Amoxicillin	**10**	**14**	**18**	**12**	**15**	**17**	-	-	-	-	-	-
Grieseofulvin	-	-	-	-	-	-	**9**	**12**	**16**	**10**	**12**	**16**

Molecular Docking Studies: Auto Dock 4.0 suite was used as a molecular-docking[xviii]software for performing computerized docking of ligands to their macromolecular receptors. In the present study we used semi-flexible docking protocols. The three dimensional structure development of orally active 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridines as a potent Pde10inhibitor for the management of schizophrenia [PDB:3UI7] was obtained from Protein Data Bank (PDB)[xix]. The target protein, phosphodiesterase type 10(PDE10), was kept as rigid. The ligands being docked were set flexible, in order to discover an arbitrary number of torsional degrees of freedom in addition to the six spatial degrees of freedom spanned by the translational and rotational parameters. The Graphical User Interface program "Auto Dock Tools" was used to prepare, run, and analyze the docking simulations. Kollman united atom charges, salvation parameters and polar hydrogens were added into the receptor PDBfile (PDB ID: 3UI7) for preparation of protein indocking. This PDE10 enzyme structure did not have any water molecules and/or ligands to remove from its PDB file and make a free receptor. Since ligands were not peptides, Gasteiger charge was assigned and then non polar hydrogens were merged. Auto Grid 4.0Program, supplied with Auto Dock 4.0, was used toproduce grid maps. Compounds **5c**–**5e** exhibited efficient interactions (Table 3 and Fig. 2, and 3).

