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ARTICLE

One-pot synthesis of novel benzimidazoles with a naphthalene moiety as antimicrobial agents and molecular docking studies

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Abstract

In an attempt to design a greener approach for the synthesis of a potent class of antimicrobials, 1,2-phenylenediamine derivatives were reacted with various 1/2-carboxylic acid-substituted naphthalene derivatives to generate a series of naphthyl-substituted benzimidazole derivatives (**11**–**19**) using polyphosphoric acid as catalyst under microwave irradiation and conventional synthesis method. This is an eco-friendly and swift reaction method for a synthetic approach to diverse benzimidazoles. Structures of the synthesized compounds were established on the basis of spectral data and they were screened for their antimicrobial activity. Compound **18** showed maximum potency against all Gram-positive and Gram-negative bacterial strains with a minimum inhibitory concentration (MIC) value in the range of 7.81–62.50 μg/ml. Only compound **17** was found to be the most active against all fungal strains with a MIC value of 15.62 μg/ml. In this study, we performed molecular docking experiments to understand the interactions between compounds **17** and **18** and *E. coli* topoisomerase I, and we compared the results obtained with that of 2-(3,4-dimethoxyphenyl)-5-[5-(4-methylpiperazin−1-yl)-1H-benzimidazol-2-yl]-1H-benzimidazole (DMA). Compounds **17** and **18** demonstrated strong interactions with important active site residues, similar to DMA. As a result, the compounds obtained from this study can be used in designing new potent inhibitors of *E. coli* topoisomerase I.

KEYWORDS

antirobial, benzimidazole, MIC, molecular docking, naphthalene

1 | INTRODUCTION

Benzimidazoles and their derivatives have a wide range of applications in medicine,[1,2] and several methods have been developed for their synthesis. Condensation of *o*-phenylene-diamine and different acids in the presence of concentrated hydrochloric acid,[3] ammonium chloride as a catalyst,[4] microwave irradiation under solvent-free conditions which are catalyzed by alumina and silica gel,[5] addition of *o*-phenylenediamine to different aldehydes in the presence of a catalytic amount of indium triflate,[6] zinc triflate in ethanol solvent at reflux temperature,[7] sodium dodecyl sulfate[8] or nickel acetate,[9] and the reaction of *o*-phenylenediamines with acid anhydrides, urea, and esters[10] are some of the methods reported so far. However, the methodologies mentioned above have some disadvantages regarding their applicability for different benzimidazole derivatives. Therefore, comparative studies

of these methods are required. Thus, more effective benzimidazole synthesis methods should be developed for each substituted benzimidazole derivatives.

In addition, recent observations suggest that substituted benzimidazoles and their derivatives possess an extensive range of biological activities including antiviral, antifungal, antimicrobial, antiprotozoal, anti-inflammatory, anticancer, antioxidant, anticoagulant, antidiabetic, and antihypertensive activities.[11–19] It has been reported that benzimidazole derivatives with a functional group at the C-1, −2, and/or − 5/−6 positions show increased biological activity.[2] Recent developments regarding 2-substituted benzimidazoles have revealed that aromatics varied at the C-2 position give rise to potent antimicrobial agents that are effective against different bacteria and fungi.[20,21] Furthermore, 2-aromatic-substituted benzimidazoles with a functional group at the C-5 position are potent antimicrobial agents.[22–25]

Similarly, naphthalene derivatives also have a variety of biological activities.[26–28] Many studies have supported the antimicrobial effect of a naphthalene ring on bacterial and fungal strains.[29–31] In fact, several naphthalene-containing drugs such as nafcillin, naftifine, tolnaftate, and terbinafine are currently available to treat microbial infections (Figure 1). Naphthalene derivatives bearing a functional group, especially an -OH group, on α and β positions possess very good antimicrobial properties.[32,33]

It has recently reported that 2-(3,4-dimethoxyphenyl)-5-[5-(4methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-benzimidazole (DMA), a bisbenzimidazole, has no effect on cell viability in mammalian cells but efficiently inhibited *E. coli* topoisomerase I by enhancing DNA cleavage products. DMA has no significant inhibitory effect on human topoisomerase I, which suggests that DMA acts as a potential antibacterial agent, selectively targeting *E. coli* topoisomerase I enzyme.[34–36]

On the basis of aforesaid facts and in continuation of our research to develop the synthesis of benzimidazoles as potent, selective, and less toxic therapeutic agents[37,38], herein we report a facile and an effective methodology for the synthesis of a variety of benzimidazoles in the presence of polyphosphoric acid (PPA) as a catalyst under microwave irradiation or conventional conditions. In this study, we demonstrated a series of naphthyl-substituted benzimidazole derivatives with or without a methyl linker to investigate the role of the methyl linker to investigate the role of the methyl linker on antimicrobial activity. Second, we substituted the naphthalene moiety of the most active compounds with a hydroxyl group and substituted an R group (CH_3, Cl, and di-Cl) in the C-5/−6 position of the most active benzimidazole derivative for the evaluation of the most active compounds (Figure 2).

Also, we performed molecular docking experiments to exhibit strong interactions between compounds and *E. coli* topoisomerase I active site residues.

2 | RESULTS AND DISCUSSION

We carried out the best reaction methods, and we compared five different synthesis methods on the first group compounds (**11** and **12**) (Table 1). The use of microwave irradiation and conventional method with PPA simplified and improved organic reactions. The microwave irradiation method with PPA demonstrated high yield, clean reactions, and short reaction time (Table 2). Thereby all compounds were synthesized for comparison by using PPA by microwave irradiation and conventional methods.[39,40] The synthetic route of the compounds is shown in Scheme 1. The synthesized compounds were classified into three groups. The compounds in the first group (**11–14**) were synthesized by reacting 1,2-phenylenediamine (**1**) with 1/2-naphthoic acid (**5** and **7**) and 2-(naphthalen-1/2-yl)acetic acid (**6** and **8**), whereas those in the second set of compounds (**15** and **16**) were synthesized by reacting 1,2-phenylenediamine (**1**) with 1-hydroxy-2-naphthoic acid (**10**) and 2-hydroxy-1-naphthoic acid (**9**). Finally, the compounds in the third group (**17–19**) were synthesized by reacting 3,4-diaminotoluene (**2**), 4-chloro-o-phenylenediamine (**3**) and 4,5-dichloro-o-phenylenediamine (**4**) with 1-hydroxy-2-naphthoic acid (**10**) (Scheme 1).

