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Synthesis, In Silico Analysis, and Larvicidal Activity of New Bis-oxadiazole Derivatives

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Abstract—Twelve new 2,2′-bi(1,2,4-oxadiazole) derivatives containing heterocyclic and long-chain substituents have been synthesized by the condensation of aldehyde azines and oximes. In silico studies of these compounds revealed their good drug likeness and drug score. Some of the synthesized compounds showed moderate to excellent larvicidal activity.

Keywords: aldehyde azines, oximes, bis-oxadiazoles, in silico studies, larvicidal activity

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INTRODUCTION

Many clinically used drugs contain N,O-heterocyclic groups [1, 2]. Bis-oxadiazole derivatives were reported to inhibit the activity of γ-GT enzymes [3]. Among seventeen 1,3,4-oxadiazole derivatives, five compounds showed excellent antibacterial activity [4]. Ghanwat et al. [5] synthesized a series of novel 2,5-disubstituted 1,3,4-oxadiazoles which exhibited anti-inflammatory and antioxidant activities [5]. 1,3,4-Oxadiazoles containing a fluoropyridine moiety were evaluated against *Echinochloa cruss-galli*, *Avena fatua*, and *Sorgum halepense* weeds [6]. Isoquinoline-based 1,3,4-oxadiazoles were shown to be potent thymidine phosphorylase inhibitors [7].

New oxadiazoles with trihydroxyphenyl and 4-hydroxyquinoline groups were reported to have better anti-COVID activity than existing potent drugs, and computational studies supported the results of in vitro anti-COVID-19 assays [8]. 3,5-Diaryl-1,2,4-oxadiazoles were tested as new apoptosis inducers and potential anticancer agents [9, 10]. Two cytotoxic alkaloids, phidianidines A and B, containing a 1,2,4-oxadiazole ring linked to indole were isolated from the marine opisthobranch mollusk *Phidiana militaris* [11–13]. Some 1,4-benzoxazine–1,2,4-oxadiazole hybrids showed a promising in vitro anticancer activity against four cancer cell lines in comparison to etoposide as reference drug [14]. Bis(5-aryl-3-benzoyl-2,3-dihydro-1,3,4-oxadiazoles) synthesized from hydrazones and acetic anhydride/benzoyl chloride showed insecticidal, herbicidal, and nematicidal activities [15]. Twenty-four 1,3,4-oxadiazole derivatives with chloro, methoxy, and hydroxy substituents were synthesized and tested for their antibacterial activity in comparison to amoxicillin and cefixime [16]. Figure 1 shows the structures of some medically relevant oxadiazole derivatives.

Herein we describe the synthesis of new 2,2′-bi(1,2,4-oxadiazole) derivatives containing heterocyclic and long-chain alkyl moieties, in silico prediction of their biological properties, and in vitro larvicidal activity.

RESULTS AND DISCUSSION

Target compounds **1**–**12** were synthesized in good yields by the condensation of the corresponding aldehyde azines and oximes in the presence of triethylamine and molecular iodine in tetrahydrofuran at 60°C

