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A Simple "Green" Synthesis of Novel Bis(3-aryl-1,8-naphthyridin-2-yl)sulfanes and 2-(Methylthio)-3-aryl-1,8-naphthyridines under Microwave Irradiation and Conventional Conditions[1]

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Abstract—An eco-friendly and highly efficient synthesis of substituted bis(3-aryl-1,8-naphthyridin-2-yl)-sulfanes and 2-(methylthio)-3-aryl-1,8-naphthyridines under microwave and conventional conditions. The products are obtained with high yields and purity within short reaction time. The synthesized derivatives are screened for anti-microbial activity against bacteria and fungi. Molecular docking of the synthesized compounds with DNA Gyrase is studied.

Keywords: 1,8-naphthyridines, anti-microbial activity, methanol, microwave Irradiation, molecular docking

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INTRODUCTION

Nitrogen-containing heterocyclic compounds annealed with 1,8-naphthyridine derivatives are attractive objects of study due to their broad spectrum of biological activities [1–3].

In continuation of our studies of solvent-free organic reactions and eco-friendly methods [4, 5], we developed the synthetic approaches to new di(3-aryl-1,8-naphthyridin-2-yl)thioethers and 2-(methylthio)-3-aryl-1,8-naphthyridines, that were characterized by short reaction time and high yields.

RESULTS AND DISCUSSION

In the current study, pyridine-based substituted 2-chloro-3-aryl-1,8-naphthyridines (**3**) could be used as suitable intermediates for the synthesis of the target compounds. The compounds **3** could be synthesized in high yields by interaction of the compounds **1, 2** with $POCl_3$ [6, 7] (Schemes 1, 2).

The following reaction with thiourea was carried out under microwave irradiation or under conventional conditions. In both cases the respective 3-aryl-1,8-naphthyridine-2-thiols (**6**) were accumulated in good yields (Table 1). The structures of compounds were confirmed on the basis of spectral data.

The reaction of **6** with sulfuric acid in methanol under solvent-free conditions in 15–20 min gave 2-(methylthio)-3-aryl-1,8-naphthyridines (**7**) in high yields (Scheme 2, Table 2).

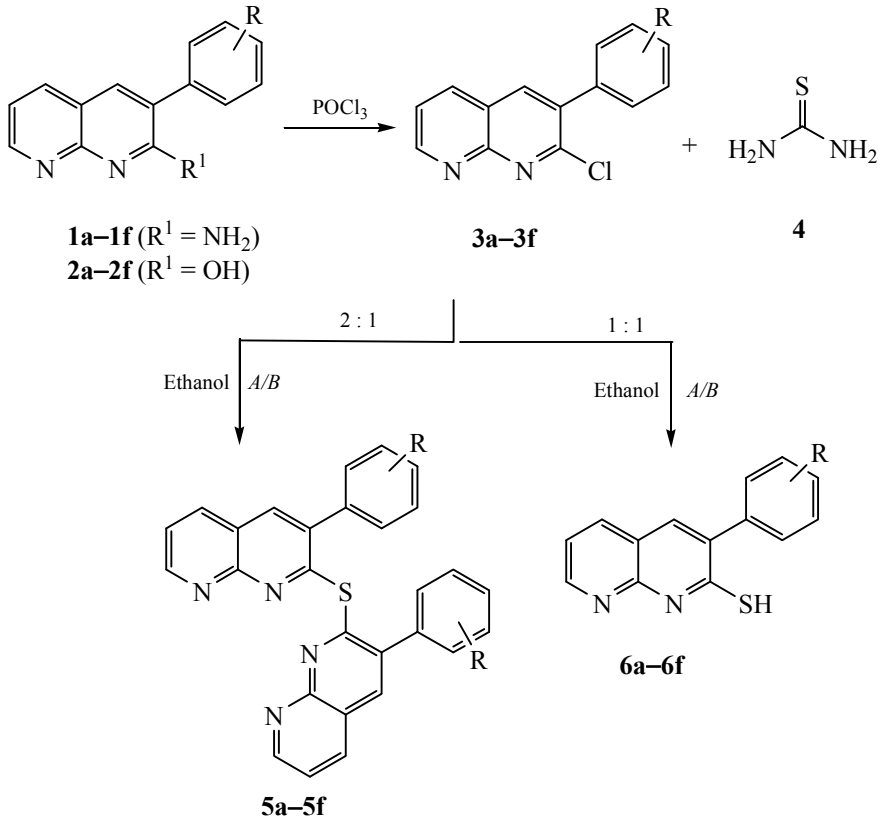
A number of acids was tested in the process (Table 2) and sulfuric acid was determined to be the most efficient.

