Synthesis of New Bis-1,2,4-Oxadiazoline Derivatives via 1,3-Dipolar Cycloaddition Reaction

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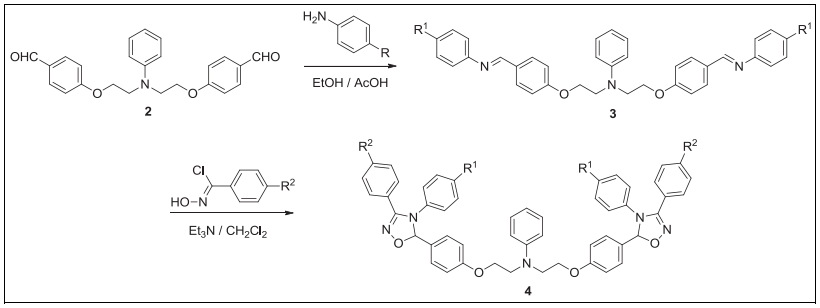

A series of novel bis-oxadiazoline derivatives **4** was synthesized via 1,3-dipolar cycloaddition reaction of bis-aldimines **3**, and nitrile oxides generated *in situ* from various benzohydroximinoyl chlorides in the presence of Et_3N. The target products were confirmed by IR, ^{1}H-NMR, and mass spectrometry.

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INTRODUCTION

The concept of 1,3-dipole was first introduced by Huisgen in 1963 [1]. Since that time, the 1,3-dipolar cycloaddition, consisting of the reaction of a dipolarophile with a 1,3-dipolar compound, has became the classic reaction in organic chemistry for the production of various five-membered heterocycles. Much work has been done on the reactions and the mechanism of 1,3-dipolar cycloaddition [2–9]. The asymmetric 1,3-dipolar cycloaddition reaction to an enviable methodology, not only for the construction of chiral functionalised normal-ring carbocycles but also for the synthesis of complex natural products. In addition, different substituents can be included in the dipole and the dipolarophile, resulting in a broad range of possible cycloadducts, which can serve as useful synthetic building blocks [10].

Oxadiazoline was important for both chemical and biological purposes. Oxadiazolines played a crucial role in the development of theory in heterocyclic chemistry and also was extensively used as useful synthon in organic synthesis. Also, a number of oxadiazoline have been reported to exhibit diverse pharmacological properties such as antimicrobial, pesticides, insecticides, and antiviral activity [11,12]. Aware of the multifactorial nature of many disease, the multi-target-directed ligand approach was accepted as an effective strategy for designing ligands and inhibitors and creating new drugs [13,14]. The new dimeric compounds, containing two identical or different structural units, connected by a linker of suitable length, have proved useful in enhancing the biological profile and selectivity of monomeric leads [15–17]. Based on this consideration, we reported here the synthesis of new 4,5-dihydro-1,2,4-oxadiazoline dimerics (Scheme 1) through 1,3-dipolar cycloaddition reaction.

RESULTS AND DISCUSSION

A series of novel 4,5-dihydro-1,2,4-oxadiazoline derivatives were synthesized using aniline as a starting material. Intermediate compound (*N,N*-bis(4-(4-formoxyl)phenoxy) ethyl)aniline **2** was synthesized by the S_N2 reaction of compound *N,N*-bis[2-(*p*-tolylsulfonoxyl)ethyl]-benzenamine **1** [18] with 4-hydroxy benzaldehyde heated to 90°C for 30 h dissolved in EtOH. Compounds imines **3a–d** [19] were synthesized via the nucleophilic addition between **2** [20] and substituted aniline. Finally, compounds **3a–d** underwent 1,3-dipolar cycloadditions with benzohydroximinoyl chlorides in the presence of Et_3N stirred in CH_2Cl_2 leading to the formation of cycloadducts. Various analytical techniques, such as IR, ^{1}H-NMR, mass spectrum (MS), and elemental analysis, were utilized to confirm the structural identities of the new products.