2.1 | Antimicrobial activity

Minimum inhibitory concentration (MIC) values for all synthesized compounds revealed good to potent antibacterial activity against *Escherichia coli*,

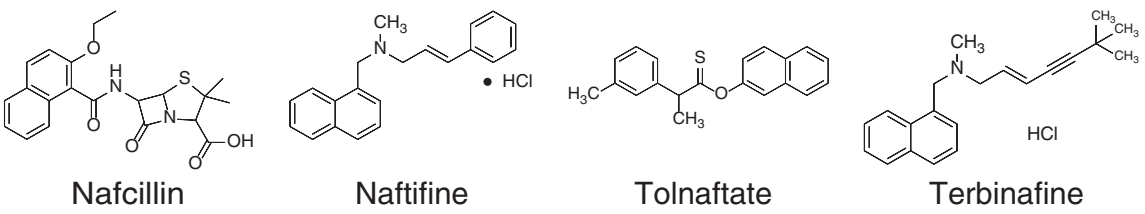


FIGURE 1 Structures of some naphthalene containing drugs

Pseudomonas aeruginosa, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Bacillus subtilis*, *Candida albicans*, and *Candida parapsilosis*.

In the first group, nonsubstituted naphthyl-benzimidazole derivatives (**11–14**) were screened for antimicrobial activity. The compounds without the methyl linker (**11** and **13**) demonstrated increased microbial growth inhibition compared to those with the methyl linker (**12** and **14**). In particular, compound **11** demonstrated good inhibitory activity against *Candida glabrata*, with a MIC value of 15.62 μg/ml, and compound **13** demonstrated good inhibitory activity against, *S. pneumoniae*, with a MIC value of 62.50 μg/ml (Table 3).

A plausible explanation could be the increased lipophilicity of these compounds compared with the standards, which should improve drug uptake via the lipid-mediated pathway. Therefore, the naphthalene moiety of the active compounds (**11** and **13**) was substituted on the α/β positions by an -OH group to generate second compounds (**15** and **16**). Compared to compound **15**, compound **16** showed increased growth inhibitory activity against *E. faecalis*, *S. aureus*, and *B. subtilis*, with a MIC value of 15.62 μg/ml (Table 4).

Third group of compounds (**17–19**) were designed to enhance antimicrobial activity by substituting the benzimidazole ring of the most active compound from the second group (**16**) on C-5/−6 positions. We found that chloro-substituted naphthyl-benzimidazole (**18**) demonstrated the most potent antibacterial activity against *S. AUREUS* and *P. AERUGINOSA*, with a MIC value of 7.81 μg/ml, which was four-fold more than the standard drug ampicillin (MIC 31.25 μg/ml). Additionally, compound **18** had a MIC value of 15.62 μg/ml against *E. coli*, *E. faecalis*, and *B. subtilis*. On the other hand, methyl-substituted naphthyl-benzimidazole (**17**) was the most active against all fungal strains, with a MIC value of 15.62 μg/ml. In addition, the activity decreased with dichloro-substituted naphthyl-benzimidazole (**19**), which had a log *p* value higher than monochloro-substituted compounds (Table 5)

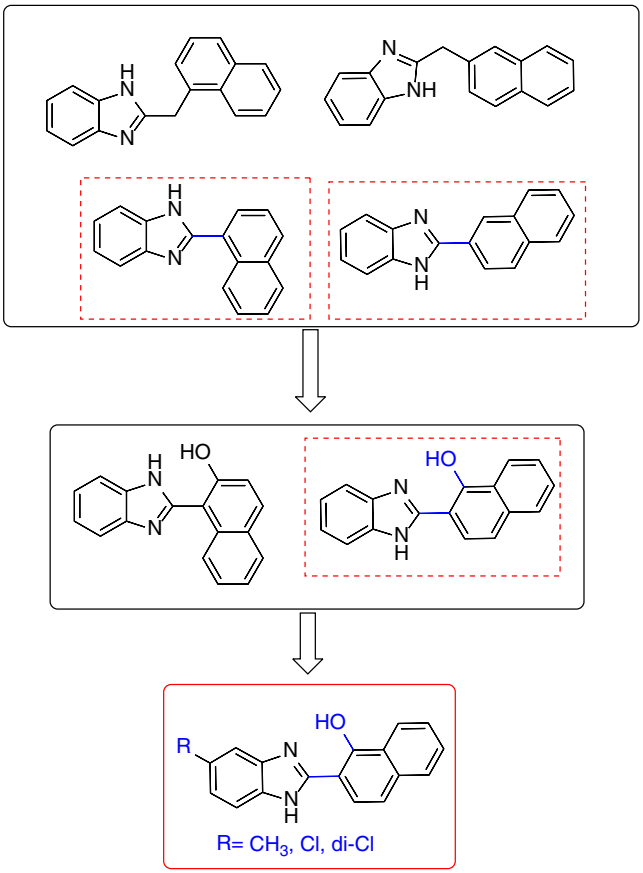


FIGURE 2 Synthetic strategy pathway

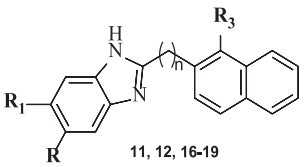
2.2 | Molecular docking studies

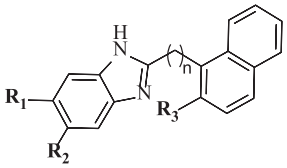
We conducted molecular docking experiments to understand the interactions between compounds **17** and **18** and

TABLE 1 Optimization of conventional method for the synthesis of compounds **11** and **12**