EXPERIMENTAL

All reagents and solvents were purchased from Merck/Aldrich and used without further purification. Melting points were measured in open capillary tubes in a Cintex apparatus. Purity of compounds was tested by TLC on Merk plates, F_{254}, and visualized under UV light or iodine vapors. IR spectra were recorded on a Perkin-Elmer spectrum BX series spectrophotometer using KBr discs. ^{1}H NMR spectra were measured on a Bruker 400-MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. EI-MS spectra were measured on a Jeol JMSD-400 spectrometer at 70 eV. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Irradiation was carried out in a domestic microwave oven.

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 3-aryl-1,8-naphthyridine-2-thiols and bis(3-aryl-1,8-naphthyridin-2-yl)sulfanes.



1a–1f ($R^1 = NH_2$)
2a–2f ($R^1 = OH$)

3a–3f

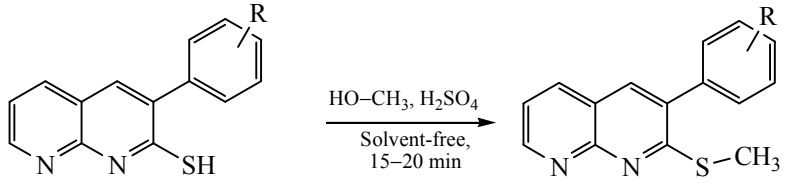
4

6a–6f

5a–5f

R = H (**1a–3a, 5a, 6a**), 2-CF_3 (**1b–3b, 5b, 6b**), 4-OCH_3 (**1c–3c, 5c, 6c**), 4-F (**1d–3d, 5d, 6d**), 4-NO_2 (**1e–3e, 5e, 6e**), 2-OPh (**1f–3f, 5f, 6f**); *A* is microwave method, 6–8 min; *B* is conventional method, reflux, 55–60 min.

Scheme 2. Synthesis of 2-(methylthio)-3-aryl-1,8-naphthyridines.



6a–6f **7a–7f**

R = H (**6a, 7a**), *o*-CF_3 (**6b, 7b**), *p*-OCH_3 (**6c, 7c**), *p*-F (**6d, 7d**), *p*-NO_2 (**6e, 7e**), *o*-OPh (**6f, 7f**).

Synthesis of 3-aryl-1,8-naphthyridin-2-ol (2a–2f). To a solution of (1 mmol, **1a–1f**) in 2 N HCl (10 mL) was added $NaNO_2$ solution (1 mmol in 10 mL of water) and the reaction mixture was stirred at room temperature for 35 min, then treated with cold water. The solid thus obtained was filtered off, washed with water and recrystallized from ethanol.

Synthesis of 2-chloro-3-phenyl-1,8-naphthyridine (3a–3f). A solution of a compounds **2a–2f** (1 mmol) with $POCl_3$ (15 mL) was heated for 6 h. Upon cooling down to room temperature, the resulting reaction mixture was dissolved in cold water and saturated $NaHCO_3$. The organic phase was evaporated. The crude product was filtered off, washed with water and recrystallized from methanol.

Synthesis of bis(3-aryl-1,8-naphthyridin-2-yl)sulfanes (5a–5f). *Method A: microwave conditions*. the mixture of 2-chloro-3-aryl-1,8-naphthyridines **3a–3f** (0.2 mmol) with thiourea (0.1 mmol, 4 mL), and ethanol (1.5 mL) was exposed to microwave irradiation at 200 W with pulses of 30 s, and gaps of 15 s for 6.0 to 8.0 min upon TLC monitoring. The reaction mixture was cooled

Table 1. Yields and reaction time for synthesis of C^3 substituted 1,8-naphthyridine derivatives

Analog	R	Microwave		Heating		mp, °C
		time, min	yield[a], %	time, min	yield[a], %	
5a	H	8	69	55	52	220–222
5b	*o*-CF_3	6	78	58	56	233–235
5c	*p*-OCH_3	7	67	55	60	228–230
5d	*p*-F	6	65	60	55	216–218
5e	*p*-NO_2	6	74	50	61	230–232
5f	*o*-OPh	8	70	60	59	236–238

[a] Yields refer to pure isolated products.

down to room temperature and treated with 2% NaOH. The solid product thus obtained was recrystallized from ethanol.