In IR spectra of the final compounds, there was a moderate strong absorption at 1682–1692 cm^{-1} due to the presence of C=N. A strong absorption at 1247–1252 and 1163–1175 cm^{-1} for C–O–C and C–N single bond of the 1,2,4-oxadiazoline moiety, respectively. In the ^{1}H-NMR spectra of the titled compounds, the presence of a singlet

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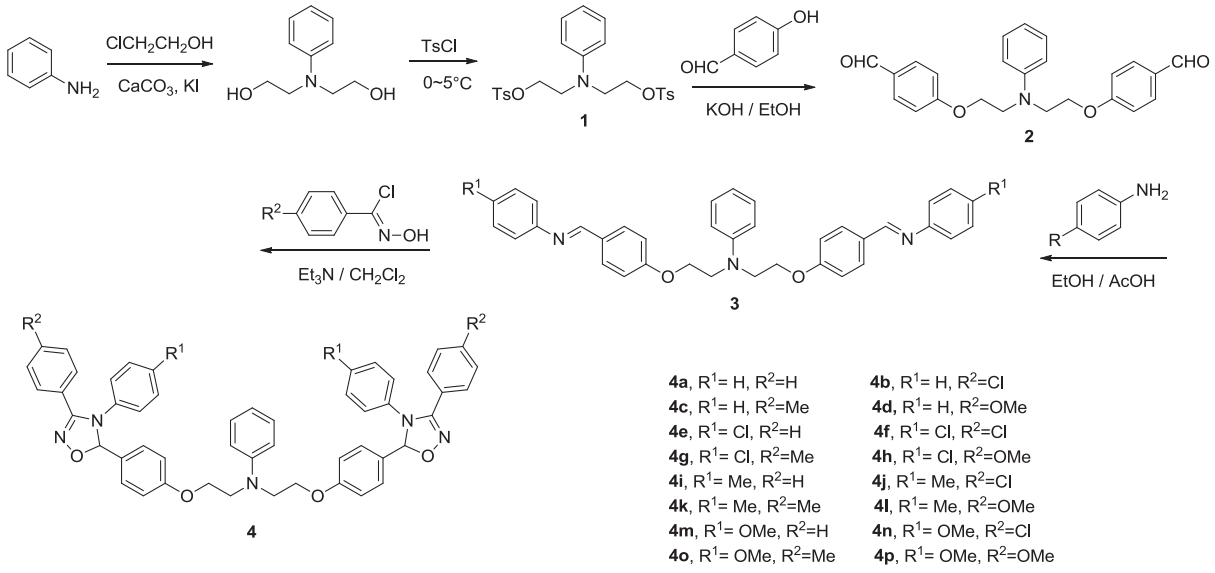
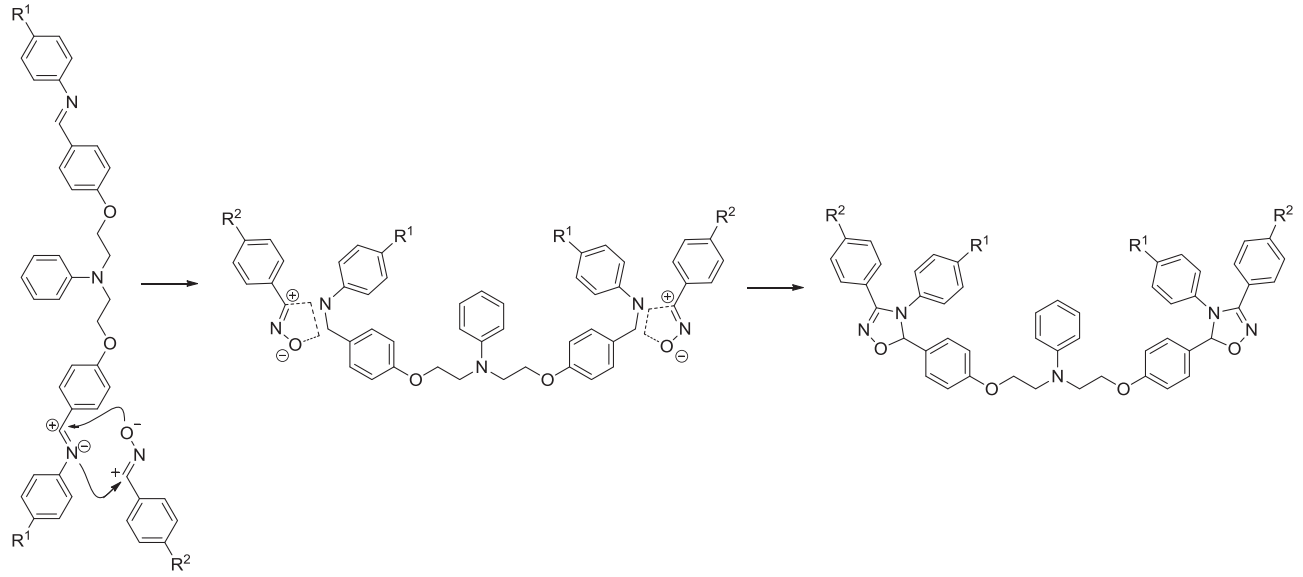
Scheme 1. Synthetic process of the title compounds.