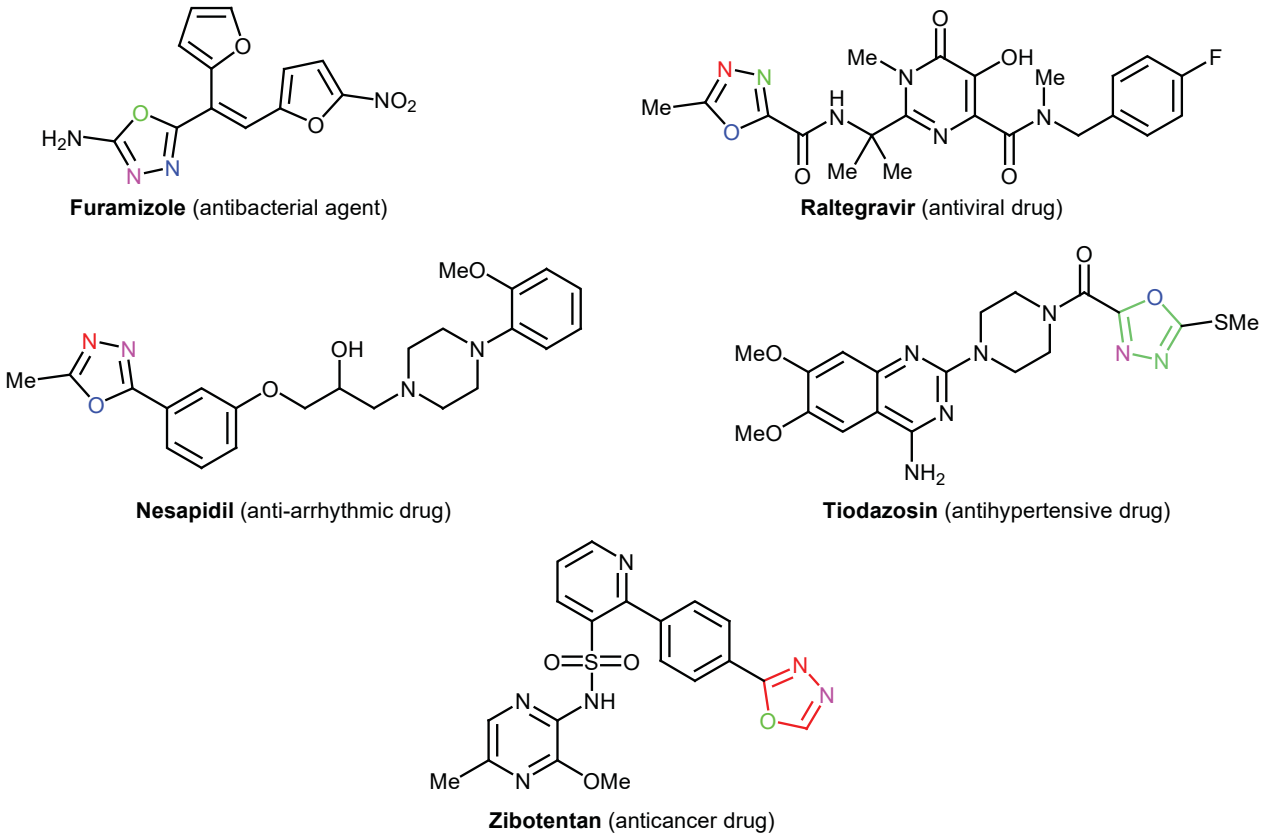


Fig. 1. Structures of some medically relevant oxadiazole derivatives.

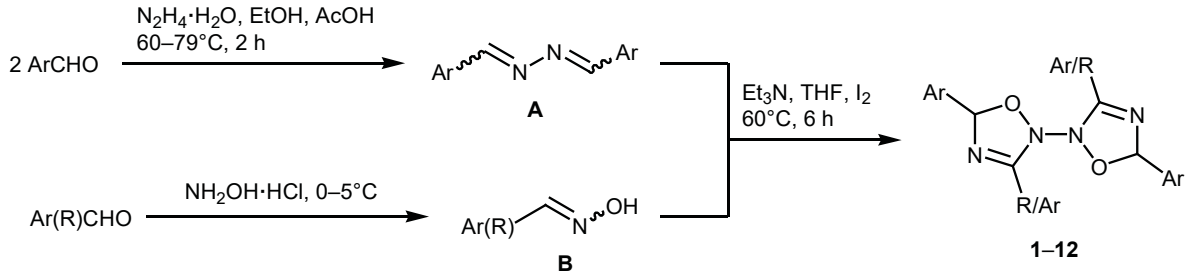
(Scheme 1). Their structure was confirmed by ^{1}H and ^{13}C NMR and mass spectra and elemental analyses (see Experimental and Supplementary Materials).