Method B: conventional conditions. A mixture of 2 mmol of a compounds **3a–3f** with 1 mmol of thiourea in ethanol (15 mL) was refluxed for 50–60 min (Table 1). Upon completion of the reaction (TLC), the mixture was cooled down and treated with 2% NaOH. The corresponding product was filtered off, washed with water and recrystallized from methanol.

Synthesis of 3-aryl-1,8-naphthyridine-2-thiols (6a–6f). A mixture of 0.1 mmol of a compounds **3a–3f** with 0.1 mmol of thiourea in ethanol (1.5 mL) was MW irradiated in an oven at 350 W for 3.0–4.0 min (2 + 2 with an intermission of 4 min). Upon completion, the reaction mixture was cooled down and treated with 2% NaOH. The corresponding product was filtered off, washed with water and recrystallized from methanol.

Bis(3-phenyl-1,8-naphthyridin-2-yl)sulfane (5a). White solid. FT–IR spectrum, ν, cm^{-1}: 3034 (Ar–CH), 1654 (C=N), 1566 (C=C), 696 (C–S–C). ^{1}H NMR spectrum, δ, ppm: 7.28 s (2H, ArH), 7.39–7.48 m (6H, ArH), 7.74 d (J = 6.7 Hz, 4H, ArH), 8.12–8.21 m (4H, ArH), 8.52 s (2H, ArH). LCMS: *m/z*: 443 $[M + H]^+$. Found, %: C 76.11; H 4.19; N 12.51. $C_{28}H_{18}N_4S$. Calculated, %: C 75.99; H 4.10; N 12.66.

Bis{3-[2-(trifluoromethyl)phenyl]-1,8-naphthyridin-2-yl}sulfane (5b). Off white solid. FT–IR spectrum, ν, cm^{-1}: 3030 (Ar–CH), 1666 (C=N), 1566 (C=C), 1271–1010 (C–F), 711 (C–S–C). ^{1}H NMR spectrum, δ, ppm: 7.26–7.31 m (2H, ArH), 7.52 d (J = 8.5 Hz, 4H, ArH), 7.80 d (J = 8.5 Hz, 4H, ArH), 8.15–8.21 m (4H, ArH), 8.53 d (J = 4.5 Hz, 2H, ArH). LCMS: *m/z*: 579 $[M + H]^+$. Found: C 62.12; H 2.81; N 9.52. $C_{30}H_{16}F_6N_4S$. Calculated %: C 62.28; H 2.79; N 9.68.

Bis[3-(4-methoxyphenyl)-1,8-naphthyridin-2-yl]-sulfane (5c). Yellow solid. FT–IR spectrum, ν, cm^{-1}: 3080 (Ar–CH), 1672 (C=N), 1581 (C=C), 1251 (C–O), 719 (C–S–C). ^{1}H NMR spectrum, δ, ppm: 3.81 s (6H, 2-OCH_3), 7.08 d (J = 8.7 Hz, 4H, ArH), 7.19 d (J = 7.7 Hz, 2H, ArH), 7.44–7.49 m (4H, ArH), 7.84 s (2H, ArH), 8.10 d (J = 7.7 Hz, 2H, ArH), 8.70 d (J = 4.5 Hz, 2H, ArH). LCMS, *m/z*: 503 $[M + H]^+$. Found,

Table 2. Methylation of 3-phenyl-1,8-naphthyridine-2-thiol (**6a**) with acidic methanol[a]

Acid	Equivalent	Yield of **7a**, %
H_2SO_4	3.0	70
p-$TsOH·H_2O$	1.5	57
$BF_3·OEt_2$	1.5	61
HCl_{aq}	2.0	56
AcOH	2.5	Ttraces

[a] **6a** 1.0 mmol, MeOH 5.0 mL, solvent-free, 15 min.

Table 3. Methylation of 3-aryl-1,8-naphthyridine-2-thiols **6b–6f** with acidic methanol[a]

Thiol	Product	Time, min	Yield[b], %
6b	**7b**	20	68
6c	**7c**	20	71
6d	**7d**	15	65
6e	**7e**	15	69
6f	**7f**	20	60

[a] Thiol 1.0 mmol, H_2SO_4 0.2 mL, MeOH 5.0 mL, solvent-free.
[b] Isolated product.