Scheme 2. Proposed intramolecular 1,3-diploar cycloaddition mechanism of cycloadduct **4a**.



at δ 6.30–6.45 ppm was ascribed to the CH of 1,2,4-oxadiazoline ring, the multiplet at δ 6.67–7.81 was attributed to the aromatic protons, and the triplet at δ 4.20–4.23, 3.89–3.91 were attributed to OCH_2 and NCH_2, respectively. In addition, the signal for OCH_3 and CH_3 appeared at δ 3.70–3.80 and 2.23–2.35 ppm, respectively. To speak of, in the IR spectra of the compound **2**, there was a strong absorption at 1678 and 1597 cm^{-1} due to the presence of CHO and C=N; in ^{1}H-NMR, the singlet at δ 9.88 ppm was attributed to the aldehyde protons. In the MS, molecular ions plus hydrogen signals of all target compounds were attained from electrospray ionization–mass spectrometry (ESI-MS).

A conceivable intramolecular 1,3-dipolar cycloaddition mechanism was proposed in Scheme 2. In the presence of Et_3N, the nitrile oxide generated *in situ* and C=N double bond forms a cyclic transition state and the σ-bonds of C–N and C–O were formed simultaneously to obtain the 1,2,4-oxadiazole ring; the plausible mechanism of compounds **4b–p** was proposed analogously.

CONCLUSION

In summary, we have synthesized a series of novel bis-oxadiazoline derivatives **4a–p** via 1,3-dipolar cycloaddition reaction of bis-aldimines and *para*-substituted aniline,

and nitrile oxides, generated *in situ* from various benzohydroximinoyl chlorides in the presence of Et_3N. The new dimeric compounds, containing two identical structural units, connected by a linker of suitable length, it is probably useful in enhancing the biological profile and selectivity of monomeric leads.

EXPERIMENTAL

All reagents were of commercial availability. All the synthesis reactions were performed under open air. Reactions were monitored by thin-layer chromatography (TLC). Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. The IR spectra were determined as potassium bromide pellet on a Bruker Equinox 55 FTIR spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. Mass spectra were recorded on an Agilent 5975 apparatus. Elemental analyses were conducted on a Perkin-Elmer 2400 elemental analyzer. Compounds **1** [18], 2,2′-(phenylazanediyl) diethanol [21], and benzohydroximinoyl chlorides [22] were synthesized according to the reported literatures.

