Synthesis of novel amides of phenyl-1, 4-dioxyacetic acid as molecular tweezers and studies on their molecular recognition

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A simple efficient method for the synthesis of novel amides of phenyl-1, 4-dioxyacetic acid as molecular tweezers under solvent-free conditions and microwave irradiation has been developed. Its main advantages are short reaction times, good conversions and the environmentally friendly nature of the process. The structures of the products were confirmed by IR, ^{1}H NMR, MS spectra and elemental analyses and their binding properties were examined by UV-vis spectral titration. Preliminary results indicated that these molecular tweezers show good selectivity for neutral organic molecules.

Keywords: molecular tweezers; microwave irradiation; synthesis; recognition

Molecular recognition is a fundamental characteristic of biochemical systems and plays a central role in biological processes. Its study is at the frontiers of bioorganic chemistry. [1–10] Neutral organic molecules, for example, barbiturate, urea, and arylamines have strong physiological activity *in vivo* and are important scaffolds in medicinal chemistry.[11–14] The developments of artificial receptors for the recognition of neutral organic molecules have important academic significance and potentially a broad application.

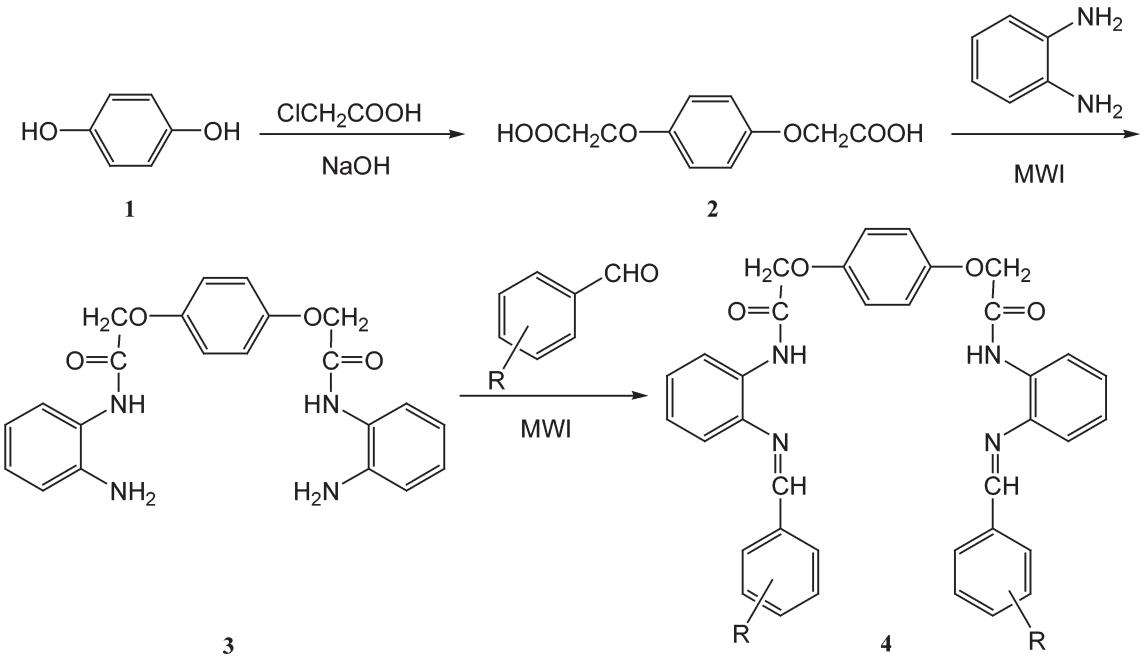
Microwave-assisted organic synthesis has attracted considerable interest and is an important technique in green synthetic chemistry.[15–20] It provides a unique chemical process with special attributes, such as ease of manipulation, enhanced reaction rates, clean reaction outcome and high yields. As part of our work on green synthesis and the study of recognition study by molecular tweezer artificial receptors, we report here our results on the synthesis of molecular tweezer receptors based on 1,4-phenoxyacetic acid under solvent-free conditions and microwave irradiation. Molecular tweezers **4a–i** were synthesised according to Scheme 1.