Compounds **1**–**12** were subjected to in silico analysis using OSIRIS and PASS Online software, and the results are summarized in Table 1. Compounds **1**–**6** were evaluated for their larvicidal activity in the concentration range from 10 to 100 μg/mL (Tables 2, 3). Compounds **1** and **4** showed moderate activity, compounds **3** and **6** exhibited good activity, and 2-butyl-4-chloro-1*H*-imidazol-5-yl (**2c**) and 2-chloroquinolin-3-yl (**5c**) derivatives showed excellent activity.

EXPERIMENTAL

Chemicals were purchased from Aldrich, SD Fine, and Avra Chemicals. Brine shrimp eggs (Artemia cysts) were obtained Sumi Pets and Aquarium (Pattabiram, Tamil Nadu). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at 400 and 100 MHz, respectively. The mass spectra (electrospray ionization) were recorded on an Agilent Technologies QTOF 6530 instrument. Elemental analysis was performed with an Elementar Vario Micro Cube CHNS analyzer.

Scheme 1.



For Ar and R, see Table 1.

Table 1. In-silico studies of compounds **1**–**12**

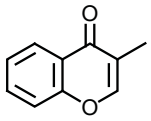
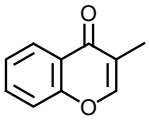
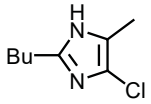
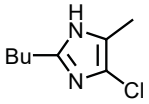
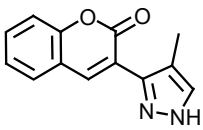
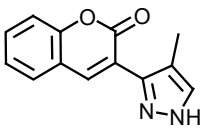
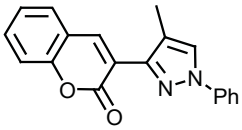
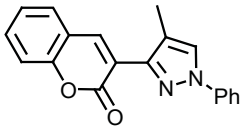
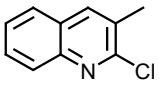
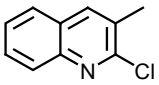
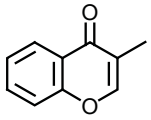
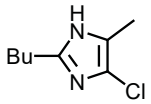
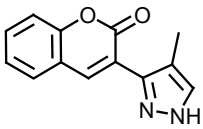
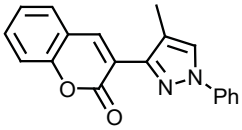
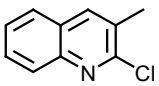
Compd. no.	Ar	R	Drug likeness/ drug score	PASS online activity
1			3.22/0.12	(1) Histidine kinase inhibitor (2) Aldehyde oxidase inhibitor
2			2.18/0.08	(1) Imidazoline I1 receptor agonist (2) Nicotinic alpha6beta3beta4alpha5 receptor antagonist
3			4.46/0.14	(1) CYP2A11 substrate (2) Antineoplastic
4			5.32/0.06	(1) CYP2A11 substrate (2) Nootropic
5			2.24/0.07	(1) Nicotinic alpha2beta2 receptor antagonist (2) CF transmembrane conductance regulator agonist
6			4.14/0.21	(1) Anaphylatoxin receptor antagonist (2) Complement factor D inhibitor
7		$(C_{16}H_{33})_2NCH_2$	–	(1) Histidine kinase inhibitor (2) Aldehyde oxidase inhibitor
8		$(C_{16}H_{33})_2NCH_2$	–	(1) Imidazoline I1 receptor agonist (2) Nicotinic alpha6beta3beta4alpha5 receptor antagonist
9		$(C_{16}H_{33})_2NCH_2$	–	(1) CYP2A11 substrate (2) Antineoplastic
10		$(C_{16}H_{33})_2NCH_2$	–	(1) CYP2A11 substrate (2) Nootropic
11		$(C_{16}H_{33})_2NCH_2$	–	(1) Nicotinic alpha2beta2 receptor antagonist (2) CF transmembrane conductance regulator agonist
12		$(C_{16}H_{33})_2NCH_2$	–	(1) Anaphylatoxin receptor antagonist (2) Complement factor D inhibitor

Table 2. In-vitro larvicidal activity (mortality rate, %) of compounds **1**–**6** at different concentrations

