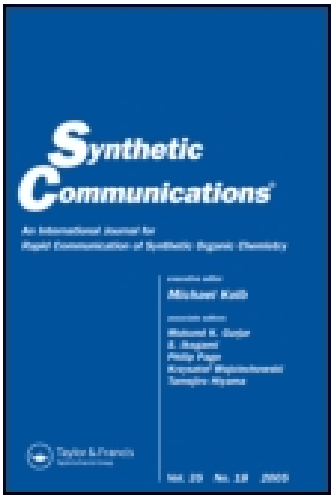

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Water-Solvent Method for the Synthesis of N-Substituted and N-,4-Disubstituted 1,8-Naphthalimides under Microwave Irradiation

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WATER-SOLVENT METHOD FOR THE SYNTHESIS OF N-SUBSTITUTED AND N-,4-DISUBSTITUTED 1,8-NAPHTHALIMIDES UNDER MICROWAVE IRRADIATION

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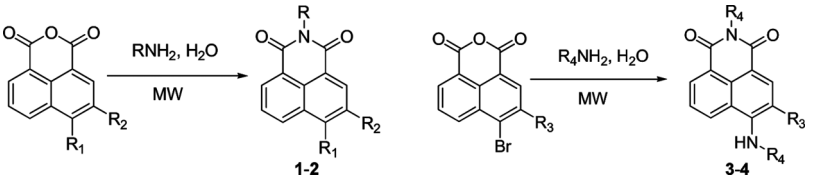
GRAPHICAL ABSTRACT



Abstract *A preparation of a series of N- and N-,4-substituted 1,8-naphthalimides using water as solvent under microwave irradiation, which proceeded via efficient and green reaction of 1,8-naphthalic anhydride derivatives with different amines, is described.*

Keywords Green chemistry; microwave; naphthalimides; water-solvent

INTRODUCTION

One of the main aims of green chemistry is the reduction of the use of organic solvents because of the economical and environmental concerns associated with them, and therefore the development of water-solvent synthetic methods is of the utmost importance.[1,2] Water is known to be one of the best green solvents, and it is cheap, readily available, nontoxic, and apyrous. Compared with many other solvents, water not only provides a medium for solution chemistry but also often takes part in elementary chemical events on a molecular scale, and it also offers practical advantages over organic solvents,[2] for example, its hydrogen bonding effects and polarity effects.[2] Thus, a considerable interest has been devoted to the reactions using water as solvent. In addition, microwave irradiation[3] has been considered a

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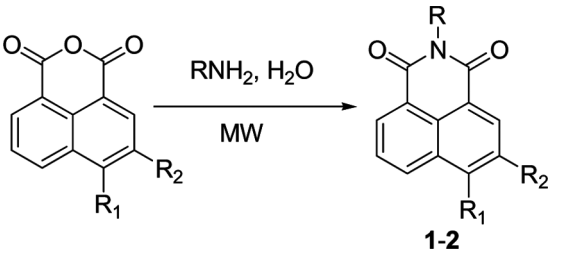
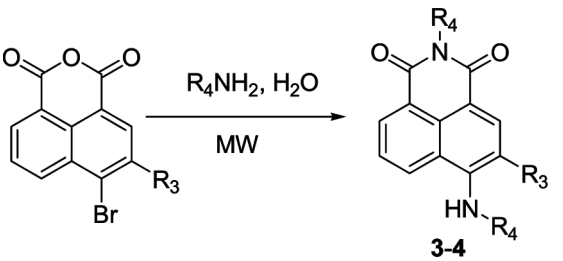


Scheme 1. Synthetic route of naphthalimides **1** and **2**.

green technology, and its level of energy consumption is low compared with most traditional methods. As well as being energy efficient, microwave heating can also enhance the rate of reactions and even in many cases improve product yields. It is well known that water is a good microwave-absorbing solvent (with a spot of electric loss and a very high dielectric constant).[3] Therefore it is very attractive to combine a water-solvent system with microwave irradiation.[3a,3d,3e]