Result and discussion

In the microwave experiments, the supporters significantly affect the yield of the products. We found that only small amounts of **4a** could be detected by TLC analysis when using silica gel H, artificial zeolite, K_2CO_3 as supporters and irradiating for 7 min, whereas the receptor **4a** was obtained in a yield of 80% when using Al_2O_3 as supporter and irradiating for 7 min. To determine the optimum condition of this reaction, we investigated the effects of microwave irradiation power and time. It was found that the highest yield of compounds **4a–i** were obtained at 240 W for 5–9 min. The typical results are shown in Table 1. There are distinct advantages of the present microwave protocol including solvent free, clean reaction conditions, together with high yields of products and short reaction times.

The molecular recognition properties of molecular tweezers **4a**, **4c, 4g** for neutral organic molecules were investigated by UV-Vis spectra titration in $CHCl_3$ at 25 °C. The association constant (*K*a) and Gibbs free energy changes ($-\Delta G^0$) were determined. Computer-aided molecular modelling was used examine further the recognition abilities of molecular tweezers.

Using a UV-Vis spectra titration method, we added benzophenone, phenol, resorcinol, hydroquinol solutions of different concentrations to **4a, 4c, 4g** of fixed concentration of 1×10^{-4}–10×10^{-4} mol L^{-1}, and measured the characteristic absorbance



Scheme 1

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Table 1 Synthesis of molecular tweezers **4a–j** under microwave irradiation

Entry	R	T/min	Yield/%
4a	H	7	80
4b	2-OH	9	87
4c	4-OH	6	84
4d	3-OH	8	82
4e	2-Cl	6	86
4f	4-Cl	7	85
4g	4-OCH_3	7	87
4h	4-Br	6	88
4i	4-$N(CH_3)_2$	5	82

value of the host-guest complexes. As the guest molecules were added, the absorbance value rose and fell in a regular pattern. The preliminary results showed that the molecular tweezers possessed the ability to form a complex with the guest molecules that were examined. The UV-Vis plot of **4a** for benzophenone is shown in Fig. 1.

The titration data were analysed by using the Hildebrand–Benesi equation.[21] Based on the equation (1), when $[G]_0>>[H]_0$, the plots of $1/[G]_0$ versus $1/\Delta A$ were measured. The plot gave a straight line (Fig. 2). It showed that the molecular tweezer **4a** possessed the ability to form a complex with the guest molecules that were examined. The supramolecular complexes consisted of 1:1 host and guest molecules.

Using the intercept and the slope of the line, we calculated the association constants (*K*a). The free energy change ($-\Delta G^0$) was obtained according to equation (2). Association constants (*K*a) and free energy changes ($-\Delta G^0$) for the inclusion complexes of neutral organic molecules with molecular tweezers **4a**, **4c, 4g** are listed in Table 2. As shown in Table 2, the recognition ability of 4a, 4c, 4g for the guest benzophenone, phenol, resorcinol, hydroquinol are different. Their values of *K*a in the same solvent ($CHCl_3$) are ranked as follows: benzophenone> hydroquinol> resorcinol> phenol, and they all show good selectivity to form a complex with benzophenone. The maximum value of *K*a of **4a**, **4c**, **4g** for benzophenone is 2763.12 $L{\cdot}mol^{-1}$. From the conformation analysis of the complex of the host and guest, suggests that the size and shape of benzophenone molecule are more suitable for complex formation with the host than other molecules.