General procedure for the synthesis of (*N,N*-bis(4-(4-formoxyl)phenoxy)ethyl)aniline 2 [20]. In a 150 ml round-bottomed three-necked flask equipped with a condenser and drying tube, KOH (1.71 g, 30.6 mmol) was dissolved in EtOH (90 cm^3), and 4-hydroxy benzaldehyde (3.74 g, 30.6 mmol) was added while stirring; 30 min later, **1** (4.92 g, 10.05 mmol) was added and the solution was heated at 90°C for 30 h (using TLC to judge the termination of the reaction). The reaction mixture was cooled and poured into water (60 cm^3), and the precipitate was collected and washed with water and ethanol, in sequence, and purified by silica gel column chromatography (ethylacetate/petroleum ether = 1:4, v/v) to afford the pale yellow solid.

Pale yellow solid (72%); mp 99–101°C; FTIR ν 1678 (CHO) 1597 (C=N), 1349 (C–N), 1261 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.88 (s, 2H, CHO), 7.82–6.78 (m, 13H, ArH), 4.28 (t, 4H, J = 5.9 Hz, OCH_2), 3.94 (t, 4H, J = 5.9 Hz, NCH_2); MS (EI): *m/z* 389 (M^+). *Anal.* Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.93; H, 5.91; N, 3.52.

General procedure for the synthesis of *N,N*-bis(2-(4-(substituted phenyl methyl)phenoxy)ethyl)anilines (3a–d) [19]. To aniline or 4-substituted aniline, 2 mmol was added a solution of the compound **2** (1 mmol) in anhydrous ethanol (10 cm^3), after dissolution of the reactants, then refluxed in the presence of a catalytic amount of glacial acetic acid for 2–4 h (monitored by TLC). The solution was filtered and concentrated under reduced pressure to afford crude produce, which was purified by silica gel column chromatography (ethylacetate/petroleum ether = 1:4, v/v) to afford the corresponding imines **3**.

***N,N*-Bis(2-(4-(phenylimino-methyl)phenoxy)ethyl)aniline (3a).** Pale white solid (89%); mp 143–144°C; FTIR ν 1602 (C=N), 1364, 1163 (C–N), 1245 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39–6.70 (m, 23H, ArH), 6.64 (s, 2H, CH=N), 4.19 (t, 4H, J = 5.9 Hz, OCH_2), 3.90 (t, 4H, J = 5.9 Hz, NCH_2); MS (ESI): *m/z* 540 (M^++1). *Anal.* Calcd for $C_{36}H_{33}N_3O_2$: C, 80.12; H, 6.16; N, 7.79. Found: C, 80.01; H, 6.12; N, 7.58.

***N,N*-Bis(2-(4-(((4-chlorophenyl)imino)methyl)phenoxy)ethyl)aniline (3b).** Yellow solid (90%); mp 174–176°C; FTIR ν 1607 (C=N), 1363, 1165 (C–N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68–6.70 (m, 21H, ArH), 6.67 (s, 2H, CH=N), 4.27 (t, 4H, J = 5.9 Hz, OCH_2), 3.92 (t, 4H, J = 5.9 Hz, NCH_2); MS (ESI): *m/z* 608 (M^++1). *Anal.* Calcd for $C_{36}H_{31}Cl_2N_3O_2$: C, 71.05; H, 5.13; N, 6.91. Found: C, 70.98; H, 5.10; N, 6.82.

***N,N1*-Bis(2-(4-((4-tolylimino)methyl)phenoxy)ethyl)aniline (3c).** Pale yellow solid (91%); mp 157–158°C; FTIR ν 1600 (C=N), \1166 (C–N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.73 (m, 21H, ArH), 6.64 (s, 2H, CH=N), 4.20 (t, 4H, J = 6.1 Hz, OCH_2), 3.89 (t, 4H, J = 6.1 Hz, NCH_2), 2.32 (s, 6H, CH_3); MS (ESI): *m/z* 568 (M^++1). *Anal.* Calcd for $C_{38}H_{37}N_3O_2$: C, 80.39; H, 6.57; N, 7.40. Found: C, 80.12; H, 6.56; N, 7.24.