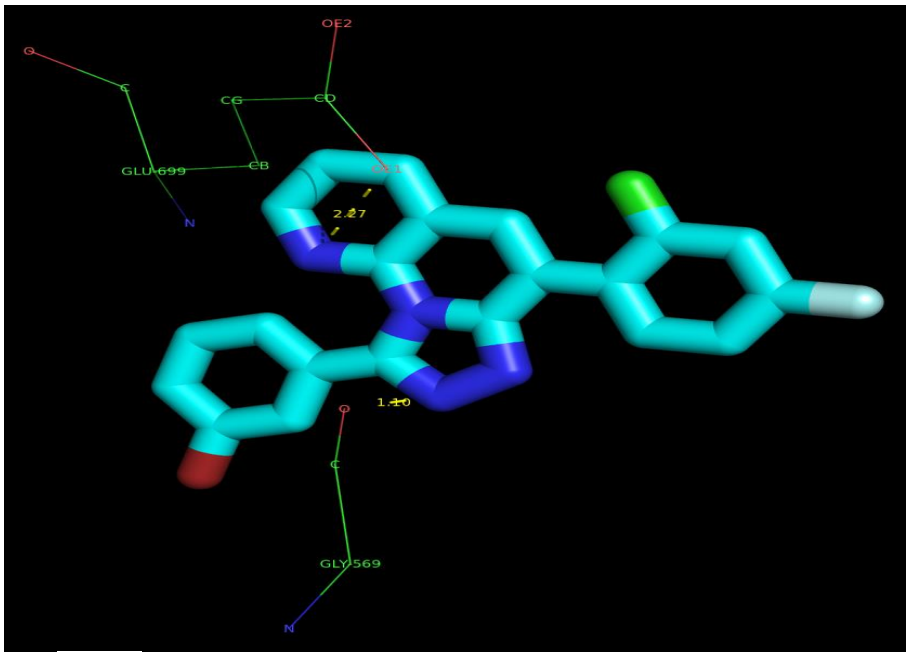


Fig .2 Binding mode of the synthesized molecule **7c** molecule

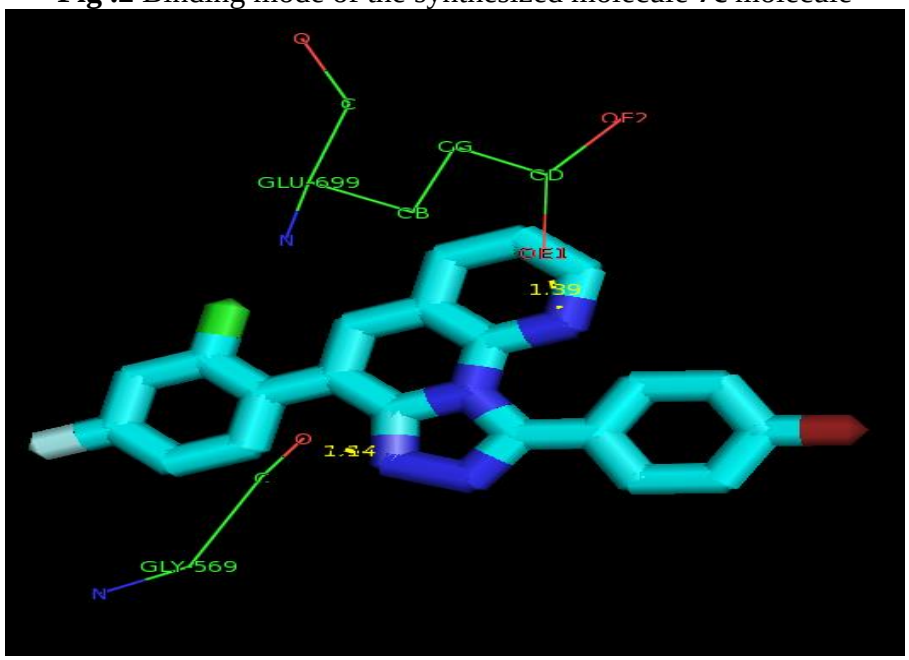


Fig .3 Binding mode of the synthesized molecule **7h** molecule.

Table 3 Atoms involved in the interactions.

Analog	**Receptor 3UI7 (Interacting atoms)**	**Ligand (Atoms)**	**H-bond Distance (A°)**	**Docking energy (Kcal/mol)**
7a	LY569O	NH	1.09	-87.6985
	GLU695OE2	NH	2.00	
7b	ASP674O	NH	2.93	-75.6218
	HIS525NE2	O	3.10	
7c	GLY569O	NH	1.10	**-88.7253**
	GLU699OE1	**NH**	**2.97**	

7d	TYR5240	NH	2.98	-79.8844
7e	GLY569O	O	1.15	-86.2321
	GLU699OE1	NH	2.14	
7f	GLY569O	NH	1.13	-77.8808
7g	GLY569O	NH	1.17	-85.2347
	GLU699OE1	NH	1.49	
7h	GLY569O	NH	1.14	**-87.8386**
	GLU699OE1	**NH**	**2.91**	

EXPERIMENTAL All the reagents and chemicals were purchased from Aldrich and used without further purification. Purity of the molecules was checked by F_{254} silica-gel precoated TLC plates using hexane and ethyl acetate (7:3) as eluent.The melting points were resolute in an open capillary tube with a Buchi melting point apparatus and are uncorrected.^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer using DMSO-$d_6$as solvent. Mass spectra were recorded on ESI mass spectrometer. IR spectra were recorded with Bruker Tensor 27 series FT-IR spectrophotometer in KBr disks. Microanalyses were performed on a Carlo-Erba model EA1108 analytical unit.

General procedure for the synthesis of 3-(2-chloro-4-fluorophenyl)-1,8-naphthyridin-2-amine (3)

Typical procedure via Microwave irradiation: A mixture of **1** (1 mmol, 122.12 mg) active methylene compound **2** (1 mmol) and 10% KOH (5 drops) was exposed to MW irradiation at 200W intermittently at 30 sec for 2.0 min. On completion of the reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The solid that separated was filtered, washed with water and purified by recrystallization from methanol to afford **3.**

General procedure for the synthesis of 3-(2-chloro-4-fluorophenyl)-2-hydrazinyl-1,8-naphthyridine (4)