$$\frac{1}{\Delta A} = \frac{1}{aKa[G]_0} + \frac{1}{a} \qquad (1)$$

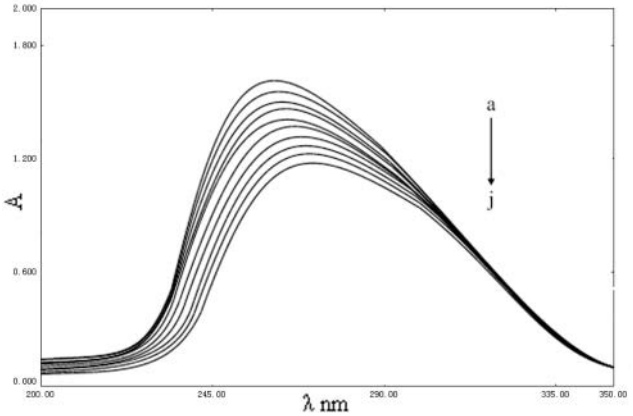

Fig. 1 UV-vis spectra of molecular tweezers **4a** (1.54×10^{-5} mol L^{-1}) in the presence of benzophenone. (a) 0, (b) 0.24×10^{-3}, (c) 0.48×10^{-3}, (d) 0.48×10^{-3}, (e) 0.72×10^{-3}, (f) 0.96×10^{-3}, (g) 1.20×10^{-3}, (h) 1.44×10^{-3}, (i) 1.68×10^{-3}, and (j) 1.92×10^{-3} mol L^{-1} with λ_{max} at 256.9 nm.

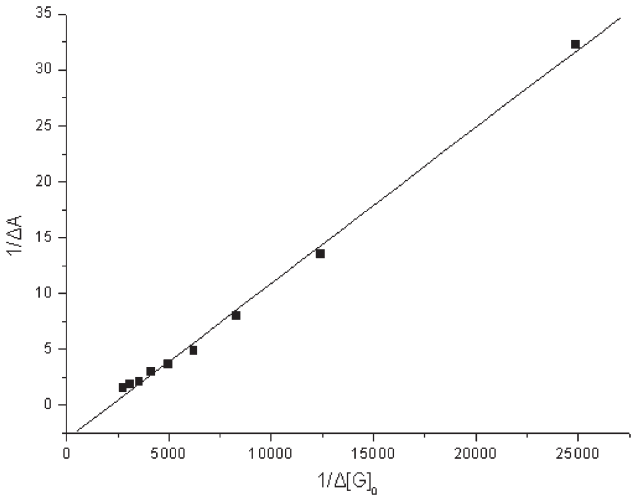

Fig. 2 Typical plot of $1/\Delta A$ versus $1/[G]_0$ for the inclusion complex of molecular tweezer **4a** with benzophenone in $CHCl_3$ at 25 °C.

$$\Delta G^0 = -RT\mathrm{Ln}Ka \qquad (2)$$

The recognition of molecular tweezer 4a for benzophenone has been investigated by computer-aided molecular modeling using a Chem 3D program. When the host **4a** at the minimum energy, its conformation is a cleft which has the ability to form complex with guest molecules. The minimum energy conformation of **4a** is shown in Fig. 3. The drive forces of molecular recognition mainly come from noncovalent forces between host and guest, such as hydrogen bonding and π–π stacking interaction. The minimum energy conformation for the 1:1 complex of molecular tweezer **4a** with benzophenone is shown in Fig. 4. The details of molecular recognition of **4a–j** are under further study.

Experimental

Melting points were determined on a micro-melting point apparatus and were uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FT-IR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using TMS as internal standard. Mass spectra were determined on Finnigan LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 autoanalyser. Microwave irradiation was carried out with a MCL-3 microwave oven at full power (700 W), which was modified from a domestic microwave oven and tested to conform to the performance index before use. All the solvents were purified before use.

Preparation of compound **2***; general procedure*

Compound **1** (0.1 mmol) **1**, NaOH (0.6 mmol) and water (50 mL) were mixed in a beaker at room temperature. Then, $ClCH_2COOH$

Table 2 Association constants (*K*a) and free energy changes ($-\Delta G^0$) for the inclusion complexes of neutral organic molecules with molecular tweezers **4a**, **4c**, **4g** in $CHCl_3$ at 25 °C