Compound no	Catalyst/mol%	Solvent	Temperature (°C)	Time	Yield (%)	Ref.
11	—	HCl	Reflux	48	8	[3]
	—	PPA	180–200	18	30	[39]
	—	**PPA**	**120**	**18**	**65**	
	—	Ethylene glycol	Reflux	42	15	[57]
	$B(oh)_3$	Toluene	Reflux	50	14	[58]
12	—	HCl	Reflux	49	6	[3]
	—	PPA	180–200	20	35	[39]
	—	**PPA**	**120**	**20**	**69**	
	—-	Ethylene glycol	Reflux	40	17	[57]
	$B(oh)_3$	Toluene	Reflux	50	19	[58]

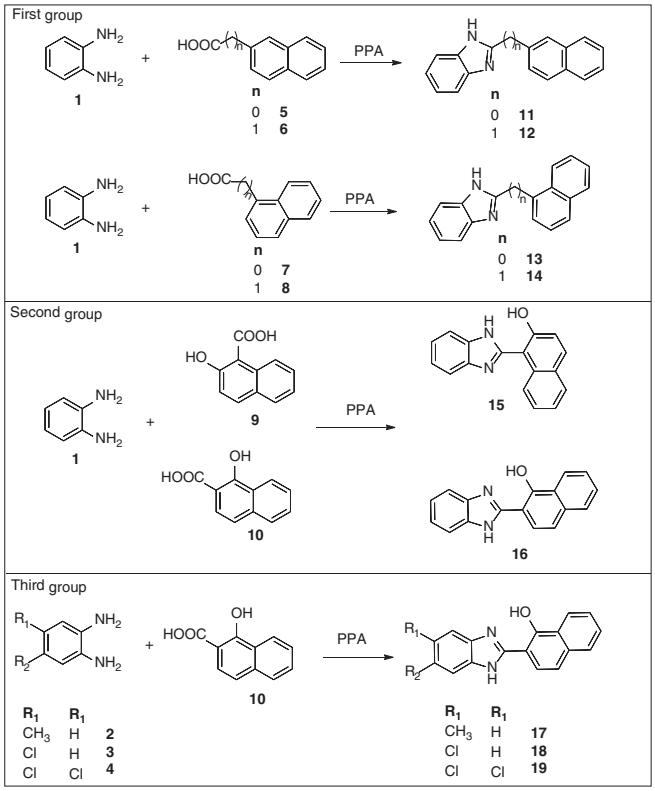
TABLE 2 Conventional method and effect of MWI in watts on the synthesis of compounds





					Microwave heating			Conventional heating PPA		
Compound no	**R^1**	**R^2**	**n**	**R^3**	**Time (min)**	**Power (watt)**	**Yield (%)**	**Temp. (°C)**	**Time (h)**	**Yield (%)**
11	H	H	0	H	12	100–150	65	120	18	45
12	H	H	1	H	10	100–150	81	120	16	57
13	H	H	0	H	10	100–150	83	120	20	59
14	H	H	1	H	12	100–150	90	120	17	65
15	H	H	0	OH	8	100–150	85	120	21	59
16	H	H	0	OH	10	100–150	82	120	21	55
17	CH_3	H	0	OH	10	100–150	90	120	20	62
18	Cl	H	0	OH	16	100–150	80	120	22	52
19	Cl	Cl	0	OH	14	100–150	83	120	22	58

E. coli topoisomerase 1, and we compared the obtained results with that of DMA, which is a known inhibitor of *E. coli* topoisomerase 1. Compounds **17** and **18** showed strong interactions with the important active site residues, similar to DMA. Compound **17** formed H-bonds with Arg114, Glu547, and Asp551 and salt bridges with Glu547 and Asp551 (Figure 3c), whereas compound **18** formed H-bonds with Asp323 and salt bridges with Asp113 and Asp323 (Figure 3d). DMA formed H-bonds with Arg493, Glu547, and Asp551 and salt bridges with Asp113, Asp323, Glu547, and Asp551. The results from the docking experiments and the interactions of the tested compounds are shown in Table 6 and Figure 3.



SCHEME 1 Synthesis of benzimidazoles with naphthalene moiety compounds (**11–19**)

3 | EXPERIMENTAL

The reagents and solvents used were obtained from Sigma–Aldrich chemicals. Reagents and solvents are used directly without further purification. Reaction progress and product mixtures were monitored by thin layer chromatography (TLC) using E-Merck 0.25 silica gel plates. Colorless products were detected by UV light (254 nm). Melting points were determined by using one end open capillary tube on an uncorrected Analab melting point apparatus. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance 400 spectrometers, operated at 400 MHz for 1H and 100 MHz for 13C nuclei, relative to TMS as the internal standard on the δ (ppm) scale with deuterated dimethylsulfoxide (DMSO-d_6) and chloroform ($CDCl_3$) as the solvents. The IR spectra were obtained on a Perkin Elmer Spectrum One FT-IR spectrometer. The spectra of all of the investigated compounds are provided as Supporting Information.

TABLE 3 MICs of first group compounds **11–14** against the selected microbial strains

No	cLog P[a]	MIC (mg/ml)							
		E. coli	*P. aeuroginosa*	*E. facealis*	*S. aureus*	*S. pneumoniae*	*B. subtilis*	*C. albicans*	*C. glabrata*
11	4,837	125,00	125,00	125,00	250,00	250,00	125,00	31,25	**15,62**
12	4,806	250,00	250,00	250,00	250,00	250,00	250,00	125,00	125,00
13	4,837	125,00	125,00	62,50	62,50	**62,50**	62,50	125,00	62,50
14	4,576	125,00	125,00	125,00	250,00	250,00	125,00	125,00	62,50
Ampicillin	-1,2045	32,25	32,25	*	*	*	*	—	—
Fluconazole	−0,44	—	—	—	—	—	—	*	*

[a]cLogP value of the synthesized compounds (calculated from ChemBioDrawUltra 12.0.3).