3-(2-chloro-4-fluorophenyl)-1,8-naphthyridin-2-amine (1 mmol) 3 reacted with an excess of 80% hydrazine hydrate and Con HCl under microwave condition formed desired product **4.**

General procedure for the synthesis of (E)-2-(2-benzylidenehydrazinyl)-3-(2-chloro-4-fluorophenyl)-1,8-naphthyridine (6)

In the presence of acetic acid (15 mol%) 3-(2-chloro-4-fluorophenyl)-2-hydrazinyl-1,8-naphthyridine(4) reacted with aromatic aldehyde (1,mmol) obtained the products **6a-h**.On the completion of reaction (monitored by TLC) the mixture was poured into ice-cold water then resulting solid product was filtered, washed with water and purified by recrystallization from ethanol to furnished compound **6**.

General procedure for the synthesis of 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine derivatives(7a-h)

Compound **7** (0.01 mol) and $Cu(OAc)_2$ (0.01 mol) were mixed thoroughly and exposed to MW at 800W intermittently at 30 sec intervals for the specified time (**Table I**). After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with methanol (20 mL). The methanol solution was poured into ice cold water (40mL), the separated solid product was filtered and purified by re-crystallization from ethanol to obtained products **(7a-h)**.

6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine (7a)

M.p.: 184-186 °C; IR: 1638 (C═C), 1591, (C═N), 1015 (C-F); 818 (C-Cl); cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.3 (s, 1H), 9.19 (s, 1H), 8.92-8.7 (d, 2H, J = 7.2 Hz), 8.6-8.4 (d, 2H, J = 7.6 Hz), 7.97-7.70 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158, 155, 153, 149,

147, 144, 140, 138 (2C), 137, 136, **1**35**,** 130(2C), 124, 118.ESI-MS: *m/z*375.07 $[M+H]^+$ Anal. Calc. For $C_{21}H_{12}ClFN_4$: C, 67.30; H, 3.23; N, 14.95; Found: C, 67.41; H, 3.19; N, 14.87; %.

6-(2-chloro-4-fluorophenyl)-9-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine (7b)
M.p.: 240-242 °C; IR: 1638 (C═C), 1426, (C═N),1015 (C-F); 915 (C-Cl); cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18-9.12 (s, 1H), 8.6-8.5 (m, 3H), 8.2-8.19 (m, 2H), 8.0-7.98 (m, 3H), 7.98-7.86 (m, 3H);^{13}C NMR (100 MHz, DMSO-d_6): δ 158.3, 155.6, 153.2,149.4, **145.6, 144.3,** 140.3, 138 (2C), 137, 132 2C, 129 2C, 122, 118. ESI-MS: *m/z*420.06 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}ClFN_5O_2$: C, 60.08; H, 2.64; N, 16.68; Found: C, 60.13; H, 2.69; N, 16.63; %.

6-(2-chloro-4-fluorophenyl)-9-(3-chlorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine (7c)
M.p.: 218-220 °C; IR: 1655 (C═C), 1605, (C═N), 959 (C-F); 854 (C-Cl); cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ δ9.28 (s, 1H), 8.9-8.6 (m, 2H), 8.31-8.27 (m, 3H), 8.10-7.96 (m, 3H), 7.95-7.87 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162, 158,152, 148, 144, 139 (2C), 135, 130 (2C), 129, 127, 126, 118. ESI-MS: *m/z*409.14 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}C_{l2}FN_4$: C, 61.63; H, 2.71; N, 13.69; Found: C, 61.68; H, 2.76; N, 13.71; %.