***N,N*-Bis(2-(4-(((4-methoxyphenyl)imino)methyl)phenoxy)ethyl)aniline (3d).** Pale white solid (93%); mp 175–176°C; FTIR ν 1603 (C=N), 1359, 1165 (C–N), 1242 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.74 (m, 21H, ArH), 6.67 (s, 2H, CH=N), 4.20 (t, 4H, J = 6.0 Hz, OCH_2), 3.89 (t, 4H, J = 6.0 Hz, NCH_2), 3.78 (s, 6H, OCH_3); MS (ESI): *m/z* 600 (M^++1). *Anal.* Calcd for $C_{38}H_{37}N_3O_4$: C, 76.10; H, 6.22; N, 7.01. Found: C, 76.03; H, 6.17; N, 6.89.

General procedure for the preparation of *N,N*-bis(2-(4-(3,4-di-substituted phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl) phenoxy)ethyl)anilines (4a–p). A mixture of the appropriate benzohydroximinoyl chlorides (2.1 mmol) and the imine **3** (1 mmol) was stirred in CH_2Cl_2 (5 cm^3). After dissolution of the reactants, a solution of triethylamine (0.5 cm^3) was added dropwise. Then, the solution was stirred at room temperature for a further 2 days. The solid mass separated out was filtered off, and the filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column using ethylacetate : petroleum ether (1:3, v/v) as eluent to afford the corresponding 4,5-dihydro-1,2,4-oxadiazolines derivatives **4**.

***N,N*-Bis(2-(4-(3,4-diphenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4a).** Pale yellow solid (62%); mp 67–68°C; FTIR ν 1684 (C=N), 1375, 1171 (C–N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.67 (m, 33H, ArH), 6.32 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.7 Hz, OCH_2), 3.89 (t, 4H, J = 5.7 Hz, NCH_2); MS (ESI): *m/z* 778 (M^++1). *Anal.* Calcd for $C_{50}H_{43}N_5O_4$: C, 77.20; H, 5.57; N, 9.00. Found: C, 77.10; H, 5.58; N, 8.87.

N,N-Bis(2-(4-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4b). Pale yellow solid (68%); mp 74–75°C; FTIR ν 1689 (C=N), 1389, 1163 (C–N), 1252 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68–6.68 (m, 31H, ArH), 6.30 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.7 Hz, OCH_2), 3.89 (t, 4H, J = 5.7 Hz, NCH_2); MS (ESI): *m/z* 846 (M^++1). *Anal.* Calcd for $C_{50}H_{41}Cl_2N_5O_4$: C, 70.92; H, 4.88; N, 8.27. Found: C, 70.81; H, 4.84; N, 8.18.

N,N-Bis(2-(4-(4-phenyl-3-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4c). Pale yellow solid (69%); mp 77–78°C; FTIR ν 1685 (C=N), 1378, 1171 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.47–6.77 (m, 31H, ArH), 6.45 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.21 (t, 4H, J = 5.7 Hz, OCH_2), 3.89 (m, 4H, J = 5.7 Hz, NCH_2), 2.33 (s, 6H, CH_3); MS (ESI): *m/z* 806 (M^++1). *Anal.* Calcd for $C_{52}H_{47}N_5O_4$: C, 77.49; H, 5.88; N, 8.69. Found: C, 77.36; H, 5.79; N, 8.53.

N,N-Bis(2-(4-(3-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4d). Pale yellow solid (69%); mp 75–77°C; FTIR ν 1684 (C=N), 1378, 1171 (C–N), 1249 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.68 (m, 31H, ArH), 6.33 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.9 Hz, OCH_2), 3.89 (t, 4H, J = 5.9 Hz, NCH_2), 3.78 (s, 6H, OCH_3); MS (ESI): *m/z* 838 (M^++1). *Anal.* Calcd for $C_{52}H_{47}N_5O_6$: C, 74.53; H, 5.65; N, 8.36. Found: C, 74.38; H, 5.54; N, 8.28.