TABLE 4 MICs of second group compounds **15**, **16** against the selected microbial strains

No	cLog P[a]	MIC (mg/ml)							
		E. coli	*P. aeuroginosa*	*E. facealis*	*S. aureus*	*S. pneumoniae*	*B. subtilis*	*C. albicans*	*C. glabrata*
15	4,060	250,00	250,00	250,00	125,00	125,00	125,00	125,00	62,50
16	4,060	125,00	125,00	**15,62**	15,62	**62,50**	**15,62**	62,50	62,50
Ampicillin	−1,2045	32,25	32,25	*	*	*	*	—	—
Fluconazole	−0,44	—	—	—	—	—	—	*	*

[a]*cLogP* value of the synthesized compounds (calculated from ChemBioDrawUltra 12.0.3).

TABLE 5 MICs of third group compounds **17–19** against the selected microbial strains

No	cLog P[a]	MIC (mg/ml)							
		E. coli	*P. aeuroginosa*	*E. facealis*	*S. aureus*	*S. pneumoniae*	*B. subtilis*	*C. albicans*	*C. glabrata*
17	4,560	**15,62**	15,62	31,25	**7,81**	**62,50**	**15,62**	**15,62**	**15,62**
18	4,851	**15,62**	**7,81**	**15,62**	**7,81**	**62,50**	**15,62**	62,50	62,50
19	5,471	62,50	62,50	31,25	31,25	125,00	31,25	62,50	62,50
Ampicillin	−1,2045	32,25	32,25	*	*	*	*	—	—
Fluconazole	−0,44	—	—	—	—	—	—	*	*

[a]*cLogP* value of the synthesized compounds (calculated from ChemBioDrawUltra 12.0.3).

3.1 | General procedure for the synthesis of 2-naphthelen substituted benzimidazole derivatives (11–19)

3.1.1 | Conventional heating method

o-Phenylenediamine derivatives (**1–4**) (1 eq) and corresponding naphthalene carboxylic acid derivatives (5–10) (1.1 eq) in PPA (5 ml) were placed in a 25 ml flask. The reaction mixture was heated at 180°C for 13–15 hr. After the reaction was monitored by TLC, the mixture was poured into ice water and neutralized by 5 M NaOH until it reached a slightly basic pH (8–9) to obtain a precipitate. The resulting precipitate was filtered off, washed with cold water, and recrystallized with a suitable solvent (H_2O, EtOH, EtOH-H_2O). The resulting crystalline compounds were filtered, and the vacuumed product was dried.

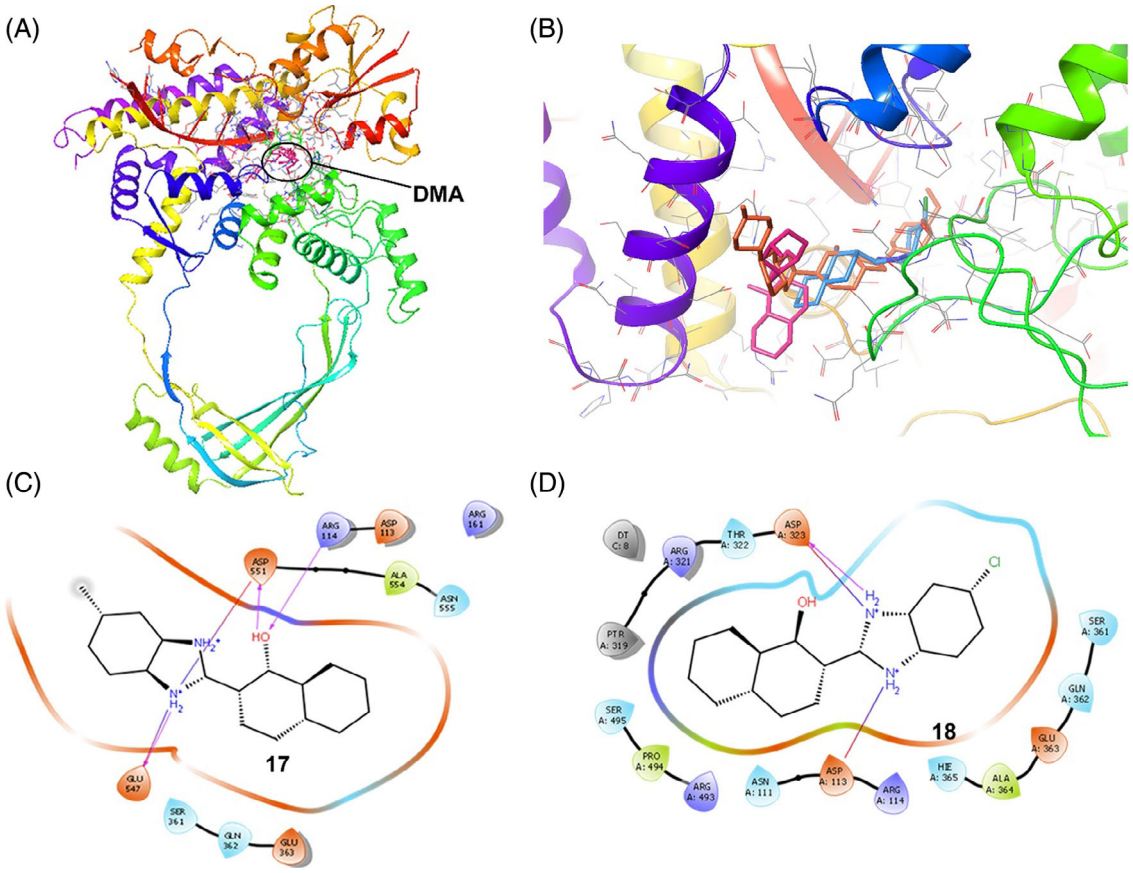


FIGURE 3 (a) Crystal structure of *E. coli* Topoisomerase I enzyme (PDB ID: 3PX7). (b) Superposition of DMA (orange), compound 17 (pink) and compound 18 (blue). (c) Docked position of compound 17: revealed H-bonds with Arg114, Glu547, Asp551; salt bridges with Glu547 and Asp551. (d) Docked position of compound 18: revealed H-bond with Asp323 and salt bridges with Asp113 and Asp323. *H-bond (green arrow), Salt-bridge (red-blue arrow), negative charge (orange), positive charge (purple), Hydrophobic (green), Polar interactions (turquoise)