Table 4. Antimicrobial activity data of the synthesized compounds **5a–5f** and **7a–7f** at two different concentrations (50 and 1000 μg/mL)[a]

Compound	Zone of inhibition, %							
	antibacterial activity				antifungal activity			
	Escherichia coli		*Staphylococcus aureus*		*Aspergillus Niger*		*Helmenthosphorium oryzae*	
	100	50	100	50	100	50	100	50
5a	5	3	6	4	6	4	7	3
5b	9	4	9	5	8.5	5	9	5
5c	**10**	**5**	**10**	**6**	**9**	**6**	**10**	**6**
5d	8	4	7	5	8	4	7	5
5e	7	3.5	8	4	8	4	8	4
5f	9.5	4.5	9.5	6	10	5.5	9.5	6
7a	4	3	7	3	6	3	7	4
7b	8	4	7	4	7	3.5	8	4
7c	**9**	**4.5**	**9**	**6**	**10**	**5.5**	**0.9**	**6**
7d	8	3.5	7	5	7	5	7.5	5.5
7e	8	3	6	4	6	3.5	7	4
7f	7	4	5	3	5	2	5	3
Pencillin	12	7	11	8	–	–	–	–
Griseofulvin	–	–	–	–	11	8	13	08

[a] The bold values indicate the compounds of the highest antimicrobial activity.

%: C 71.62; H 4.22; N 10.96. $C_{30}H_{22}N_4O_2S$. Calculated, %: C 71.69; H 4.41; N 11.15.

Bis[3-(4-fluorophenyl)-1,8-naphthyridin-2-yl]-sulfane (5d). White solid. FT–IR spectrum, ν, cm^{-1}: 3070 (Ar–CH), 1666 (C=N), 1579 (C=C), 1350-1201 (C–F), 719 (C–S–C). ^1H NMR spectrum, δ, ppm: 7.25–7.32 m (3H, ArH), 7.38–7.48 m (2H, ArH), 7.68–7.78 m (3H, ArH), 7.87–7.95 m (2H, ArH), 8.11–8.19 m (1H, ArH), 8.44–8.58 m (5H, ArH). LCMS, *m/z*: 479 $[M + H]^+$. Found, %: C 70.15; H 3.24; N 11.85. $C_{28}H_{16}F_2N_4S$. Calculated, %: C 70.28; H 3.37; N 11.71.

Bis[3-(4-nitrophenyl)-1,8-naphthyridin-2-yl]-sulfane (5e). Pale yellow solid. FT–IR spectrum, ν, cm^{-1}: 3107 (Ar–CH), 1656 (C=N), 1579 (C=C), 1346 (N–O), 696 (C–S–C). ^1H NMR spectrum, δ, ppm: 7.23–7.37 m (6H, ArH), 7.75–7.84 m (4H, ArH), 8.09–8.23 m (4H, ArH), 8.51–8.60 m (2H, ArH). LCMS, *m/z*: 533 $[M + H]^+$. Found, %: C 63.20; H 3.00; N 15.85. $C_{28}H_{16}N_6O_4S$. Calculated, %: C 63.15; H 3.03; N 15.78.

Bis[3-(2-phenoxyphenyl)-1,8-naphthyridin-2-yl]-sulfane (5f). Brown solid. FT–IR spectrum, ν, cm^{-1}: 3059 (Ar–CH), 1670 (C=N), 1581 (C=C), 1251, 1197 (C–O–C), 721 (C–S–C). ^1H NMR spectrum, δ, ppm: 7.21 d (J = 7.7 Hz, 1H, ArH), 7.37–7.44 m (5H, ArH), 7.57 d (J = 4.0 Hz, 3H, ArH), 7.72–7.78 m (5H, ArH), 7.91 s (1H, ArH), 8.10–8.23 m (5H, ArH), 8.52–8.58 m (4H, ArH), 8.70–8.75 m (2H, ArH). LCMS, *m/z*: 627 $[M + H]^+$. Found, %: C 76.51; H 4.19; N 9.05. $C_{40}H_{26}N_4O_2S$. Calculated, %: C 76.66; H 4.18; N 8.94.

Synthesis of 2-(methylthio)-3-aryl-1,8-naphthyridines (7a–7f) *(general procedure).* To a solution of 3-aryl-1,8-naphthyridine-2-thiols (**6a–6f**) (1.0 mmol) in Me-OH (5.0 mL) was added H_2SO_4 (0.2 mL), and the mixture was stored for 15-20 min. On completion of the process (TLC), the reaction mixture was poured into cold water. The solid product was filtered off, washed with water and recrystallized from methanol.

