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One-Pot Synthesis of Bis(4,5-diphenylimidazol-2-yl-phenyl)glycols and Evaluation of Their Antimicrobial Activity[1]

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Abstract—A new series of bis(4,5-diphenylimidazol-2-yl-phenyl)glycols were synthesized by reaction of bis-(formylphenyl)glycols with benzil/benzoin and ammonium acetate in presence of iodine/acetic acid in ethanol. All newly synthesized compounds were characterised by IR, ^{1}H, ^{13}C NMR, and MS data and tested for antimicrobial and antifungal activity.

Keywords: bis-aldehyde, bis-imidazole, ammonium acetate, antimicrobial activity

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INTRODUCTION

Importance of imidazole and its derivatives in pharmacology and organic synthesis is well documented [1–3]. Various substituted imidazoles possess anti-allergic, analgesic [4], antiparasitic [5], anti-epileptic [6], anti-inflammatory [7], anticancer [8,9], antimycobacterial, and antifungal activities [10]. Substituted imidazoles are core molecules in biological systems such as biotin, histamine and histidine. Bis-imidazoles act as desensitizing agents, protein analogues [11], and artificial multi-dentate ligands in binding metal ions [12].

RESULTS AND DISCUSSION

As a part of our ongoing study of synthesis of biodynamic heterocycles [13, 14] we synthesized new bis-imidazole derivatives from bis-benzaldehydes **IIIa–IIIo** (Scheme 1) and benzil in the presence of ammonium acetate and iodine in ethanol with high yields. The preliminary study of the reaction of benzil/benzoin under various catalytic conditions such as acetic acid and iodine in ethanol (Table 1) was carried out. The results revealed that the reaction of bis-benzaldehyde with benzil in presence of iodine in ethanol gave significantly improved yields of products compared to other conditions.

Based on the above data we have carried out synthesis of the title compounds by using iodine catalyst as presented in Scheme 2.

Antibacterial activity. All synthesized compounds were screened *in vitro* for their antibacterial activity against gram +ve bacterial strains *Staphylococcus aureus* (ATCC-9144), *Bacillus cereus* (ATCC-11778) and gram –ve bacterial strains *Escherichia coli* (ATCC-8739), *Proteus vulgaris* (ATCC-29213) by the cup-plate agar diffusion method at 25, 50, and 100 μg/mL concentrations. The zone of inhibition (in mm) was compared with the standard drug Ampicillin (Table 2). All newly synthesized compounds were active against the tested strains. Compounds **Vg, Vj, Vm,** and **Vo** were more potent or of same activity as the standard drug.

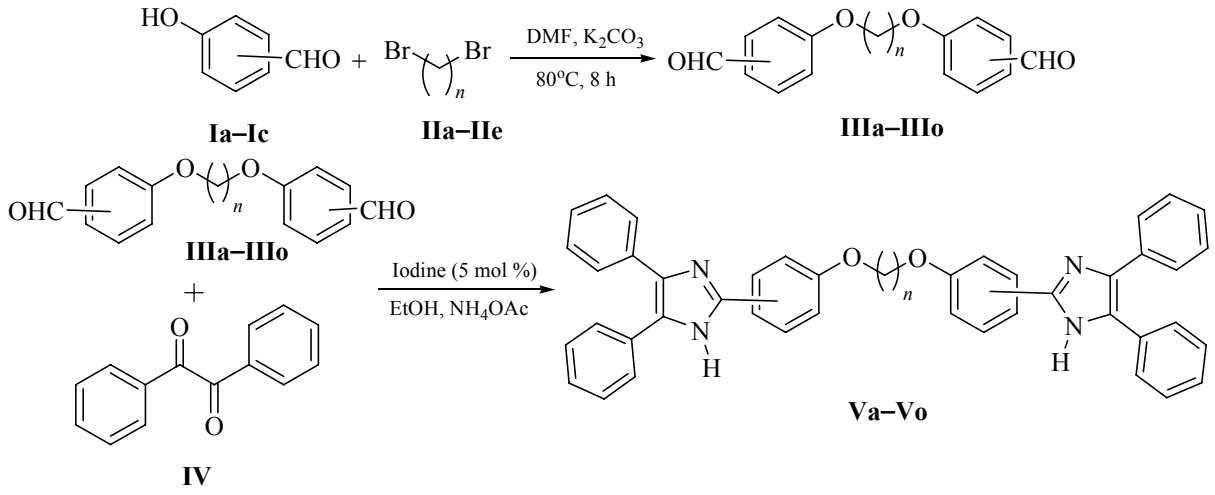
Antifungal activity. All synthesized compounds were screened *in vitro* for antifungal activity against *Aspergillus Niger* (ATCC-9029), *Candida albicans*