Host	Guest	*K*a/M^{-1}	$-\Delta G^0$/kJ·mol^{-1}
4a	Benzophenone	2763.12	19.63
	Phenol	57.61	10.04
	Resorcinol	431.5	15.03
	Hydroquinol	153.90	12.48
4c	Benzophenone	2550.87	18.20
	Phenol	92.30	11.21
	Resorcinol	524.51	15.52
	Hydroquinol	129.9	12.06
4g	Benzophenone	1935.2	18.75
	Phenol	73.38	10.64
	Resorcinol	394.22	14.81
	Hydroquinol	172.01	12.75

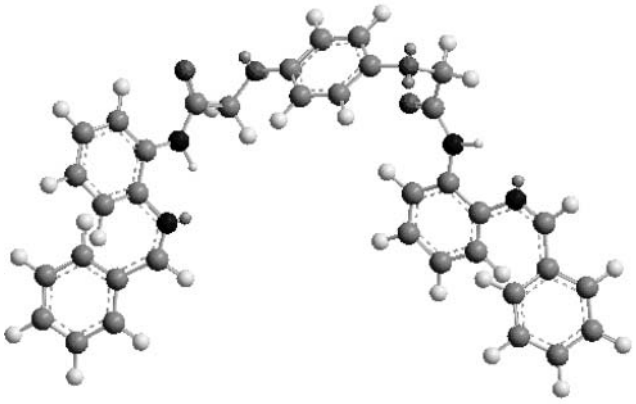

Fig. 3 Minimum energy conformation of molecular tweezer **4a**.

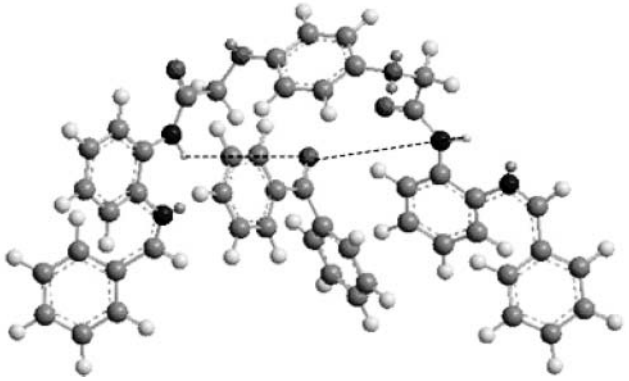

Fig. 4 Minimum energy conformation for the 1:1 complex of molecular tweezer **4a** with benzophenone.

(0.6 mmol) was added to the mixture and the temperature was raised to 100 °C for 15 min. After being cooled, the reaction mixture was made strongly acidic by adding HCl. The solid product was collected by vacuum filtration, washed well with water and recrystallised from 1% HCl solution to give the desired compound **2** as a white solid, yield 86%, m.p. 212–213 °C, ESI–MS *m/z* (%): 249 [(M+Na)$^+$, 100].

Preparation of compound ***3****; general procedure*

A mixture of **2** (1 mmol), 1,2-diaminobenzene (2 mmol), DCC (1 mmol), permutite (0.1 g) and DMAP (0.02 g) was placed in a round-bottomed flask and mixed thoroughly. Then, the mixture was irradiated with microwave (150 W) for 8 min in an atmosphere of nitrogen gas. After the reaction was complete, the reaction mixture was cooled to room temperature and extracted with dichloromethane (15 mL×2). The organic layer was washed successively with 10% $NaHCO_3$ (15 mL×2), brine (15 mL×2), and finally dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product **3**. The crude product was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate as eluant.

3: Yellow solid, yield 70%, m.p. 242–244 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 9.30 (s, 2H, NH), 7.14 (d, J = 8.0 Hz, 2H, ArH), 6.99 (s, 4H, ArH), 6.91–6.95 (m, 2H, ArH), 6.73 (d, J = 8.0 Hz, 2H, ArH), 6.54–6.58 (m, 2H, ArH), 4.93 (s, 4H, NH_2), 4.64 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3315, 3042, 1663, 1514, 1448, 1369, 1229, 1074, 744, ESI–MS *m/z* (%): 407 [(M+1)$^+$, 100]. Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 65.18; H, 5.52; N, 13.86%.