2-(Methylthio)-3-phenyl-1,8-naphthyridine (7a). Off white solid, mp 190–192°C. FT–IR spectrum, ν,

Table 5. Molecular docking interactions of the synthesized compounds **5a–5f** and **7a–7f**

Comp. no.	Interacting residues		Distance, Å	Comp. no.	Interacting residues		Distance, Å
	ligand	receptor (2XCT)			ligand	receptor (2XCT)	
5a	NH	ASP437- OD2	3.01	**7a**	NH	GLU435- OE2	3.07
5b	NH	GLU435-OE2	2.23	**7a**	NH	GLU435- O	3.28
5b	NH	GLU435-OE2	2.57	**7b**	NH	HIS1081-O	4.09
5b	NH	GLU435-OE1	3.04	**7c**	NH	GLU435-OE2	2.91
5c	NH	ASP437- OD1	2.93	**7c**	NH	GLY459-O	3.08
5c	NH	ASP437- OD2	2.99	**7d**	NH	GLU435-O	2.88
5d	NH	ASP437-OD2	2.98	**7e**	O	GLY459-NH	3.09
5e	O	SER438-NH	2.92	**7e**	NH	GLU435-OE2	3.10
5e	NH	GLU435-OE1	3.06	**7f**	O	GLY459-NH	3.03
5f	O	SER438-NH	2.76				

cm^{-1}: 3032 (Ar–CH), 1602 (C=N), 1514 (C=C), 796 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.97 s (3H, SCH_3), 6.91–7.00 m (3H, ArH), 7.23–7.34 m (3H, ArH), 7.60–7.70 m (3H, ArH). LCMS, *m/z*: 253 $[M + H]^+$. Found: C 71.09; H 4.98; N 11.12. $C_{15}H_{12}N_2S$. Calculated, %: C 71.40; H 4.79; N 11.10.

2-(Methylthio)-3-[(2-(trifluoromethyl)phenyl]-1,8-naphthyridine (7b). Colorless solid, mp 182–184°C. FT–IR spectrum, ν, cm^{-1}: 3032 (Ar–CH), 1664 (C=N), 1510 (C=C), 1296-1028 (C–F), 775 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.96 s (3H, SCH_3), 6.87 s (1H, ArH), 7.05 d (*J* = 2.2 Hz, 1H, ArH), 7.23 s (1H, ArH), 7.28–7.37 m (3H, ArH), 7.66 d.d (*J* = 9.0, 4.2 Hz, 2H, ArH). LCMS, *m/z*: 321 $[M + H]^+$. Found, %: C 60.12; H 3.19; N 8.55. $C_{16}H_{11}F_3N_2S$. Calculated, %: C 59.99; H 3.46; N 8.75.

3-(4-Methoxyphenyl)-2-(methylthio)-1,8-naphthyridine (7c). Light yellow solid, mp 195–197°C. FT–IR spectrum, ν, cm^{-1}: 3026 (Ar–CH), 1604 (C=N), 1548 (C=C), 1120 (C–O), 769 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.86 s (3H, SCH_3), 3.81 s (3H, OCH_3), 7.64 d (2H, *J* = 8.2 Hz, ArH), 8.05 d (1H, *J* = 8.2 Hz, ArH), 8.26 t (*J* = 7.5 Hz, 2H, ArH), 8.86 d (*J* = 5.0 Hz, 3H, ArH). LCMS, *m/z*: 283 $[M + H]^+$. Found, %: C 68.01; H 5.09; N 9.84. $C_{16}H_{14}N_2OS$. Calculated, %: C 68.06; H 5.00; N 9.92.

3-(4-Fluorophenyl)-2-(methylthio)-1,8-naphthyridine (7d). White solid, mp 194–196°C. FT–IR spectrum, ν, cm^{-1}: 3140 (Ar–CH), 1666 (C=N), 1583 (C=C), 1352–1012 (C–F), 775 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.78 s (3H, SCH_3), 7.58 d.d (*J* = 7.7, 3.0 Hz, 1H, ArH), 7.90– 8.07 m (4H, ArH), 8.43–8.52 m (2H, ArH), 8.83 d (*J* = 4.2 Hz, 1H, ArH). LCMS, *m/z*: 271 $[M + H]^+$. Found, %: C 66.57; H 4.23; N 10.18. $C_{15}H_{11}FN_2S$. Calculated, %: C 66.65; H 4.10; N 10.36.