TABLE 6 Docking results of the tested compounds

No	Docking score	Glide score	Interactions
17	−7.243	−7.243	Asp113[a], **Arg114**[b], Arg161, Ser361[b,e], Gln362[e], Glu363[a], Ala554[d], **Glu547**[a,c], **Asp551**[a,c], Asn555[e]
18	−7.158	−7.158	Asn111[e], Asp113[a,c], Arg114[b], Ptr319, Arg321[b], Thr322[e], **Asp323**[a,c], Ser361[e], Gln362[e], Glu363[a], Ala364[d], Hie365[e], Arg493[b], Pro494[d], Ser495[e], DT8
DMA	−10.640	−10.797	Asn111[e], Asp113[a,c], Arg114[b], Glu115[a], Ptr319, Arg321[b], Thr322[e], Asp323[a,c], Ser361[e], Gln362[e], Glu363[a], Ala364[d], Hie365[e], **Arg493**[b], Pro494[d], Ser495[e], Ala544[a], **Glu547**[a,c], **Asp551**[a,c], DT8

Note: **Bold:** H-bond, a: negative charge, b: positive charge, c: Salt-bridge, d: Hydrophobic, e: Polar interactions.

3.1.2 | Microwave irradiation method

In the presence of PPA, the mixture of o-phenylenediamine derivatives (**1–4**) (1 eq) and corresponding naphthalene carboxylic acid derivatives (**5–10**) (1.1 eq) was stirred and irradiated in MW (7–12 min, 100–150 W). After monitoring of the reaction with TLC, the mixture was poured into ice water and neutralized with 5 M NaOH until it reached a slightly basic pH (8–9) to obtain the precipitate. The resulting precipitate was filtered off, washed with cold water, and recrystallized with a suitable solvent (H_2O, EtOH, EtOH-H_2O). The resulting crystalline compounds were filtered, and the vacuumed product was dried.

3.1.3 | 2-(Naphthalen-2-yl)-1H-benzo[d] imidazole (11)

m.p.: 188–191°C; IR (KBr, cm^{-1}) 3,268 (aromatic = C-H), 1,733 (C=N), 1,510–1,419 (aromatic C=C); ^{1}H NMR (400 MHz, d6-DMSO): δ 13.12 (s, 1H, -NH), 8.76 (bs, 1H, Ar-H), 8.34 (dd, J = 1.62, 8.76 Hz, 1H, Ar-H), 8.09 (d, J = 8.76 Hz, 1H, Ar-H), 8.08–7.98 (m, 2H, Ar-H), 7.70 (bs, 1H, Ar-H), 7.63–7.58 (m, 3H, Ar-H), 7.25–7.24 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, d6-DMSO):δ 151.2, 133.4, 132.8, 128.5, 128.4, 128.0,127.7, 127.1, 126.9, 125.8, 123.9. Anal. calcd for C17H12N2: C, 83.58; H, 4.95; N, 11.47; Found: C, 83.47; H, 4.77; N, 11.38.[41,42]

3.1.4 | 2-(naphthalen-2-ylmethyl)-1H-benzo[d]imidazole (12)

m.p.: 196–199°C; IR (KBr, cm^{-1}) 3,049 (aromatic = C-H), 1,576(C=N), 1,567(aromatic C = C); ^{1}H NMR (400 MHz, d6-DMSO): δ 7.97–7.84 (m, 5H, Ar-H), 7.80 (bs, 1H, Ar-H), 7.59–7.42 (m, 5H, Ar-H), 3.72 (s, 2H, CH2); ^{13}C NMR (100 MHz, d6-DMSO):δ 155.6, 152.4, 134.7, 128.0, 127.6, 125.8, 124.7, 122.8, 122.3, 118.5, 105.4. Anal. calcd for C18H14N2: C, 83.69; H, 5.46; N, 10.84; Found: C, 83.75; H, 5.33; N, 10.71.[43,44]

3.1.5 | 2-(naphthalen-1-yl)-1H-benzo[d] imidazole (13)

m.p.: 186–189°C; IR (KBr, cm^{-1}) 3,045 (aromatic = C-H), 1,532 (C=N), 1,488 (aromatic C=C); ^{1}H NMR (400 MHz, CDCl3): δ 8.93 (d, J = 8.51 Hz, 1H, Ar-H), 8.20 (d, J = 8.15 Hz, 1H, Ar-H), 8.00–7.92 (m, 4H, Ar-H), 7.64–7.43 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, CDCl3):δ 151.4, 143.9, 133.6, 130.5, 130.1, 128.4, 127.0, 126.3, 125.2, 122.6, 121.6, 111.3. Anal. calcd for C17H12N2: C, 83.58; H, 4.95; N, 11.47; Found: C, 83.63; H, 4.83; N, 11.55.[45,46]

3.1.6 | 2-(naphthalen-1-ylmethyl)-1H-benzo[d]imidazole (14)

m.p.: 210–213°C; IR (KBr, cm^{-1}) 3,087 (aromatic = C-H), 2,900 (aliphatic –C-H), 1,541 (C=N), 1,493 (aromatic C=C); ^{1}H NMR (400 MHz, CDCl3): 8.11–8.01 (m, 2H, Ar-H), 7.89–7.69 (m, 3H, Ar-H), 7.56–7.42 (m, 5H, Ar-H), 7.32–7.25 (m, 1H, Ar-H), 4.90 (bs, 2H, -CH2); ^{13}C NMR (100 MHz, CDCl3): δ 137.0, 133.3, 132.6, 127.9, 126.9, 125.5, 125.4, 125.3, 125.0, 44.3. Anal. calcd for C18H14N2: C, 83.69; H, 5.46; N, 10.84; Found: C, 83.58; H, 5.49; N, 10.77.[47,48]