Compound no.	10 μg/mL	25 μg/mL	50 μg/mL	75 μg/mL	100 μg/mL
1	19.2	31.5	43.8	52.1	63.2
2	33.1	47.4	62.8	74.6	88.3
3	22.3	36.8	47.5	56.2	69.6
4	15.2	27.8	39.5	49.2	55.4
5	30.9	42.5	57.3	69.6	75.5
6	27.1	38.2	52.6	63.1	71.8

Table 3. Average mortality rates, standard deviations, and LC_{50} of compounds **1**–**6**

Compound no.	Average larvicidal activity (mortality rate, %)	Standard deviation	LC_{50}, μg/mL
1	41.96	17.21	61.96
2	61.24	21.77	42.46
3	46.48	18.08	55.93
4	37.42	16.22	69.48
5	55.16	18.54	47.13
6	50.56	18.13	51.42

General procedure for the synthesis of compounds 1–12. A mixture of the corresponding aldehyde (0.04 mol), hydrazine hydrate (0.02 mol), and one drop of acetic acid in 15 mL of ethanol was stirred at 60–70°C for 2 h to obtain aldehyde azine **A**. Oxime **B** was prepared from 0.01 mol of the same aldehyde (for **1**–**6**) or 2-(dihexadecylamino)acetaldehyde (for **7**–**12**) and 0.01 mol of hydroxylamine hydrochloride at 0–5°C. A mixture of **A** and **B**, triethylamine, and iodine (catalyst) in tetrahydrofuran was stirred at 60°C for 6 h. The mixture was poured into cold water, and the solid product was filtered off and dried.

3,3′,3″,3‴-{5*H*,5′*H*-[2,2′-Bi(1,2,4-oxadiazole)]-3,3′,5,5′-tetrayl}tetrakis(4*H*-chromen-4-one) (1). Yield: 92%, R_f 0.4 (hereinafter, EtOAc–hexane, 50:50 by volume). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.1 s (2H, (OCHN), 6.7 s (2H, =CH), 7.1 s (2H, =CH), 7.4 m (4H, H_{arom}), 7.5–7.6 m (8H, H_{arom}), 8.08 m (4H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 183.0, 177.5, 160.6, 157.2, 152.6, 150.6, 135.2, 125.7, 125.4, 123.9, 123.4, 116.1, 114.2, 83.7. Mass spectrum: *m*/*z* 803.3 [*M* + DMSO-d_6]$^+$. Found, %: C 66.05; H 3.89; N 7.28; O 22.78. $C_{40}H_{22}N_4O_{10}$. Calculated, %: C 66.85; H 3.09; N 7.80; O 22.26.

3,3′,5,5′-Tetrakis(2-butyl-4-chloro-1*H*-imidazol-5-yl)-5*H*,5′*H*-2,2′-bi(1,2,4-oxadiazole) (2). Yield 94%, R_f 0.5. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.9 t (12H, CH_3), 1.31 m (8H, CH_2), 1.6 m (8H, CH_2), 2.88 t (8H, 2′-CH_2), 5.84 s (2H, OCHN), 11.1 s (1H, NH), 11.3 s (1H, NH), 12.5 s (1H, NH), 13.0 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 157.9, 148.2, 147.9, 136.5, 134.2, 122.9, 116.1, 84.6, 51.5, 30.6, 27.6, 27.9, 22.3, 14.1. Mass spectrum: *m*/*z* 798 [*M* + CH_3OH]$^+$. Found, %: C 50.55; H 5.45; Cl 18.51; N 21.17; O 4.32. $C_{32}H_{42}Cl_4N_{12}O_2$. Calculated, %: C 50.01; H 5.51; Cl 18.45; N 21.87; O 4.16.