In recent years, 1,8-naphthalimide derivatives have been the subjects of numerous synthetic efforts, because they have applications in dyeing synthetic polymers and textile materials,[4] in solar energy collectors[5], as fluorescent tags for use in molecular biology,[6] for potential photosensitizing biological activity,[7] and in liquid-crystalline displays.[8] Available methods for naphthalimides are listed in the literature.[9] Dehydrative condensation of 1,8-naphathalic anhydride with amines at high temperatures[9a] and the cyclization of N-substituted amic acid in the presence of acidic reagents[9d] are well-known methods. Direct N-alkylation under Mitsunobu conditions is another method for the synthesis of naphathlimide derivatives.[9*a*] The condensation of iminophosphoranes with phthaloyl dichloride followed by alkaline hydrolysis also affords naphthalimides.[9e] However, most of these routes are environmentally harmful or require long reaction times.[9] Therefore, preparation of functionalized 1,8-naphtalimide derivatives is still a major challenge in organic synthesis. In view of the important application of 1,8-naphthalimide derivatives and our general interest in green chemistry processes, we explore herein a new, efficient, mild, and water-solvent method for the synthesis of 1,8-naphthalimide derivatives under microwave irradiation (Schemes 1 and 2). It is important to point out that the reaction in this method not only includes the formation of imides from



Scheme 2. Synthetic route of naphthalimides **3** and **4**.

anhydrides but also the Ullmann arylation reaction on naphthalene moiety. To our knowledge, this method has not been described previously in literature and it is very simple but useful compared with previously reported methods.

RESULTS AND DISCUSSION

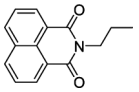
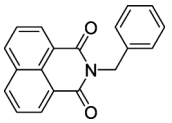
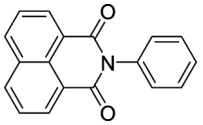
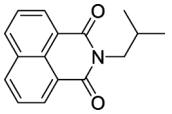
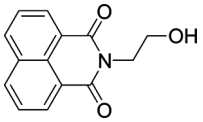
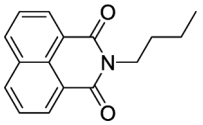
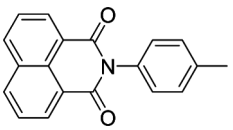
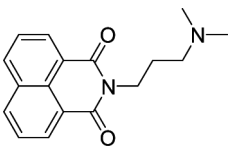
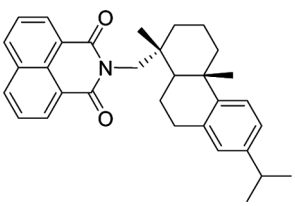
In a sealed and pressurized tube, we carried out the transformation of N-substituted naphthalimides 1a–1i and 2a–2f in a reaction of 1,8-naphtalic anhydride or 4-bromo-1,8-naphtalic anhydride with different amines in an aqueous mixture at 80 °C and 450 W under microwave irradiation (Scheme 1). The transformation was complete within 5–8 min, and the N-substituted products of 1 and 2 were obtained in good yields (51–96%) (Table 1) by filtering off the solution after the reaction system cooled to the room temperature.

It is important to note that in the synthesis of **2a–2f** there was another new product (it shows as green light in thin-layer chromatography [TLC] under the ultraviolet [UV] instrument at 365 nm) when the irradiation time in the reaction of 4-bromo-1,8-naphthalic anhydride with amines is prolonged. The new product was confirmed to be N,4-disubstituted naphthalimides 3 by ^{1}H NMR after separation, demonstrating that this reaction simultaneously included the formation of imides and the Ullmann arylation on naphthalene moiety. To the best of our knowledge, this reaction has not been reported previously under this condition and it aroused our interest for further progress. Additionally, this class of naphthalimides **3** exhibit excellent photochemical properties, good light stability, and good spectral properties, and they have become increasingly popular in a number of areas including laser active media,[10] potential photosensitive biological units,[7] analgesics in medicine,[11] ion probes,[12] and so forth. More effort has been invested in search for the best synthetic conditions. Through an optimized experiment, the optimized parameters of the reaction are summarized in Table 1. Heightening the reaction temperature to 100 °C and the microwave power to 850 W resulted in the formation of 4-alkylamino-naphthalimides **3** in 66–82% yields within 8–10 min.

To enlarge the scope of this method, 3-nitro-4-bromo-1,8-naphthalic anhydride was used to replace 4-bromo-1,8-naphthalic anhydride. In an aqueous mixture, the condensation of 3-nitro-4-bromo-1,8-naphthalic anhydride and different primary amines at 100 °C and 850 W under microwave irradiation afforded 3-nitro-4-alkylamino-naphthalimides **4** in good yield (82–92%). Because of the presence of an electron-withdrawing nitro group, the elimination of the bromogroup in the naphthalene moiety was more efficient and easy. It did not yield any N-substituted naphthalimides as that of **1** or **2** in the course of the transformation of **4**, even though microwave power and the temperature were reduced and reaction time was prolonged. It showed high selectivity in this reaction.