3.1.7 | 1-(1H-benzo[d]imidazol-2-yl) naphthalen-2-ol (15)

m.p.: 186–189°C; IR (KBR, cm^{-1}) 3,045 (aromatic = C-H), 1,532 (C=N), 1,488 (aromatic C=C); ^{1}H NMR (400 MHZ, CDCL3): δ 8.93 (d, J = 8.51 Hz, 1H, AR-H), 8.20 (d, J = 8.15 Hz, 1H, AR-H), 8.00–7.92 (m, 4H, AR-H), 7.64–7.43 (m, 5H, AR-H); ^{13}C NMR (100 MHZ, CDCL3): δ 151.4, 143.9, 133.6, 130.5, 130.1, 128.4, 127.0, 126.3, 125.2, 122.6, 121.6, 111.3. Anal. calcd for C17H12N2O: C, 78.44; H, 4.65; N, 10.76; Found: C, 78.29; H, 4.77; N, 10.59.[49,50]

3.1.8 | 2-(1H-benzo[d]imidazol-2-yl) naphthalen-1-ol (16)

m.p.: 198–201°C; IR (KBr, cm^{-1}) 3,057 (aromatic = C-H), 1,657 (C=N), 1,584 (aromatic C=C); ^{1}H NMR (400 MHz, d6-DMSO): δ 8.37–8.35 (m, 1H, Ar-H), 8.12–8.10 (m, 1H, Ar-H), 7.92–7.90 (m, 1H, Ar-H), 7.71 (bs, 2H, Ar-H), 7.63–7.53 (m, 3H, Ar-H), 7.33–7.29 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, d6-DMSO):δ 133.0, 131.6, 128.3, 127.4, 127.3, 127.1, 125.8, 125.2, 121.1, 14.6. Anal. calcd for C17H12N2O: C, 78.44; H, 4.65; N, 10.76; Found: C, 78.39; H, 4.61; N, 10.65.[51,52]

3.1.9 | 2-(5-METHYL-1H-benzo[d] imidazol-2-yl)naphthalen-1-ol (17)

m.p.: 202–205°C; IR (KBr, cm^{-1}) 3,057 (aromatic = C-H), 2,853 (aliphatic–C-H), 1,657 (aromatic C=C); ^{1}H NMR (400 MHz, d6-DMSO): δ 14.64 (s, 1H, -OH), 13.22 (s, 1H, -NH), 8.40–8.88 (m, 4H, Ar-H), 7.68–7.40 (m, 4H, Ar-H), 7.15 (d, J = 7.15 Hz, 1H, Ar-H), 2.49 (s, 3H, -CH3); ^{13}C NMR (100 MHz, d6-DMSO):δ 155.5, 135.9, 134.6, 129.9, 128.3,

127.8, 127.7, 127.6, 125.7, 124.8, 124.7, 123.7, 122.8, 122.3, 120.6, 118.4, 105.5,21.3. Anal. calcd for C18H14N2O: C, 78.81; H, 5.14; N, 10.21; Found: C, 78.73; H, 5.25; N, 10.33.

3.1.10 | 2-(5-chloro-1H-benzo[d]imidazol-2-yl)naphthalen-1-ol (18)

m.p.: 194–197°C; IR (KBr, cm^{-1}) 3,050 (aromatic = C-H), 1,515 (aromatic C=C); ^{1}H NMR (400 MHz, d6-DMSO): δ 8.44–8.08 (m, 2H, Ar-H), 8.06–7.49 (m, 6H, Ar-H), 7.34 (d, J = 1.92 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, d6-DMSO): δ 155.7, 153.7, 134.9, 128.2, 127.6, 125.9, 124.7, 123.1, 122.9, 122.3, 118.7, 105.1. Anal. calcd for C17H11ClN2O: C, 69.28; H, 3.76; N, 9.50; Found: C, 69.14; H, 3.88; N, 9.41.

3.1.11 | 2-(5,6-dichloro-1H-benzo[d] imidazol-2-yl)naphthalen-1-ol (19)

m.p.: 207–210°C; IR (KBr, cm^{-1}) 3,057 (aromatic = C-H), 1,657 (C=N), 1,520 (aromatic C=C); ^{1}H NMR (400 MHz, d6-DMSO): δ 8.87–8.24 (m, 2H, Ar-H), 8.15–7.92 (m, 3H, Ar-H), 7.85–7.48 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, d6-DMSO): δ 155.8, 154.9, 134.9, 128.21, 127.8, 127.8, 125.9, 125.0, 124.6, 122.9, 122.5, 118.7, 105.0. Anal. calcd for C17H10Cl2N2O: C, 62.03; H, 3.06; N, 8.51; Found: C, 61.95; H, 3.17; N, 8.44.

3.2 | Antimicrobial assay

Antimicrobial susceptibility testing was performed by a modification of literature methods.[53,54] We used the microbial strains *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 25853), *Enterococcus faecalis* (ATTC 29212), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pneumoniae* (ATCC 10353), *Bacillus subtilis* ATCC 6633, *Candida albicans* (ATCC 4322), and *Candida parapsilosis* (ATTC 22019).

The fungal and bacterial cell inoculum were prepared from a stock culture grown in tryptic soy agar at 28°C for 24 hr, and Mueller–Hinton agar (MHA) at 37°C for 24 hr, respectively. The concentrations of microorganism suspension were adjusted according to MCFARLAND 0.5 turbidity tubes using sterilized saline. Stock solutions of the title compounds were prepared in DMSO at 1000 μg/ml. A modified microdilution test was applied for antimicrobial activity, and the experiments were run in duplicate independently

For antifungal activity testing, 100 μl Tryptic Soy Broth was added to each of the 11 wells. A 100 μl aliquot of the tested chemical solution was added to the first well, and two-fold dilutions were prepared. Then, 5 μl of fungal suspension was added to each tube except the last one, which acted as the control well. For antibacterial activity testing, 100 μl Mueller–Hinton broth (MHB) was added to each of the 11 wells. A 100 μl aliquot of the chemical derivative solution was added to the first tube, and two-fold dilutions were prepared. Then, 5 μl of the bacterial suspension was added to each tube, except the last control well. A control tube containing 5 μl of the fungal and bacterial suspensions alone without the tested compounds was also prepared. All plates were incubated at 28°C (for fungi) and at 37°C (for bacteria) for 24 hr. After incubation, the MICs (Tables 3–5) were obtained by noting the growth inhibition. The concentration resulting in a 50% reduction in the optical density (OD) values was compared to a replicate plate control at 450 nm by spectrophotometric evaluation and defined as the MIC value. Fluconazole and ampicillin were used as reference drugs. The results were read visually and by measuring OD for 24 hr.