3,3′,3″,3‴-{5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-3,3′,5,5′-tetrayltetrakis(1*H*-pyrazole-4,3-diyl)}-tetrakis(2*H*-chromen-2-one) (3). Yield 90%, R_f 0.4. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.6 s (2H, NCHO), 7.4 m (8H, H_{arom}), 7.5 m (4H 5′-H), 7.6 m (4H, H_{arom}), 7.8 m (4H, H_{arom}), 8.1 m (4H, =CH), 12.6 m (4H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 161.9, 158.9, 153.0, 146.1, 138.9, 132.5, 132.1, 129.4, 128.3, 127.9, 125.4, 120.9, 116.1, 112.8, 85.7. Mass spectrum: *m*/*z* 982 [*M*]$^+$. Found, %: C 63.28; H 3.08; N 17.24; O 16.40. $C_{52}H_{30}N_{12}O_{10}$. Calculated, %: C 63.54; H 3.08; N 17.10; O 16.28.

3,3′,3″,3‴-{5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-3,3′,5,5′-tetrayltetrakis(1-phenyl-1*H*-pyrazole-4,3-diyl)}tetrakis(2*H*-chromen-2-one) (4). Yield 91%, R_f 0.6. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.6 s (2H, NCHO), 7.4 m (12H, H_{arom}), 7.5 m (8H, H_{arom}), 7.6 m (12H, H_{arom}), 7.8 m (4H, H_{arom}), 8.1 m (4H,

=CH), 8.4 s (4H, 5′-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 161.9, 153.0, 146.1, 140.9, 139.7, 129.4, 129.3, 128.3, 127.9, 126.2, 125.4, 120.9, 119.9, 118.4, 116.1, 114.0, 86.0. Mass spectrum: *m*/*z* 1286 $[M]^+$. Found, %: C 70.45; H 3.91; N 13.24; O 12.40. $C_{76}H_{46}N_{12}O_{10}$. Calculated, %: C 70.91; H 3.60; N 13.06; O 12.43.

3,3′,5,5′-Tetrakis(2-chloroquinolin-3-yl)-5*H*,5′*H*-2,2′-bi(1,2,4-oxadiazole) (5). Yield 94%, R_f 0.4. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.6 s (2H, NCHO), 7.6 m (4H, H_{arom}), 7.7 m (4H, H_{arom}), 7.9 d (4H, H_{arom}), 8.0 d (4H, H_{arom}), 8.2 s (2H, H_{arom}), 9.06 s (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 158.3, 152.0, 151.9, 149.7, 148.8, 145.4, 136.3, 134.6, 131.0, 130.9, 129.9, 128.1, 127.8, 127.5, 127.3, 127.2, 127.0, 126.8, 126.6, 126.2, 86.1. Mass spectrum: *m*/*z* 786 $[M]^+$. Found, %: C 60.78; H 2.91; Cl 17.99; N 14.24; O 4.08. $C_{40}H_{22}Cl_4N_8O_2$. Calculated, %: C 60.93; H 2.81; Cl 17.99; N 14.21; O 4.06.

3,3′,5,5′-Tetrakis(1,3-thiazol-2-yl)-5*H*,5′*H*-2,2′-bi(1,2,4-oxadiazole) (6). Yield 91%, R_f 0.4. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.64 s (2H, OCHN)), 7.3 d.d (2H, H_{arom}), 7.5 d.d (2H, H_{arom}), 7.65 d.d (4H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 168.5, 164.6, 157.6, 143.9, 141.9, 132.7, 118.7. Mass spectrum: *m*/*z* 473.98. Found, %: C 40.39; H 2.22; N 23.71; O 6.64; S 27.04. $C_{16}H_{10}N_8O_2S_4$. Calculated, %: C 40.49; H 2.12; N 23.61; O 6.74; S 27.03.