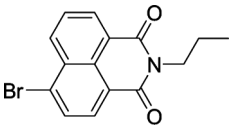
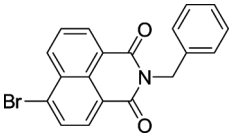
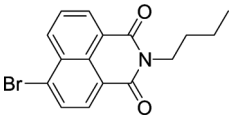
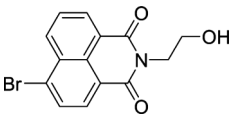
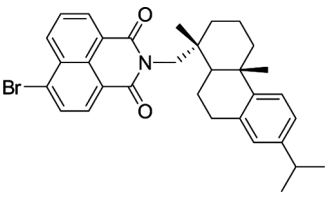
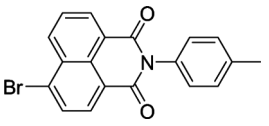
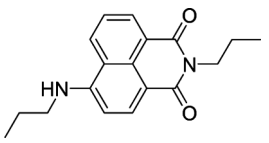
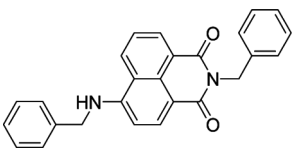
In ^{1}H NMR spectra for compounds **1**–**3**, the peaks of the nucleus in naphthalimides moiety ranged from 7.50 to 8.80 ppm. The peaks of N-H of compound **3** were in the range of 5.24–5.61 ppm. For compounds **4**, as a result of the presence of electron-withdrawing nitro group, the peaks of naphthalimide moiety beside the nitro group shifted to 8.70–9.40 ppm, and the peaks of N-H shifted to the range of 9.91–10.74 ppm.

Table 1. Synthesis of 1,8-naphthalimides **1–4**

Product	Structure	Amines (eq.[a])	Power (W)	Temperature (°C)	Time (min)	Yield (%)
1a		1.2	450	80	8	51
1b		1.2	450	80	5	96
1c		1.2	450	80	8	78
1d		1.2	450	80	8	65
1e		1.2	450	80	5	92
1f		1.2	450	80	8	68
1g		1.2	450	80	8	81
1h		1.2	450	80	8	83
1i		1.2	450	80	8	85

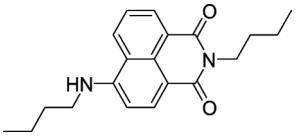
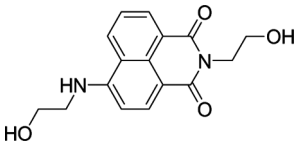
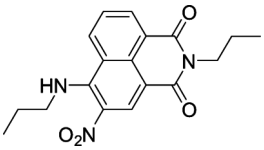
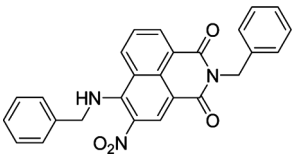
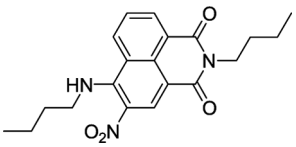
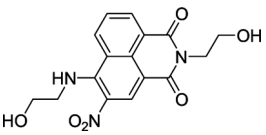
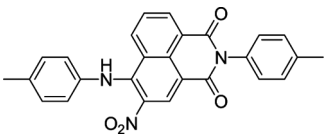
(*Continued*)

Table 1. Continued

Product	Structure	Amines (eq.[a])	Power (W)	Temperature (°C)	Time (min)	Yield (%)
2a		1.2	450	80	5	56
2b		1.2	450	80	6	95
2c		1.2	450	80	8	61
2d		1.2	450	80	8	80
2e		1.2	450	80	8	81
2f		1.2	450	80	8	83
3a		2.1	850	100	10	73
3b		2.1	850	100	10	66

(*Continued*)

Table 1. Continued

Product	Structure	Amines (eq.[a])	Power (W)	Temperature (°C)	Time (min)	Yield (%)
3c		2.1	850	100	10	80
3d		2.1	850	100	8	82
4a		2.1	850	100	10	84
4b		2.1	850	100	10	90
4c		2.1	850	100	10	82
4d		2.1	850	100	8	92
4e		2.1	850	100	8	88

[a]The dosages of 1,8-naphthalic anhydride, 4-bromo-1,8-naphthalic anhydride, and 3-nitro-4-bromo-1,8-naphthalic anhydride were 1 mmol.