3.3 | Molecular docking methodology

Molecular docking studies were performed by using Schrödinger molecular modeling software.[55] Ligands were prepared by using the LigPrep module and the 2D structures of the ligands converted to the full 3D structure by assigning the OPLS-2005 force field. LigPrep can generate the expected ionized forms at significant concentrations corresponding to the pH 7.0 ± 3.0, generate variations, perform verification, and optimize structures. It generates a maximum of 32 stereochemical structures per ligand. Binding of ligands to the receptors adopts more than one conformation, and the lowest energy conformer is important for docking studies. The crystal structure of the *E. coli* topoisomerase I enzyme was extracted from the Protein Data Bank (PDB ID: 3PX7)[56] (Figure 3a). Prior to docking the ligands onto the protein's active site, the protein was prepared using the protein preparation wizard in the Schrödinger software. During protein preparation all hetero atoms and water molecules were removed. Hydrogen atoms were added, and the active site of the protein was defined to generate the grid. The grid box was limited to a size of 20 Å at the active site. Finally, docking studies were carried out using the Grid-based Ligand Docking with Energetics module of the Schrödinger Software, the ligands were docked into the prepared grid by using "Extra precision mode", and no constraints were defined. To determine the spatial fit into the active site of the receptor, favorable ligand poses were generated, and the best-fit conformations of the ligands were evaluated and minimized to generate glide scores. To predict the binding affinities and best

alignment of the compounds at the active site of the enzyme, hydrogen bonds and other interactions formed with the surrounding amino acids and glide scores were used. All the results are shown in Table 6.

4 | CONCLUSIONS

Investigation of the structure–activity relationships of a series of 2-naphthyl-substituted benzimidazole derivatives (**11–19**) were designed and synthesized by microwave irradiation and conventional method. These compounds showed good to potent in vitro antibacterial activity and moderate antifungal activity. Substitution at the benzimidazole moiety by scrutinizing of the point of incorporation of methyl, one chlorine, and two chlorine atoms at the fifth and sixth positions of benzimidazole, mono chloro-substituted compound **18** showed 8- and 16-fold increased activity against *E. coli* and *P. aeuroginosa*, respectively, compared to unsubstituted compound **16**.

In conclusion, we have demonstrated that mono chloro substitution of the benzimidazole moiety at the C-5 position and the presence of an -OH group on the C-1 position of the naphthalene moiety are crucial elements of antimicrobial activity. Studies suggest that DMA is a selective *E. coli* topoisomerase I inhibitor and acts as a potential antibacterial agent. Therefore, we assessed the most active compounds against *E. coli* (**17** and **18**) using molecular modeling studies. According to the docking results, compound **18** and, especially, compound **17** showed strong interactions with important active site residues, similar to DMA. Therefore, the compounds generated in this study can be useful in designing new potent inhibitors of *E. coli* topoisomerase I, as lead compounds.