3,3′-{3,3′-Bis[(dihexadecylamino)methyl]-5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-5,5′-diyl}bis(4*H*-chromen-4-one) (7). Yield 94%, R_f 0.7. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (12H, CH_3), 1.26 m (56H, CH_2), 1.29 m (40H, CH_2)), 1.30 m (8H, CH_2, 1.36 m (8H, CH_2), 2.46 t (8H, NC**H**$_2$$CH_2$), 2.48 s (4H, NCH_2C), 3.90 s (2H, OCHN), 7.20 s (2H, 2′-H), 7.47 t (2H, H_{arom}), 7.55 t (4H, H_{arom}), 8.08 d (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 183.1, 166.0, 157.4, 150.9, 135.9, 125.7, 123.4, 116.9, 116.1, 57.1, 53.0, 32.0, 29.7, 29.2, 28.1, 27.4, 22.7, 14.1. Found, %: C 76.05; H 10.96; N 6.69; O 6.30. $C_{88}H_{148}N_6O_6$. Calculated, %: C 76.25; H 10.76; N 6.06; O 6.93.

***N*,*N*′-{(5,5′-Bis(2-butyl-4-chloro-1*H*-imidazol-5-yl)-5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-3,3′-diyl)-bis(methylene)}bis(*N*-hexadecylhexadecan-1-amine) (8).** Yield 92%, R_f 0.8. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.89 t (18H, CH_3), 1.26 m (56H, CH_2), 1.29 m (40H, CH_2), 1.31 m (12H, CH_2), 1.36 m (8H, CH_2), 1.60 m (4H, CH_2), 2.46 t (8H, NC**H**$_2$$CH_2$), 2.48 s (4H, NCH_2C), 2.87 t (4H, CH_2N), 4.3 s (2H, OCHN), 13.0 s (2H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 166.0, 147.4, 136.4, 120.7, 90.1, 57.1, 52.9, 31.9, 30.6, 29.7, 29.2, 28.1, 27.9, 27.3, 22.7, 22.3, 14.1. Found, %: C 71.45; H 11.34; Cl 5.05; N 9.86; O 2.30. $C_{84}H_{158}Cl_2N_{10}O_2$. Calculated, %: C 71.50; H 11.29; Cl 5.02; N 9.93; O 2.27.

3,3′-{3,3′-Bis[(dihexadecylamino)methyl]-5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-5,5′-diylbis(1*H*-pyrazole-4,3-diyl)}bis(2*H*-chromen-2-one) (9). Yield 90%, R_f 0.7. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (12H, CH_3), 1.26 m (56H, CH_2)), 1.29 m (40H, CH_2), 1.30 m (8H, CH_2), 1.36 m (8H, CH_2), 2.46 t (8H, NC**H**$_2$$CH_2$), 2.48 s (4H, NCH_2C), 3.9 s (2H, OCHN), 7.42 t (4H, H_{arom}), 7.55 t (2H, H_{arom}), 7.65 t (2H, H_{arom}), 7.84 t (2H, H_{arom}), 8.08 d (2H, 5′-H), 12.62 s (2H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 164.7, 161.9, 153.2, 146.2, 132.1, 129.4, 128.3, 127.9, 125.4, 122.4, 120.9, 116.1, 112.8, 58.1, 55.1, 49.0, 32.0, 31.4, 29.7, 29.2, 28.1, 27.2, 22.7, 14.1. Found, %: C 74.33; H 10.12; N 9.25; O 6.30. $C_{94}H_{152}N_{10}O_6$. Calculated, %: C 74.36; H 10.09; N 9.23; O 6.32.

3,3′-{3,3′-Bis[(dihexadecylamino)methyl]-5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-5,5′-diylbis(1-phenyl-1*H*-pyrazole-4,3-diyl)}bis(2*H*-chromen-2-one) (10). Yield 91%, R_f 0.4. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (12H, CH_3), 1.26 m (56H, CH_2), 1.29 m (40H, CH_2), 1.30 m (8H, CH_2), 1.36 m (8H, CH_2), 2.46 t (8H, NC**H**$_2$$CH_2$), 2.48 s (4H, NCH_2C)), 4.6 s (2H, OCHN), 7.42 t (4H, H_{arom}), 7.45 t (2H, H_{arom}), 7.55 t (4H, H_{arom}), 7.64 t (6H, H_{arom}), 7.84 t (2H, H_{arom}), 8.08 d (2H, 5′-H), 8.2 s (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 166.0, 161.9, 158.0, 153.0, 146.2, 140.9, 139.8, 134.1, 128.4, 127.9, 129.5, 126.3, 125.4, 122.4, 120.8, 119.8, 116.3, 91.4, 57.0, 55.1, 52.9, 49.3, 32.0, 31.4, 29.7, 29.2, 28.1, 27.9, 27.2, 22.7, 14.1. Found, %: C 76.26; H 9.40; N 8.47; O 5.87. $C_{106}H_{160}N_{10}O_6$. Calculated, %: C 76.21; H 9.65; N 8.38; O 5.75.