Table 1. Preliminary tests of mixtures substrate-catalyst

Product	Substrate	Catalyst	Time, min	Yield, %
Va	Benzil	AcOH	210	65–75
	Benzil	I_2	15	90–95
	Benzoin	AcOH	240	62–70
	Benzoin	I_2	20	80–85

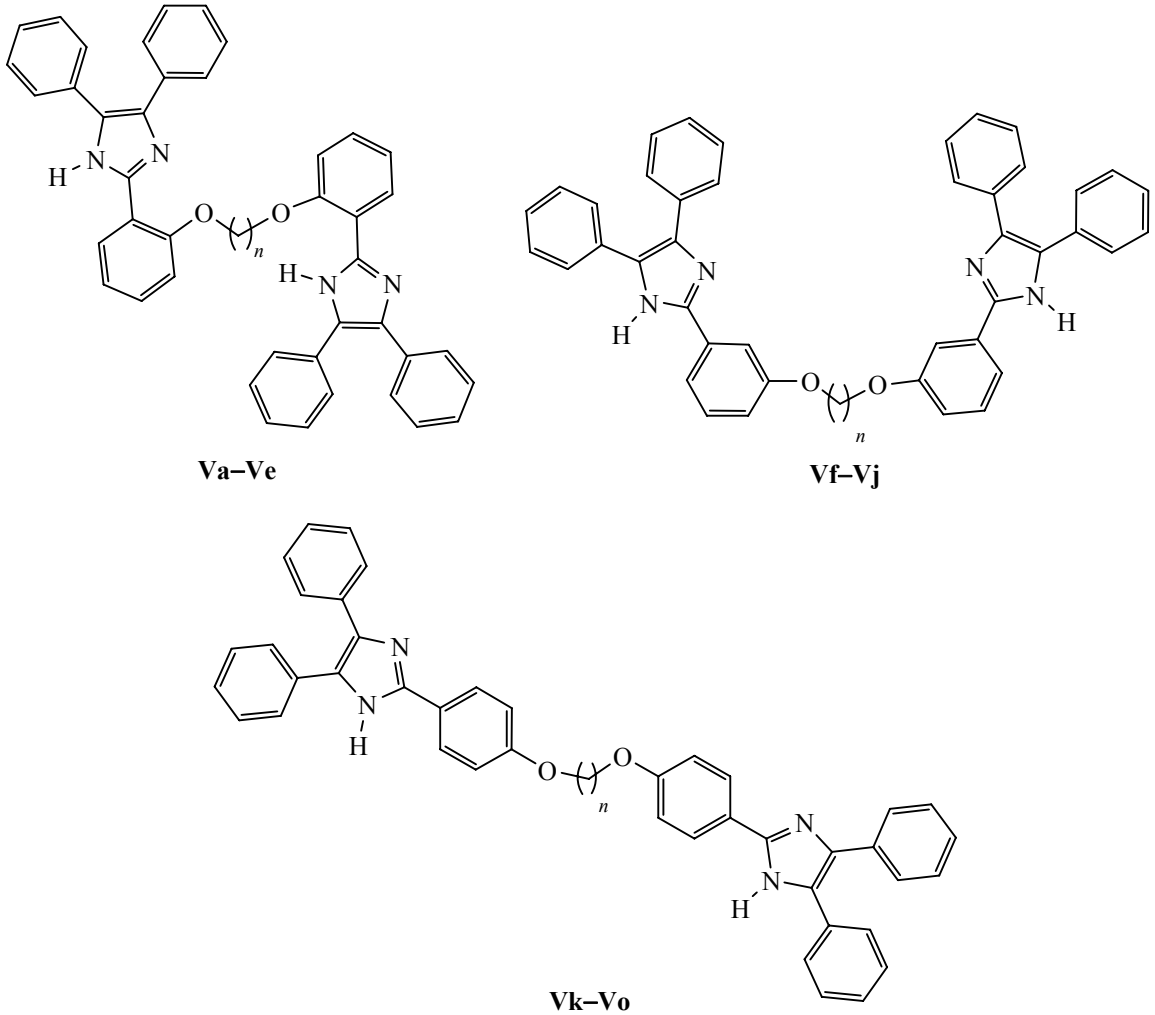
[1] The text was submitted by the authors in English.