6-(2-chloro-4-fluorophenyl)-9-(3-nitrophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine (7d)
M.p.: 238-239 °C; IR: 1659 (C═C), 1606, (C═N),951 (C-F); 857 (C-Cl); cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.48-8.46 (d, 2H, J = 7.2 Hz), 8.16 (s, 1H), 7.93-7.81 (m, 2H), 7.71- 7.69 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159, 156, 153, **152,** 141, 140, 138 (2C), 137, 136, 134, 130, 129, 126, 124, 118. ESI-MS: *m/z*420.10 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}ClFN_5O_2$: C, 60.08; H, 2.64; N, 16.68; Found: C, 60.11; H, 2.69; N, 16.71; %.

6-(2-chloro-4-fluorophenyl)-9-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine (7e)
M.p.: 221-223 °C; IR: 1655 (C═C), 1606, (C═N),957 (C-F); 854 (C-Cl); cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.43 (s, 1H), 8.02 (d, 2H, J = 7.2 Hz), 7.91-7.87 (m, 3H), 7.24-7.21(m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ δ158, 155, 151,141, 140, 138 (2C), 137, 136, 133, 130, 129, 126, 123, 118. ESI-MS: *m/z*409.14 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}C_{l2}FN_4$: C, 61.63; H, 2.71; N, 13.69; Found: C, 61.69; H, 2.77; N, 13.74; %.

6-(2-chloro-4-fluorophenyl)-9-(3-fluorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine (7f)
M.p.: 212-214 °C; IR: 1661 (C═C), 1608, (C═N),952 (C-F); 858 (C-Cl); cm^{-1}.
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.**8** (s, 1H), 8.43 (s, 1H), 7.83-7.51 (m, 5H), 7.23-7.17 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ162, 158, 153, 148 (2C), 142, 139, 136, 131, 129.7 (2C), 128, 126, 125,118.; ESI-MS: *m/z*393.12 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}ClF_2N_4$: C, 64.21; H, 2.82; N, 14.26; Found: C, 64.31; H, 2.89; N, 14.36;%.

3-(6-(2-chloro-4-fluorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridin-9-yl)phenol (7g)
M.p.: 210-212 °C; IR: 1650 (C═C), 1609, (C═N),957 (C-F); 858 (C-Cl); cm^{-1}.
^{1}H NMR (400 MHz, DMSO-d_6): δ 9. 8 (s, 1H), 8.80 (s, 1H), 8.17 (s, 1H), 8.17 (s, 1H), 8.16-7.82 (m, 7H), 7.19- 6.97(m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159, 152, 14**8**, 147. (2C), 142, 140, 133, 132, 130 (2C), 129 (2C), 128, 127, 125, 118; ESI-MS: *m/z*393.07 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}ClF_2N_4$: C, 64.21; H, 2.82; N, 14.26; Found: C, 64.34; H, 2.89; N, 14.21; %.

6-(2-chloro-4-fluorophenyl)-9-(4-fluorophenyl)-[1,2,4]triazolo[4,3-a][1,8]naphthyridine(7h)

Pale brown solid; M.p.: 175-176 °C; IR: 1657 (C═C), 1608, (C═N),957 (C-F); 856 (C-Cl); cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H), 8.**3** (s, 1H), 8.41 (s, 1H), 7.94-7.84 (m, 5H), 7.33-7.27 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158, 155, 152, 148, 145,143, 142, 138 2C, 136, 132, 130, 129 (2C), 128, 118. ESI-MS: *m/z* 393.07 $[M+H]^+$ Anal. Calc. For $C_{21}H_{11}ClF_2N_4$: C, 64.21; H, 2.82; N, 14.26; Found: C, 64.27; H, 2.92; N, 14.31; %.

CONCLUSION:

The $Cu(OAc)_2$ catalyzed expedient and eco-friendly method developed for the synthesis of 6-(2-chloro-4-fluorophenyl)-9-phenyl-[1,2,4]triazolo[4,3-a][1,8]naphthyridine scaffolds under microwave irradiation. Antimicrobial activity of the synthesized products is evaluated against pathogenic bacterial and fungal strains. Among these compounds **7c** and **7h** displayed the maximum activity. Molecular modeling studies proved that their strong binding affinity and H-bond interactions.

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