***N*,*N*′-{(5,5′-Bis(2-chloroquinolin-3-yl)-5*H*,5′*H*-[2,2'-bi(1,2,4-oxadiazole)]-3,3′-diyl)bis(methylene)}-bis(*N*-hexadecylhexadecan-1-amine) (11).** Yield 91%, R_f 0.7. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (12H, CH_3), 1.26 m (56H, CH_2), 1.29 m (40H, CH_2), 1.30 m (8H, CH_2), 1.36 m (8H, CH_2), 2.46 t (8H, NC**H**$_2$$CH_2$), 2.48 s (4H, NCH_2C), 4.5 s (2H, OCHN), 7.60 t (2H, H_{arom}), 7.75 t (2H, H_{arom}), 7.91 d (2H, H_{arom}), 8.04 d (2H, H_{arom}), 8.30 s (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 166.0, 151.8, 145.2, 136.8, 130.9, 130.1, 127.9, 127.6, 127.0, 126.3, 91.4, 57.0, 52.8, 32.0, 31.4, 29.7, 29.2, 28.1, 27.9, 27.2, 22.7, 14.1. Found, %: C 74.30; H 10.58; Cl 4.95; N 7.84; O 2.33. $C_{88}H_{148}Cl_2N_8O_2$. Calculated, %: C 74.38; H 10.50; Cl 4.99; N 7.89; O 2.25.

***N*,*N*′-{5,5′-Bis(1,3-thiazol-2-yl)-5*H*,5′*H*-[2,2′-bi(1,2,4-oxadiazole)]-3,3′-diylbis(methylene)}bis-(*N*-hexadecylhexadecan-1-amine) (12).** Yield 95%, R_f 0.4. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (12H, CH_3), 1.26 m (56H, CH_2), 1.29 m (40H, CH_2), 1.30 m (8H, CH_2), 1.36 m (8H, CH_2), 2.46 t (8H, NCH_2CH_2), 2.48 s (4H, NCH_2C), 4.5 s (2H, OCHN), 7.31 d (2H, 5′-H), 7.53 d (2H, 4′-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 166.0, 165.8, 141.8, 118.9, 96.8, 57.1, 53.0, 32.0, 29.7, 29.2, 28.1, 27.9, 27.2, 22.7, 14.1. Found, %: C 72.31; H 11.23; N 8.82; O 2.54; S 5.10. $C_{76}H_{142}N_8O_2S_2$. Calculated, %: C 72.21; H 11.32; N 8.86; O 2.53; S 5.07.

Larvicidal activity. A sterilized test tube was charged with 25 mL of distilled water, a small amount of sodium chloride was added, and a required pH value was adjusted by adding sodium hydrogen carbonate. Magnesium sulfate was added to obtain an alkaline solution, *Artemia* cysts were added, and the tube was incubated at 27°C for 24 h to produce larvae. Solutions of each compound **1**–**6** DMSO with concentrations of 10, 25, 50, 75, and 100 μg/mL were prepared in test tubes, 10 larvae were taken in each test tube, the test tubes were incubated at 27°C for 24 h, and the number of dead larvae was counted to determine percent mortality.

CONCLUSIONS

Bis-oxadiazoles containing heterocyclic groups and long chains have been synthesized in high yields and evaluated for their larvicidal activity. The compounds substituted with heterocyclic groups showed higher activity than those with long-chain substituents. The biological potential of the synthesized compounds has been estimated by in silico studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1070428023010177.

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