Preparation of compounds ***4a–i****; general procedure*

Compound **3** (1.0 mmol), aryl aldehyde (2.0 mmol), Al_2O_3 (0.5 g) and two drops of CH_3COOH were placed in a beaker and mixed thoroughly. Then, the mixture was irradiated with microwave (240 W) for 5–9 min. The reaction was monitored by TLC until it was complete. After cooling to room temperature, the mixture was extracted by DMF. The solvent was evaporated to give the crude product **4a–i**. The crude product was recrystallised from DMF to give a pure sample.

4a: White solid, yield 80%, m.p. 290–292 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.89 (s, 2H, NH), 8.58 (d, J = 8.0 Hz, 2H, ArH), 8.53 (s, 2H, =CH), 7.86–7.87 (m, 4H, ArH), 7.40–7.45 (m, 6H, ArH), 7.21–7.32 (m, 4H, ArH), 7.14–7.16 (m, 2H, ArH), 6.87 (s, 4H, phenoxy ring-H), 4.57 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3334, 3050, 2909, 1673, 1505, 1231, 1070, 735; ESI–MS *m/z* (%): 583 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{30}N_4O_4$: C, 74.21; H, 5.19; N, 9.62. Found: C, 74.38; H, 5.17; N, 9.66%.

4b: Pale yellow solid, yield 87%, m.p. >300 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.14 (s, 2H, NH), 8.59 (s, 2H, =CH), 8.51 (d, J = 8.0 Hz, 2H, ArH), 7.43–7.47 (m, 4H, ArH), 7.33–7.35 (m, 2H, ArH), 7.14–7.21 (m, 4H, ArH), 7.09–7.11 (m, 2H, OH), 7.00–7.12 (m, 4H, ArH), 6.92 (s, 4H, phenoxy ring-H), 4.55 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3379, 3060, 2907, 1677, 1615, 1530, 1227, 1074, 750; ESI–MS *m/z* (%): 615 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{30}N_4O_6$: C, 70.35; H, 4.92; N, 9.12. Found: C, 70.22; H, 4.91; N, 9.15%.

4c: White solid, yield 84%, m.p. >300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.26 (s, 2H, OH), 9.86 (s, 2H, NH), 8.66 (s, 2H, =CH), 8.39 (d, J = 8.0 Hz, 2H, ArH), 7.82 (d, J = 8.0 Hz, 4H, ArH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 7.23–7.27 (m, 2H, ArH), 7.13–7.17 (m, 2H, ArH), 7.05 (s, 4H, phenoxy ring-H), 6.90 (d, J = 8.0 Hz, 4H, ArH), 4.71 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3317, 3223, 2900, 1658, 1587, 1509, 1229, 1074, 742; ESI–MS *m/z* (%): 615 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{30}N_4O_6$: C, 70.35; H, 4.92; N, 9.12. Found: C, 70.47; H, 4.93; N, 9.10%.

4d: White solid, yield 82%, m.p. >300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 9.82 (s, 2H, OH), 9.81 (s, 2H, NH), 8.71 (s, 2H, =CH), 8.41 (d, J = 8.0, 2H, ArH), 7.40–7.46 (m, 6H, ArH), 7.28–7.33 (m, 4H, ArH), 7.15–7.19 (m, 2H, ArH), 7.02 (s, 4H, phenoxy ring-H), 6.97 (m, 2H, ArH), 4.69 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3319, 3181, 2979, 1660, 1589, 1539, 1230, 1075, 744; ESI–MS *m/z* (%): 615 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{30}N_4O_6$: C, 70.35; H, 4.92; N, 9.12. Found: C, 70.11; H, 4.90; N, 9.16%.

4e: Yellow solid, yield 86%, m.p. 248–250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.89 (s, 2H, NH), 9.00 (s, 2H, =CH), 8.59 (m, 2H, ArH), 8.13 (d, J = 8.0 Hz, 2H, ArH), 7.14–7.42 (m, 12H, ArH), 6.86 (s, 4H, phenoxy ring-H), 4.60 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3346, 3054, 1683, 1589, 1506, 1438, 1227, 1056, 752; ESI–MS *m/z* (%): 651 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{28}Cl_2N_4O_4$: C, 66.36; H, 4.33; N, 8.60. Found: C, 66.23; H, 4.32; N, 8.54%.