N,N-Bis(2-(4-(4-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4e). Pale yellow solid (67%); mp 73–74°C; FTIR ν 1690 (C=N), 1389, 1163 (C–N), 1252 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.78–6.69 (m, 31H, ArH), 6.38 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.7 Hz, OCH_2), 3.90 (t, 4H, J = 5.7 Hz, NCH_2); MS (ESI): *m/z* 846 (M^++1). *Anal.* Calcd for $C_{50}H_{41}Cl_2N_5O_4$: C, 70.92; H, 4.88; N, 8.27. Found: C, 70.86; H, 4.85; N, 8.20.

N,N-Bis(2-(4-(3,4-bis(4-chlorophenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4f). Pale yellow solid (65%); mp 76–78°C; FTIR ν 1690 (C=N), 1378, 1163 (C–N), 1251 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.81–6.73 (m, 29H, ArH), 6.38 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.22 (t, 4H, J = 5.7 Hz, OCH_2), 3.91 (t, 4H, J = 5.7 Hz, NCH_2); MS (ESI): *m/z* 916 (M^++1). *Anal.* Calcd for $C_{50}H_{39}Cl_4N_5O_4$: C, 65.58; H, 4.29; N, 7.65. Found: C, 65.46; H, 4.28; N, 7.56.

N,N-Bis(2-(4-(4-(4-chlorophenyl)-3-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4g). Pale yellow solid (70%); mp 78–79°C; FTIR ν 1684 (C=N), 1387, 1172 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.68 (m, 29H, ArH), 6.41 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.23 (s, 4H, J = 4.8 Hz, OCH_2), 3.91 (t, 4H, J = 4.8 Hz, NCH_2), 2.35 (s, 6H, CH_3); MS (ESI): *m/z* 874 (M^++1). *Anal.* Calcd for $C_{52}H_{45}Cl_2N_5O_4$: C, 71.39; H, 5.18; N, 8.01. Found: C, 71.30; H, 5.13; N, 7.96.

N,N-Bis(2-(4-(4-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4h). Pale yellow solid (65%); mp 83–84°C; FTIR ν 1692 (C=N), 1381, 1175 (C–N), 1252 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.47–6.69 (m, 29H, ArH), 6.41 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.7 Hz, OCH_2), 3.90 (t, 4H, J = 5.7 Hz, NCH_2), 3.80 (s, 6H, OCH_3); MS (ESI): *m/z* 906 (M^++1). *Anal.* Calcd for $C_{52}H_{45}Cl_2N_5O_6$: C, 68.87; H, 5.00; N, 7.72. Found: C, 68.65; H, 4.93; N, 7.61.

N,N-Bis(2-(4-(3-phenyl-4-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4i). Pale yellow solid (67%); mp 72–74°C; FTIR ν 1685 (C=N), 1378, 1171 (C–N), 1247 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.68 (m, 31H, ArH), 6.32 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.9 Hz, OCH_2), 3.89 (t, 4H, J = 5.9 Hz, NCH_2), 2.23 (s, 6H, CH_3); MS (ESI): *m/z* 806 (M^++1). *Anal.* Calcd for $C_{52}H_{47}Cl_2N_5O_4$: C, 77.49; H, 5.88; N, 8.69. Found: C, 77.36; H, 5.89; N, 8.54.

N,N-Bis(2-(4-(3-(4-chlorophenyl)-4-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4j). Pale yellow solid (70%); mp 73–74°C; FTIR ν 1692 (C=N), 1379, 1171 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.76–6.68 (m, 29H, ArH), 6.34 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.9 Hz, OCH_2), 3.89 (t, 4H, J = 5.9 Hz, NCH_2), 2.24 (s, 6H, CH_3); MS (ESI): *m/z* 874 (M^++1). *Anal.* Calcd for $C_{52}H_{45}Cl_2N_5O_4$: C, 71.39; H, 5.18; N, 8.01. Found: C, 71.30; H, 5.18; N, 7.96.