Scheme 1.



n = 2–6.

Scheme 2.



n = 2–6.

Table 2. Antibacterial activity of compounds **Va–Vo**

Product	Zone of inhibition, mm											
	S. aureus (ATCC-9144)			*B. cereus* (ATCC-11778)			*E. coli* (ATCC-8739)			*P. vulgaris* (ATCC- 29213)		
	25	50	100	25	50	100	25	50	100	25	50	100
Va	9	10	11	5	7	8	10	12	14	9	10	11
Vb	8	9	11	4	5	7	11	14	16	8	9	11
Vc	10	11	12	3	5	6	6	6	7	10	11	12
Vd	10	10	13	6	7	7	11	13	15	10	10	13
Ve	8	10	11	4	6	7	9	10	12	8	10	11
Vf	8	11	12	4	6	8	9	9	10	8	11	12
Vg	10	13	15	6	7	8	8	10	10	10	13	15
Vh	10	10	12	5	6	8	11	12	13	10	10	12
Vi	10	12	14	4	5	5	10	11	12	10	12	14
Vj	11	13	16	6	7	8	12	13	15	11	13	16
Vk	11	12	14	5	7	9	8	10	10	11	12	14
Vl	10	11	13	4	6	8	7	8	10	10	11	13
Vm	10	12	15	6	7	9	10	12	14	10	12	15
Vn	9	10	12	4	5	7	10	14	16	9	10	12
Vo	9	12	15	5	7	9	11	13	16	9	12	15
Ampicillin	7	10	12	11	13	15	14	15	17	9	11	14

(ATCC-2091), *Aspergillus foetidus* (NCIM-0505), and *Candida rogosa* (ATCC-9849). The zone of inhibition (in mm) was compared with standard drugs Amphotericin-B and Clotrimazole (Table 3). The products demonstrated moderate to high activity against the tested fungal strains. Compounds **Vg, Vj, Vm,** and **Vo** were more potent than the standard drugs. Compounds **Vd** and **Vh** were inactive against *Candida albicans*.

EXPERIMENTAL

Melting points were determined in open glass capillary tube on a Gallen-Kamp MFB-595 apparatus. The IR spectra were recorded on a Perkin-Elmer FT-IR-8400s using samples in KBr disks. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Avance II 400 spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as the internal standard. Mass spectra were measured on SHIMADZU LCMS 2020 mass spectrometers. Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer.

Bis(4,5-diphenylimidazol-2-yl-phenyl)glycols (Va–Vo) *(general procedure)*. A mixture of benzil/benzoin (10 mmol), ammonium acetate (20 mmol), 2,3,4-[(2,3,4-formylphenoxy)alkoxy]benzaldehydes (5 mmol) and iodine (5 mol) in ethanol (2 mL) was refluxed for 15–20 min. Progress of the reaction was monitored by TLC (Silica gel, aluminium sheets 60 F_{254}, Merck). Upon completion of the process the reaction mixture was poured in water. The precipitated solid was filtered off, washed with water, dried and purified by column chromatography to yield title compounds **Va–Vo** (90–95 %) (Scheme 2).

Compound Va (*n* = 2). Yield 93%, mp 245–247°C. IR spectrum, ν, cm^{-1}: 1555 (C=N), 1660 (C=C), 3435 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.63 s (4H, 2OCH_2), 6.78–7.60 m (26H, Ar-H), 8.44 d.d (2H, Ar-H), 10.49 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 65.2, 112.4, 119.3, 120.3, 121.5, 122.6, 127.0, 127.9, 128.2, 128.8, 129.6, 144.6, 152.6. *M* 651 [*M* + H]$^+$. Found, %: C 81.12; H 5.16; N 8.52. $C_{44}H_{34}N_4O_2$. Calculated, %: C 81.21; H 5.27; N 8.61.

Compound Vb (*n* = 3). Yield 92%, mp 245–247°C. IR spectrum, ν, cm^{-1}: 1565 (C=N), 1672 (C=C), 3431 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20–1.25 m (2H, C–CH_2–C), 4.25 t (4H, 2OCH_2), 6.88 d.d (2H,