4f: White solid, yield 85%, m.p. >300 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.84 (s, 2H, NH), 8.58 (d, J = 8.0 Hz, 2H, ArH), 8.50 (s, 2H, =CH), 7.78 (d, J = 8.0 Hz, 4H, ArH), 7.30–7.39 (m, 6H, ArH), 7.22 (d, J = 8.0 Hz, 2H, ArH), 7.12–7.16 (m, 2H, ArH), 6.89 (s, 4H, phenoxy ring-H), 4.61 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3338, 3056, 1672, 1591, 1521, 1446, 1228, 1077, 823, 746; ESI–MS *m/z* (%): 651 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{28}Cl_2N_4O_4$: C, 66.36; H, 4.33; N, 8.60. Found: C, 66.21; H, 4.32; N, 8.56%.

4g: White solid, yield 87%, m.p. 212–213 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.89 (s, 2H, NH), 8.54 (d, J = 8.0 Hz, 2H, ArH), 8.43 (s, 2H, =CH), 7.78 (d, J = 8.0 Hz, 4H, ArH), 7.26–7.29 (m, 2H, ArH), 7.11–7.19 (m, 4H, ArH), 6.91 (d, J = 8.0 Hz, 4H, ArH), 6.88 (s, 4H, phenoxy ring-H), 4.57 (s, 4H, CH_2), 3.80(s, 6H, OCH_3); IR (KBr, cm^{-1}): 3343, 3049, 2975, 1668, 1595, 1509, 1441, 1228, 1070, 825; ESI–MS *m/z* (%): 643 [(M+1)$^+$, 100]. Anal. Calcd for $C_{38}H_{34}N_4O_6$: C, 71.01; H, 5.33; N, 8.72. Found: C, 71.21; H, 5.34; N, 8.76%.

4h: Yellow solid, yield 88%, m.p. >300 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.84 (s, 2H, NH), 8.58 (d, J = 8.0 Hz, 2H, ArH), 8.49 (s, 2H, =CH), 7.70 (d, J = 8.0 Hz, 4H, ArH), 7.54 (d, J = 8.0 Hz, 4H, ArH), 7.30–7.34 (m, 2H, ArH), 7.23–7.26 (m, 2H, ArH), 7.12–7.21 (m, 2H, ArH), 6.94 (s, 4H, phenoxy ring-H), 4.60 (s, 4H, CH_2); IR (KBr, cm^{-1}): 3336, 3056, 1673, 1589, 1516, 1442, 1225, 1065, 817, 744; ESI–MS *m/z* (%): 741 [(M+1)$^+$, 100]. Anal. Calcd for $C_{36}H_{28}Br_2N_4O_4$: C, 58.40; H, 3.81; N, 7.57. Found: C, 58.21; H, 3.80; N, 7.55%.

4i: Yellow solid, yield 82%, m.p. 279–281 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.96 (s, 2H, NH), 8.52 (d, J = 8.0 Hz, 2H, ArH), 8.36 (s, 2H, =CH), 7.69 (d, J = 8.0 Hz, 4H, ArH), 7.11–7.23 (m, 6H, ArH), 6.90 (s, 4H, phenoxy ring-H), 6.62 (d, J = 8.0 Hz, 4H, ArH), 4.55 (s, 4H, CH_2), 4.55 (s, 12H, N-CH_3); IR (KBr, cm^{-1}): 3332, 3049, 2896, 1676, 1594, 1520, 1441, 1362, 1227, 1171, 710, 735; ESI–MS *m/z* (%): 669 [(M+1)$^+$, 100]. Anal. Calcd for $C_{40}H_{40}N_6O_4$: C, 71.84; H, 6.03; N, 12.57. Found: C, 71.99 H 6.05; N, 12.59%.

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