N,N-Bis(2-(4-(3,4-di-4-tolyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4k). Pale yellow solid (67%); mp 65–66°C; FTIR ν 1685 (C=N), 1375, 1171 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.68 (m, 29H, ArH), 6.34 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.9 Hz, OCH_2), 3.88 (t, 4H, J = 5.9 Hz, NCH_2), 2.23 (s, 12H, CH_3); MS (ESI): *m/z* 834 (M^++1). *Anal.* Calcd for $C_{54}H_{51}N_5O_4$: C, 77.77; H, 6.16; N, 8.40. Found: C, 77.59; H, 6.11; N, 8.32.

N,N-Bis(2-(4-(3-(4-methoxyphenyl)-4-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4l). Pale yellow solid (65%); mp 79–80°C; FTIR ν 1684 (C=N), 1376, 1172 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.48–6.68 (m, 29H, ArH), 6.38 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 6.0 Hz, OCH_2), 3.89 (t, 4H, J = 6.0 Hz, NCH_2), 3.78 (s, 6H, OCH_3), 2.23 (s, 6H, CH_3); MS (ESI): *m/z* 866 (M^++1). *Anal.* Calcd for $C_{54}H_{51}N_5O_6$: C, 74.89; H, 5.94; N, 8.09. Found: C, 74.68; H, 5.95; N, 8.00.

N,N-Bis(2-(4-(4-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4m). Pale yellow solid (66%); mp 69–70°C; FTIR ν 1684 (C=N), 1375, 1171 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.45–6.68 (m, 31H, ArH), 6.32 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 6.1 Hz, OCH_2), 3.89 (t, 4H, J = 6.1 Hz, NCH_2), 3.70 (s, 6H, OCH_3); MS (ESI): *m/z* 838 (M^++1). *Anal.* Calcd for $C_{54}H_{47}N_5O_6$: C, 74.53; H, 5.65; N, 8.36. Found: C, 74.34; H, 5.59; N, 8.27.

N,N-Bis(2-(4-(3-(4-chlorophenyl)-4-(4-methoxyphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4n). Pale yellow solid (65%); mp 77–78°C; FTIR ν 1684 (C=N), 1369, 1170 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.80–6.71 (m, 29H, ArH), 6.33 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 5.9 Hz, OCH_2), 3.90 (t, 4H, J = 5.9 Hz, NCH_2), 3.70 (s, 6H, OCH_3); MS (ESI): *m/z* 906 (M^++1). *Anal.* Calcd for $C_{52}H_{45}Cl_2N_5O_6$: C, 68.87; H, 5.00; N, 7.72. Found: C, 68.61; H, 4.86; N, 7.53.

N,N-Bis(2-(4-(4-(4-methoxyphenyl)-3-(4-tolyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4o). Pale yellow solid (65%); mp 86–87°C; FTIR ν 1687 (C=N), 1376, 1171 (C–N), 1248 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44–6.67 (m, 29H, ArH), 6.32 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.23 (t, 4H, J = 5.9 Hz, OCH_2), 3.91 (t, 4H, J = 5.9 Hz, NCH_2), 3.70 (s, 6H, OCH_3), 2.32 (s, 6H, CH_3); MS (ESI): *m/z* 866 (M^++1). *Anal.* Calcd for $C_{54}H_{51}N_5O_6$: C, 74.89; H, 5.94; N, 8.09. Found: C, 74.71; H, 5.87; N, 8.02.

N,N-Bis(2-(4-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)phenoxy)ethyl)aniline (4p). Pale yellow solid (68%); mp 78–79°C; FTIR ν 1682 (C=N), 1374, 1172 (C–N), 1250 (C–O–C) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.45–6.67 (m, 29H, ArH), 6.33 (s, 2H, 1,2,4-oxadiazoline ring CH), 4.20 (t, 4H, J = 6.1 Hz, OCH_2), 3.90 (t, 4H, J = 6.1 Hz, NCH_2), 3.71 (s, 12H, OCH_3); MS (ESI): *m/z* 898 (M^++1). *Anal.* Calcd for $C_{54}H_{51}N_5O_8$: C, 72.22; H, 5.72; N, 7.81. Found: C, 71.99; H, 5.67; N, 7.73.

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