Table 3. Antifungal activity of compounds **Va–Vo**

Product	Zone of inhibition, mm											
	A. niger (ATCC-9021)			*A. foetidus* (NCIM-505)			*C. albicans* (ATCC-2091)			*C. rogosa* (ATCC-9849)		
	25	50	100	25	50	100	25	50	100	25	50	100
Va	5	7	8	7	8	9	4	6	7	7	8	9
Vb	4	5	7	6	7	9	5	8	9	6	7	9
Vc	3	5	6	4	6	8	5	5	7	4	6	8
Vd	6	7	7	7	8	9	–	–	–	7	8	9
Ve	4	6	7	6	7	8	5	6	8	6	7	8
Vf	4	6	8	5	6	7	3	5	7	5	6	7
Vg	6	7	8	8	9	10	7	9	10	8	9	10
Vh	5	6	8	7	8	8	–	–	–	7	8	8
Vi	4	5	5	4	5	6	4	5	6	4	5	6
Vj	6	7	8	8	9	10	8	9	11	8	9	10
Vk	5	7	9	6	7	8	6	7	8	6	7	8
Vl	4	6	8	7	8	8	3	4	6	7	8	8
Vm	6	7	9	8	9	10	5	8	8	8	9	10
Vn	4	5	7	8	9	10	4	5	5	8	9	10
Vo	5	7	9	9	9	10	8	10	11	9	9	10
Amphotericin B	8	10	13	9	10	11	8	10	12	6	8	9
Clotrimazole	9	11	13	11	12	14	9	10	11	7	8	10

Ar-H), 6.93–6.98 m (4H, Ar-H), 7.05–7.16 m (4H, Ar-H), 7.25–7.28 m (8H, Ar-H), 7.30–7.36 m (8H, Ar-H), 7.50 d.d (2H, Ar-H), 10.98 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.6, 68.2, 112.4, 114.3, 119.3, 120.4, 123.2, 124.8, 125.2, 126.9, 127.8, 128.6, 144.6, 154.6. *M* 665 $[M + H]^+$. Found, %: C 81.22; H 5.38; N 8.40. $C_{45}H_{36}N_4O_2$. Calculated, %: C 81.30; H 5.46; N 8.43.

Compound Vc (*n* = 4). Yield 90%, mp 240–241°C. IR spectrum, ν, cm^{-1}: 1545 (C=N), 1665 (C=C), 3432 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 t [4H, 2(C–CH_2–C)], 4.20 t (4H, 2OCH_2), 6.95 d.d (2H, Ar-H), 7.12–7.15 m (4H, Ar-H), 7.25–7.28 m (4H, Ar-H), 7.27–7.32 m (8H, Ar-H), 7.33–7.38 m (8H, Ar-H), 7.96 d.d (2H, Ar-H), 10.85 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 29.5, 67.3, 112.5, 114.4, 119.5, 120.8, 122.6, 126.2, 126.8, 127.9, 128.2, 129.5, 143.2, 154.5. *M* 679 $[M + H]^+$. Found, %: C 81.32; H 5.56; N 8.22. $C_{46}H_{38}N_4O_2$. Calculated, %: C 81.39; H 5.64; N 8.25.

Compound Vd (*n* = 5). Yield 91%, mp: 208–210°C. IR spectrum, ν, cm^{-1}: 1550 (C=N), 1662 (C=C), 3432 (N–H). ^{1}H NMR spectrum (DMSO), δ, ppm: 1.63–1.70 m (2H, C–CH_2–C), 1.89–1.99 m [4H, 2(C–CH_2–C)], 4.08 t (4H, 2OCH_2), 7.05–7.36 m (26H, Ar-H), 7.96 d.d (2H, Ar-H), 11.73 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.3, 28.3, 67.9, 112.5, 114.5, 119.0, 120.6, 126.5, 127.0, 127.4, 128.0, 128.8, 129.8, 143.3, 155.4. *M* 693 $[M + H]^+$. Found, %: C 81.40; H 5.76; N 8.02. $C_{47}H_{40}N_4O_2$. Calculated, %: C 81.48; H 5.82; N 8.09.

Compound Ve (*n* = 6). Yield 95%, mp: 225–227°C. IR, ν, cm^{-1}: 1548 (C=N), 1660 (C=C), 3434 (N–H). ^{1}H NMR spectrum (DMSO), δ, ppm: 1.63–1.70 m [4H, 2(C–CH_2–C)], 1.89–1.99 m [4H, 2(C–CH_2–C)], 4.08 t (4H, 2OCH_2), 7.05 d.d (2H, Ar-H), 7.08–7.36 m (24H,

Ar-H), 7.96 d.d (2H, Ar-H), 11.73 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 24.3, 28.2, 67.8, 112.5, 114.6, 119.0, 120.2, 120.6, 122.5, 126.6, 127.4, 128.7, 129.8, 143.2, 155.4. *M* 707 $[M + H]^+$. Found, %: C 81.50; H 5.92; N 7.89. $C_{48}H_{42}N_4O_2$. Calculated, %: C 81.56; H 5.99; N 7.93.