Upon recrystallization, the single crystal of the representative compounds **1b**, **2e**, **3b**, **4b**, and **4d** (Fig. 1) were obtained and their structures were determined and confirmed by x-ray method. That provides good proof of the confirmation of their

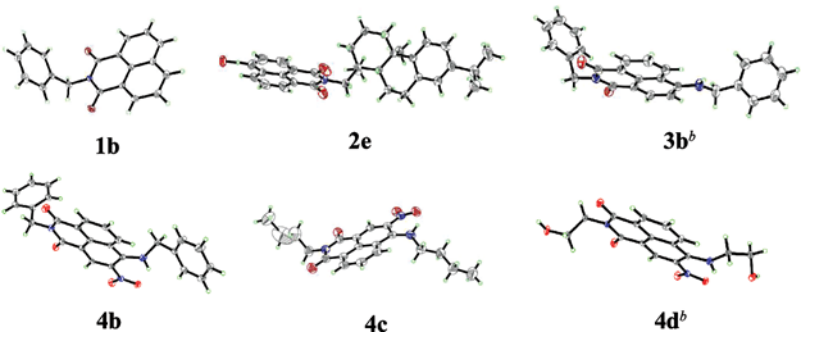


Figure 1. Single-crystal structures of the representative compounds **1b, 2e, 3b, 4b**, and **4d**. [b]Compounds **3b** and **4d** are cited here for comparison. (Figure is provided in color online.)

structures. It is well known that naphthalimides have been used as electro-optically sensitive materials,[4a] anion chemosensors,[13] and human medicines,[14] and so the single crystals of **3b, 4b,** and **4d** are expected to be very useful in the design of new kinds of naphthalimide analogs with novel functions and properties.

In conclusion, we have demonstrated a rapid, green, and efficient water-solvent method for the synthesis of N- and N-,4-substituted 1,8-naphthalimides under microwave irradiation. The procedure has the advantages of good yields, short reaction times, environmental friendliness, and easy workup.

EXPERIMENTAL

All reagents were of analytical grade and were dried and purified if necessary. Microwave irradiation was performed on a WF-4000 M microwave oven. Melting points were determined on a WRS-IA apparatus without correction. Infrared (IR) spectra were recorded on a PE Spectrum One Fourier transform (FT)–IR spectrometer as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer in $CDCl_3$ or dimethylsulfoxide (DMSO). Mass spectra were recorded on Bruker Esquire HCT or VG ZAB-HS spectrometers. All elemental analyses were performed on a PE 2400II analyzer. The data of single crystals were collected in a Rigaku Mercury CCD Area Detector.

Compounds 1 and 2

The mixture of primary amine (1.2 mmol), water (10 mL), and 1,8-naphthalic anhydride (or 4-bromo-1,8-naphthalic anhydride) (1 mmol) was blended together in a sealed and pressurized tube and reacted at 450 W and 80 °C under microwave irradiation for a few minutes. After reaction, it was filtered to afford 8-naphthalimides **1** and **2**. Upon recrystallization from ethanol, the crystals of **1** (white crystals) and **2** (pale yellow crystals) were obtained.

Compound 1i. Mp: 98–100 °C (from ethanol). IR (KBr, cm^{-1}): 3066, 2957, 2927, 2866, 1704, 1663, 1628, 1589, 1512, 1496, 1435, 1416 1379, 1335; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.59 (d, $J = 7.3$ Hz, 2H), 8.23 (d, $J = 8.0$ Hz, 2H), 7.77 (t, $J = 7.7$ Hz, 2H), 7.15 (s, 1H), 6.95 (d, $J = 8.0$ Hz, 2H), 4.24–4.35 (dd, $J = 13.3$ and 13.4 Hz, 2H, CH_2), 3.02–3.04 (m, 2H, CH_2), 2.83–2.84 [m, 1H, C<u>H</u>$(CH_3)_2$], 2.24–2.26 (m, 2H, CH_2), 1.61–1.91 (m, 6H, CH_2), 1.27–1.29 (m, 3H), 1.26 [s, 6H, $(CH_3)_2$], 1.11 (s, 3H, CH_3), 1.01–1.03 (m, 1H); ^{13}C NMR (125 MHz): 18.1, 18.5, 19.2, 19.7, 20.0, 24.0, 26.1, 30.5, 32.6, 33.4, 34.4, 37.5, 37.8, 37.9, 38.1, 46.4, 49.8, 50.4, 122.4, 123.3, 123.8, 127.0, 128.1, 128.9, 130.1, 131.1, 132.2, 133.3, 135.2, 145.5, 147.4, 164.8. Anal. calcd. for $C_{32}H_{35}NO_2$: C, 82.54; H, 7.58; N, 3.01. Found: C, 82.71; H, 7.45; N, 3.14.