2-(Methylthio)-3-(4-nitrophenyl)-1,8-naphthyridine (7e). Light yellow solid, mp 181–183°C. FT–IR spectrum, ν, cm^{-1}: 3085 (Ar–CH), 1637 (C=N), 1552 (C=C), 1398 (N–O), 742 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.80 s (3H, SCH_3), 7.54–7.64 m (1H, ArH), 7.90–8.09 m (4H, ArH), 8.41–8.55 m (2H, ArH), 8.83 d (*J* = 4.7 Hz, 1H, ArH). LCMS, *m/z*: 298 $[M + H]^+$. Found, %: C 60.68; H 3.41; N 14.00. $C_{15}H_{11}N_3O_2S$. Calculated, %: C 60.59; H 3.73; N 14.13.

2-(Methylthio)-3-(2-phenoxyphenyl)-1,8-naphthyridine (7f). Light brown solid, mp 199–201°C. FT–IR spectrum, ν, cm^{-1}: 3032 (Ar–CH), 1660 (C=N), 1573 (C=C), 1166–1114 (C–O–C), 769 (C–S). ^{1}H NMR spectrum, δ, ppm: 2.76 s (3H, SCH_3), 6.78 s (3H, ArH), 7.45 d.d (*J* = 7.7, 3.5 Hz, 2H, ArH), 7.75–7.85 m (3H, ArH), 8.14 s (2H, ArH), 8.36 d (*J* = 6.0 Hz, 2H, ArH), 8.97 d (*J* = 2.3 Hz, 1H, ArH). LCMS, *m/z*: 345 $[M + H]^+$. Found, %: C 73.01; H 4.76; N 8.01%. $C_{21}H_{16}N_2OS$. Calculated, %: C 73.23; H 4.68; N 8.13.

Antibacterial and antifungal activities. Antimicrobial screening of the newly synthesized compounds **5a–5f** and **7a–7f** was carried out using the agar diffusion method [9]. Antibacterial activity of the compounds

was assayed against the growth of *Escherichia coli* (gram –ve) and *Staphylococcus aureus* (gram +ve) species along with the standard antibiotic Pencillin at concentrations of 100 and 50 ppm (Table 4). Majority of the compounds exhibited moderate to high activity against both bacteria. The same compounds **5a–5f, 7a–7f** were screened for their antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* species at concentrations 100 and 50 ppm. The antibiotic Griseofulvin was used as a standard. Majority of compounds **5a–5f, 7a–7f** demonstrated moderate to high antifungal activity (Table 4).

Molecular docking studies. Accelry's Discovery Studio (version 2.5) was used to design lead molecules, estimate docking interactions of synthesized compounds with protein binding, and number of bonds formed by the ligands **5a–5f** and **7a–7f** with the target (DNA Gyrase). The molecular docking of synthesized compounds was performed using Ligfit which is a high-throughput algorithm for docking ligands into an active binding site on the receptor, which is also a site-features docking algorithm. Accelry's CHARMm force field was used throughout the simulation before running Ligfit. The crystal structure of S. aureus Gyrase complex with Ciprofloxacin and DNA receptor was downloaded from RCSB database (PDB ID-2XCT) [10]. The synthesized compounds **5a–5f** and **7a–7f** were sketched using the tools Chemsketch, and docked into the target binding sites. The scoring functions have been used to estimate binding affinity to single out active and inactive compounds in the course of the process of virtual screening [11].

According to the accumulated data, compounds **5c**, **5f**, and **7c** exhibited the highest docking score (Table 5). The active site pocket residues of DNA Gyrase were involved in hydrogen bonding formation with synthesized compounds.

CONCLUSIONS

We have developed an efficient procedure for the synthesis of new symmetrical bis(3-aryl-1,8-naphthyridin-2-yl)sulfanes and unsymmetrical 3-aryl-1,8-naphthyridine-2-thiol by the reaction of thiourea with 2-chloro-3-aryl-1,8-naphthyridines under microwave radiation. High yields of the products, easy work-up, short reaction times, and non-toxicity of the reagents are the advantages of this method. Antimicrobial activity of the synthesized compounds was tested against pathogenic bacteria and fungal strains.

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