Compound Vf (*n* = 2). Yield 94%, mp 240–241°C. IR spectrum, ν, cm^{-1}: 1552 (C=N), 1665 (C=C), 3432 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.37 s (4H, $2OCH_2$), 6.92 d (2H, Ar-H), 7.21–7.55 m (22H, Ar-H), 7.66 d.d (4H, Ar-H), 12.35 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 65.6, 112.6, 119.5, 120.5, 121.6, 122.5, 127.0, 127.8, 128.6, 128.7, 129.3, 144.0, 152.5. *M* 651 $[M + H]^+$. Found, %: C 81.12; H 5.16; N 8.52. $C_{44}H_{34}N_4O_2$. Calculated, %: C 81.21; H 5.27; N 8.61.

Compound Vg (*n* = 3). Yield 95%, mp 260–261°C. IR spectrum, ν, cm^{-1}: 1552 (C=N), 1665 (C=C), 3428 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.95–2.20 m (2H, C–CH_2–C), 4.32 t (4H, $2OCH_2$), 6.90 d (4H, Ar-H), 7.21–7.46 m (22H, Ar-H), 7.50 d.d (2H, Ar-H), 10.85 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.5, 68.3, 112.6, 114.8, 119.8, 120.9, 124.5, 125.0, 126.9, 127.5, 128.8, 129.8, 145.7, 158.6. *M* 655 $[M + H]^+$. Found, %: C 81.28; H 5.38; N 8.40. $C_{45}H_{36}N_4O_2$. Calculated, %: C 81.30; H 5.46; N 8.43.

Compound Vh (*n* = 4). Yield 91%, mp 225–228°C. IR spectrum, ν, cm^{-1}: 1548 (C=N), 1662 (C=C), 3430 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.92 t [4H, 2(C–CH_2–C)], 4.29 t (4H, $2OCH_2$), 6.93 d (4H, Ar-H), 6.99–7.50 m (22H, Ar-H), 7.70 d.d (2H, Ar-H), 10.89 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 29.0, 67.9, 112.6, 114.6, 119.8, 120.5, 122.9, 124.5, 126.8, 127.9, 128.6, 129.0, 144.2, 156.5. *M* 679 $[M + H]^+$. Found, %: C 81.32; H 5.56; N 8.22. $C_{46}H_{38}N_4O_2$: Calculated, %: C 81.39; H 5.64; N 8.25.

Compound Vi (*n* = 5). Yield 90%, mp 235–237°C. IR spectrum, ν, cm^{-1}: 1554 (C=N), 1665 (C=C), 3436 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.47–1.54 m (2H, C–CH_2–C), 1.68–1.80 m [4H, 2(C–CH_2–C)], 4.37 t (4H, $2OCH_2$), 6.92 d (4H, Ar-H), 7.20–7.50 m (22H, Ar-H), 7.75 d.d (2H, Ar-H), 11.89 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 23.0, 28.5, 67.0, 112.5, 114.8, 119.0, 120.5, 126.5, 127.0, 127.5, 128.7, 128.9, 129.8, 145.3, 158.6. *M* 693 $[M + H]^+$. Found, %: C 81.45; H 5.79; N 8.02. $C_{47}H_{40}N_4O_2$. Calculated, %: C 81.48; H 5.82; N 8.09.

Compound Vj (*n* = 6). Yield 94%, mp 180–182°C. IR spectrum, ν, cm^{-1}: 1550 (C=N), 1664 (C=C), 3431 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.63–1.70 m [4H, 2(C–CH_2–C)], 1.89-1.99 m [4H, 2(C–CH_2–C)], 4.37 t (4H, $2OCH_2$), 6.92 d (2H, Ar-H), 7.21–7.52 m (22H, Ar-H), 7.70 d.d (4H, Ar-H), 11.50 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.3, 28.0, 66.9, 112.5, 114.4, 119.1, 121.6, 126.6, 127.0, 127.4, 128.5, 128.8, 129.6, 142.8, 158.0. *M* 707 $[M + H]^+$. Found, %: C 81.52; H 5.97; N 7.90. $C_{48}H_{42}N_4O_2$. Calculated, %: C 81.56; H 5.99; N 7.93.