Compound 2e. Mp 152–154 °C (from ethanol). IR (KBr, cm^{-1}): 3469, 3055, 2938, 2876, 1705, 1663, 1617, 1586, 1571; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, $J = 7.2$ Hz, 1H), 8.59 (d, $J = 8.5$ Hz, 1H), 8.40 (d, $J = 7.8$ Hz, 1H), 8.05 (d, $J = 7.8$ Hz, Hz, 1H), 7.86 (t, $J = 8.1$ Hz, 1H), 7.14 (s, 1H), 6.95 (d, $J = 8.1$ Hz, 2H), 4.22–4.32 (dd, $J = 13.3$ and 13.3 Hz, 2H, CH_2), 3.03–3.05 (m, 2H, CH_2), 2.85–2.87 [m, 1H, C<u>H</u>$(CH_3)_2$], 2.24–2.26 (m, 2H, CH_2), 1.58–1.90 (m, 6H, CH_2), 1.28–1.31 (m, 3H), 1.26 [s, 6H, $(CH_3)_2$], 1.12 (s, 3H, CH_3), 1.02–1.04 (m, 1H); ^{13}C NMR (125 MHz): 18.2, 18.6, 19.2, 19.8, 20.0, 24.0, 26.0, 30.5, 32.6, 33.4, 34.4, 37.5, 37.8, 37.9, 38.1, 46.4, 49.8, 50.4, 122.4, 123.3, 123.8, 127.0, 128.1, 128.9, 130.0, 131.2, 132.2, 133.1, 135.2, 145.4, 147.5, 164.7. Anal. calcd. for $C_{32}H_{34}BrNO_2$: C, 70.58; H, 6.29; N, 2.57. Found: C, 70.41; H, 6.13; N, 2.72.

Compounds 3

The mixture of amines (2.1 mmol), water (10 mL), and 4-bromo-1,8-naphthalic anhydride (1.0 mmol) was blended together in a sealed and pressurized tube and reacted at 850 W and 100 °C under microwave irradiation for a few minutes. After reaction, the gum obtained was purified by silica column chromatography with petroleum ether–ethyl acetate (5:1) as the eluent. Upon recrystallization from ethanol, yellow crystals of **3** were obtained.

Compound 3a. Mp 229.9–231.6 °C (from ethanol). IR (KBr, cm^{-1}): 3496, 3371, 2959, 2930, 2870, 1683, 1636, 1618, 1573, 1549; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, $J = 7.2$ Hz, 1H), 8.46 (d, $J = 8.4$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.59 (t, $J = 7.8$ Hz, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 5.31 (s, 1H, NH), 4.13 (t, $J = 7.68$ Hz, 2H), 3.38–3.42 (m, 2H), 1.81–1.90 (m, 2H), 1.74–1.78 (m, 2H), 1.14 (t, $J = 7.4$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz): 11.8, 12.0, 21.4, 21.6, 41.3, 45.2, 104.2, 107.9, 120.6, 122.3, 124.7, 129.0, 129.9, 131.1, 134.7, 151.2, 163.4, 164.2; MS (ESI) m/z: 295 (M^+–1). Anal. calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.81; H, 6.98; N, 9.62.

Compound 3b. Mp 158.2–159.6 °C (from ethanol). IR (KBr, cm^{-1}): 3443, 2949, 2871, 1694, 1657, 1625, 1591; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, $J = 7.3$ Hz, 1H), 8.48 (d, $J = 8.5$ Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, Hz, 1H), 7.32–7.37 (m, 5H), 7.30–7.36 (m, 5H), 6.78 (d, $J = 7.4$ Hz, 1H), 5.58 (s, NH), 5.54 (s, 2H), 4.63 (d, $J = 5.1$ Hz, 2H); ^{13}C NMR (125 MHz): 48.4, 52.3, 110.3, 122.8, 123.8, 126.9, 127.6, 128.0, 128.2, 128.4, 128.8, 129.3, 129.7, 130.6,

131.5, 133.1, 133.7, 137.8, 149.0, 162.6, 163.7; MS (ESI) m/z: 392 (M^+). Anal. calcd. for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.44; H, 5.26; N, 7.28.