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REFERENCES

[1] A. A. Spasov, I. N. Yozhitsa, L. I. Bugaeva, V. A. Anisimova, *Pharm. Chem. J.* **1999**, *33*, 232.
[2] Y. Bansal, O. Silakari, *Bioorg. Med. Chem.* **2012**, *20*, 6208.
[3] M. A. Phillips, *J. Chem. Soc.* **1928**, *0*, 2393.
[4] S. R. Rithe, R. S. Jagtap, S. S. Ubarhande, *Rasayan J. Chem.* **2015**, *8*, 213.
[5] A. Saberi, *Iran. J. Sci. Technol.* **2015**, *39*, 7.
[6] R. Trivedi, S. K. De, R. A. Gibbs, *J. Mol. Catal. A-Chem.* **2006**, *245*, 8.
[7] R. Srinivasulu, K. R. Kumar, P. V. V. Satyanarayana, *Green Sustain. Chem.* **2014**, *4*, 33.
[8] S. D. Pardeshi, S. N. Thore, *Int. J. Chem. Phys. Sci.* **2015**, *4*, 300.
[9] D. P. Vishvanath, P. P. Ketan, *Int. J. Chem. Tech. Res.* **2014**, *8*, 457.
[10] C. P. Rathod, R. M. Rajurkar, S. S. Thonte, *Indo. Am. J. Pharm. Res.* **2013**, *3*, 2323.
[11] K. C. Achar, K. M. Hosamani, H. R. Seetharamareddy, *Eur. J. Med. Chem.* **2010**, *45*, 2048.
[12] J. Bauer, S. Kinast, A. Burger-Kentischer, D. Finkelmeier, G. Kleymann, W. A. Rayyan, K. Schroppel, A. Singh, G. Jung, K. H. Wiesmuller, S. Rupp, *J. Med. Chem.* **2011**, *54*, 6993.
[13] H. B. El-Nassan, *Eur. J. Med. Chem.* **2012**, *53*, 22.
[14] B. Garudachari, M. N. Satyanarayana, B. Thippeswamy, C. K. Shivakumar, K. N. Shivananda, G. Hegde, A. M. Isloor, *Eur. J. Med. Chem.* **2012**, *54*, 900.
[15] Y. F. Li, G. F. Wang, P. L. He, W. G. Huang, F. H. Zhu, H. Y. Gao, W. Tang, Y. Luo, C. L. Feng, L. P. Shi, Y. D. Ren, W. Lu, J. P. Zuo, Y. D. Ren, *J. Med. Chem.* **2006**, *9*, 4790.
[16] A. T. Mavrova, D. Vuchev, K. Anichina, N. Vassilev, *Eur. J. Med. Chem.* **2010**, *45*, 5856.
[17] C. S. Mizuno, A. G. Chittiboyina, F. H. Shah, A. Patny, T. W. Kurtz, H. A. Pershadsingh, M. A. Avery, *J. Med. Chem.* **2010**, *53*, 1076.
[18] C. G. Neochoritis, T. Zarganes-Tzitzikas, C. A. Tsoleridis, J. Stephanidou-Stephanatou, C. A. Kontogiorgis, D. J. Hadjipavlou-Litina, T. Choli-Papadopoulou, *Eur. J. Med. Chem.* **2011**, *46*, 297.
[19] R. V. Patel, P. K. Patel, P. Kumari, D. P. Rajani, K. H. Chikhalia, *Eur. J. Med. Chem.* **2012**, *53*, 41.
[20] H. Goker, M. Alp, S. Yildiz, *Molecules* **2005**, *10*, 1377.
[21] S. Tahlan, S. Kumar, B. Narasimhan, *BMC Chem.* **2019**, *13*, 18.
[22] F. Gumus, I. Pamuk, T. Ozden, S. Yildiz, N. Diril, E. Oksuzoglu, S. Gur, A. Ozkul, *J. Inorg. Biochem.* **2003**, *94*, 255.
[23] S. Ozden, A. Dilek, S. Yildiz, H. Goker, *Bioorg. Med. Chem.* **2005**, *13*, 1587.
[24] V. S. Padalkar, B. N. Borse, V. D. Gupta, K. R. Phatangare, V. S. Patil, P. G. Umape, N. Sekar, *Arab. J. Chem.* **2016**, *9*, S1125.
[25] M. Tuncbilek, T. Kiper, N. Altanlar, *Eur. J. Med. Chem.* **2009**, *44*, 1024.
[26] S. Sharma, T. Singh, R. Mittal, K. K. Saxena, V. K. Srivastava, A. Kumar, *Archiv. Pharm.* **2006**, *339*, 145.
[27] G. Sahin, E. Palaska, M. Ekizoglu, M. Ozalp, *Il Farmaco* **2002**, *57*, 539.
[28] Y. Dong, Q. Shi, Y. N. Liu, X. Wang, K. F. Bastow, K. H. Lee, *J. Med. Chem.* **2009**, *52*, 3586.
[29] Z. Ates-Alagöz, M. Alp, C. Kus, S. Yildiz, E. Buyukbingöl, H. Göker, *Archiv. Pharm.* **2006**, *339*, 74.
[30] V. Mkpenie, G. Ebong, I. B. Obot, *J. Chem.* **2008**, *5*, 431.
[31] S. Göksu, M. T. Uguz, H. Ozdemir, H. Seçen, *Turk J Chem.* **2005**, *29*, 199.
[32] A. Y. Shen, M. H. Hwang, S. Roffler, C. F. Chen, *Archiv. Pharm.* **1995**, *328*, 197.
[33] H. Kaur, J. Singh, B. Narasimhan, *BMC Chem.* **2019**, *13*, 49.
[34] U. Tawar, S. Bansal, S. Shrimal, M. Singh, V. Tandon, *Mol. Cell Biochem.* **2007**, *305*, 221.
[35] M. Singh, V. Tandon, *Eur. J. Med. Chem.* **2011**, *46*, 659.
[36] S. Bansal, D. Sinha, M. Singh, B. Cheng, Y. C. Tse-Dinh, V. J. Tandon, *Antimicrob. Chemother.* **2012**, *67*, 2882.

[37] M. Shaharyar, A. Mazumder, *Arab. J. Chem.* **2017**, *10*, S157.
[38] P. J. Preethi, E. Karthikeyan, M. Lohita, P. G. Teja, M. Subhash, P. Shaheena, N. K. Sai, *AJP Tech.* **2015**, *5*, 138.
[39] M. Karthik, P. Suresh, *New J. Chem.* **2018**, *42*, 17931.
[40] K. Bahrami, M. Bakhtiarian, *ChemistrySelect* **2018**, *3*, 10875.
[41] J. Charton, S. Girault-Mizzi, M. A. Debreu-Fontaine, F. Foufelle, I. Hainault, J. G. Bizot-Espiard, D. H. Caignard, C. Sergheraert, *Bioorg. Med. Chem.* **2006**, *14*, 4490.
[42] M. R. Grimmett, *Sci. Syn.* **2002**, *12*, 529.
[43] A. Mazumder, M. Shaharyar, *Med. Chem. Res.* **2015**, *24*, 2514.
[44] C. Mukhopadhyay, S. Ghosh, S. Sengupta, S. De, *RSC Adv.* **2011**, *1*, 1033.
[45] H. Naeimi, Z. Babaei, *Polycycl. Aromat. Comp.* **2016**, *36*, 490.
[46] H. Naeimi, Z. Babaei, *Green Chem. Lett. Rev.* **2017**, *10*, 129.
[47] S. Li, Z. M. Sheng, *Youji Huaxue* **1986**, *1*, 32.
[48] V. S. Belykh, G. A. Podobuev, *Voprosy Khimii Khimich. Tekhnol.* **1983**, *72*, 57.
[49] G. L. Woods, J. A. Washington, *Manual of clinical Microbiology*, 6th ed., Vol. 1327, American Society for Microbiology, Washington, DC **1995**.
[50] J. H. Jorgensen, M. J. Ferraro, *Clin. Infect. Dis.* **1998**, *26*, 973.
[51] Schrödinger LLC. New York: Schrodinger Inc.; **2008**. http://www.schrodinger.com
[52] Z. Zhang, B. Cheng, Y. C. Tse-Dinh, *PNAS* **2011**, *108*, 6939.
[53] F. Ayaz, R. Kheeree, Q. A. Isse, R. H. Ersan, O. Algul, *Turk. J. Chem.* **2019**, *43*, 963.
[54] Z. Z. Yan, Z. H. Xu, G. L. Dai, H. D. Liang, S. L. Zhao, *J. Coord. Chem.* **2010**, *63*, 1097.
[55] M. Perrone, E. Lo Presti, S. Dell'Acqua, E. Monzani, L. Santagostini, L. Casella, *Eur. J. Inorg. Chem.* **2015**, *2015*(21), 3493.
[56] N. Maraš, M. Kočevar, *Helv. Chim. Acta* **2011**, *94*, 1860.

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