Compound Vk (*n* = 2). Yield 95%, mp 230–231°C. IR spectrum, ν, cm^{-1}: 1552 (C=N), 1665 (C=C), 3432 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.32 s (4H, $2OCH_2$), 6.93 d.d (4H, Ar-H), 7.23–7.70 m (20H, Ar-H), 8.01 d.d (4H, Ar-H), 11.68 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 66.5, 114.6, 122.7, 127.0, 128.2, 128.3, 128.5, 129.0, 135.5, 136.2, 158.6. *M* 651 $[M + H]^+$. Found, %: C 81.12; H 5.16; N 8.52. $C_{44}H_{34}N_4O_2$. Calculated, %: C 81.21; H 5.27; N 8.61.

Compound Vl (*n* = 3). Yield 91%, mp 253–255°C. IR spectrum, ν, cm^{-1}: 1548 (C=N), 1663 (C=C), 3429 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.91–2.27 m (2H, C–CH_2–C), 4.22 t (4H, $2OCH_2$), 7.06 d.d (4H, Ar-H), 7.15–7.88 m (22H, Ar-H), 8.00 d.d (2H, Ar-H), 12.52 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 31.8, 66.0, 113.6, 122.7, 123.9, 127.1, 128.1, 128.4, 129.0, 135.6, 136.0, 158.7. *M* 665 $[M + H]^+$. Found, %: C 81.26; H 5.40; N 8.38. $C_{45}H_{36}N_4O_2$. Calculated, %: C 81.30; H 5.46; N 8.43.

Compound Vm (*n* = 4). Yield 90%, mp 210–213°C. IR spectrum, ν, cm^{-1}: 1552 (C=N), 1661 (C=C), 3430 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.90 t [4H, 2(C–CH_2–C)], 4.22 t (4H, $2OCH_2$), 7.08 d.d (4H, Ar-H), 7.19–7.32 m (3H, Ar-H), 7.35–7.45 m (10H, Ar-H), 7.59–7.62 m (7H, Ar-H), 8.01 d.d (4H, Ar-H), 10.52 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.8, 65.0, 113.0, 122.5, 123.6, 127.2, 128.2, 128.5, 129.1, 134.9, 136.2, 157.9. *M* 679 $[M + H]^+$. Found, %: C 81.32; H 5.56; N 8.22. $C_{46}H_{38}N_4O_2$. Calculated, %: C 81.39; H 5.64; N 8.25.

Compound Vn (*n* = 5). Yield 93%, mp 250–253°C. IR spectrum, ν, cm^{-1}: 1552 (C=N), 1658 (C=C), 3430 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45–1.49 m (2H, C–CH_2–C), 1.90–2.10 m [4H, 2(C–CH_2–C)], 4.31 t (4H, $2OCH_2$), 7.02 d.d (4H, Ar-H), 7.20–7.30 m (12H, Ar-H), 7.40–7.50 m (8H, Ar-H), 8.00 d.d (4H, Ar-H), 10.52 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.6, 31.0, 65.2, 113.3, 122.5, 123.6, 127.2, 127.5, 128.5, 129.2, 134.0, 136.2, 157.8. *M* 693 $[M + H]^+$. Found, %: C 81.46; H 5.78; N 8.04. $C_{46}H_{40}N_4O_2$. Calculated, %: C 81.48; H 5.82; N 8.09.

Compound Vo (n = 6). Yield 93%, mp 205–207°C. IR spectrum, ν, cm^{-1}: 1552 (C=N), 1658 (C=C), 3430 (N–H). ^1H NMR spectrum (DMSO), δ, ppm: 1.63–1.67 m [4H, 2(C–CH_2–C)], 1.90–2.20 m [4H, 2(C–CH_2–C)], 4.31 t (4H, 2OCH_2), 7.08 d.d (4H, Ar-H), 7.19–7.32 m (12H, Ar-H), 7.45–7.55 m (8H, Ar-H), 8.01 d.d (4H, Ar-H), 10.52 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.8, 29.3, 63.2, 113.3, 122.5, 123.6, 127.1, 127.8, 128.6, 129.5, 134.2, 136.2, 157.6. M 707 [M + $H]^+$. Found, %: C 81.52; H 5.94; N 7.88. Calculated, %: $C_{48}H_{42}N_4O_2$: C 81.56; H 5.99; N 7.93.

CONCLUSIONS

We have carried out one-pot synthesis of new substituted derivatives of imidazole, i.e. bis(4,5-diphenylimidazol-2-yl-phenyl)glycols (**Va–Vo**), with high yields. All synthesized compounds demonstrated high antimicrobial activity.

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