Compound 3c. Mp 231.4–232.8 °C (from ethanol). IR (KBr, cm^{-1}): 3382, 2956, 2931, 2865, 1685, 1635, 1571, 1544; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, $J = 8.5$ Hz, 1H), 8.49 (d, $J = 7.5$ Hz, 1H), 8.09 (d, $J = 8.6$ Hz, 1H), 7.65 (d, $J = 7.5$ Hz, Hz, 2H), 6.74 (d, $J = 7.4$ Hz, 1H), 5.24 (s, 1H, NH), 4.17 (t, $J = 7.6$ Hz, 2H), 3.44 (t, $J = 7.5$ Hz, 2H), 1.84–1.87 (m, 2H), 1.59–1.61 (m, 2H), 1.45–1.48 (m, 4H), 1.01–1.06 (m, 6H, CH_3); ^{13}C NMR (125 MHz): 14.1, 14.2, 20.3, 29.5, 30.3, 30.4, 43.0, 104.2, 108.0, 120.6, 122.3, 124.7, 129.1, 129.9, 131.1, 134.7, 151.2, 163.4, 164.2; MS (ESI) m/z: 323 (M^+–1). Anal. calcd. for $C_{20}H_{24}N_2O_2$: C, 74.01; H, 7.46; N, 8.64. Found: C, 74.15; H, 7.62; N, 8.46.

Compound 3d. Mp 165.4–167.1 °C (from ethanol). IR (KBr, cm^{-1}): 3420, 3045, 2918, 2832, 2796, 2775, 2752, 2730, 1675, 1631, 1600, 1560; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, $J = 7.9$ Hz, 1H), 8.41 (d, $J = 7.3$ Hz, 1H), 8.24 (d, $J = 8.5$ Hz, 1H), 7.66 (t, $J = 8$ Hz, 2H), 7.37 (d, $J = 7.9$ Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 1H), 4.90 (t, $J = 5.15$ Hz, 1H), 4.78 (t, $J = 5.6$ Hz, 1H), 4.09 (t, $J = 6.8$ Hz, 2H), 3.69 (s, 2H, OH), 3.66–3.69 (dd, $J = 4.9$ and 5.1 Hz, 2H); ^{13}C NMR (125 MHz): 44.8, 50.0, 58.4, 59.3, 108.1, 120.5, 122.3, 124.6, 128.9, 129.8, 131.0, 134.5, 151.2, 164.3; MS (ESI) m/z: 300 (M^+). Anal. calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.84; H, 5.14; N, 9.65.

Compounds 4

The mixture of amines (2.1 mmol), water (10 mL), and 3-nitro-4-bromo-1,8-naphthalic anhydride (1 mmol) was blended together in a sealed and pressurized tube and reacted at 850 W and 100 °C under microwave irradiation for a few minutes. After reaction, it was filtered and recrystallized in hot N,N-dimethylformamide–water solution (V_{DMF}:V_{water} = 4:1) to afford red-brown crystals of **4**.

Compound 4a. Mp 224.3–225.9 °C (from DMF-H_2O). IR (KBr, cm^{-1}): 3453, 2965, 2933, 2856, 2812, 1694, 1652, 1602, 1581, 1536; ^1H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H, NH), 9.25 (s, 1H), 8.65 (t, $J = 7.1$ Hz, 2H), 7.71 (t, $J = 7.8$ Hz, 1H), 4.18 (t, $J = 7.5$ Hz, 2H), 3.96 (t, $J = 5.4$ Hz, 2H), 1.73–1.91 (m, 4H), 1.03 (s, 6H, CH_3); ^{13}C NMR (125 MHz): 16.4, 17.2, 27.1, 35.6, 41.3, 45.2, 109.2, 122.7, 123.6, 126.5, 129.4, 129.6, 130.7, 132.1, 133.0, 149.5, 162.7, 163.8; MS (ESI) m/z: 340 (M^+–1). Anal. calcd. for $C_{18}H_{19}N_3O_4$: C, 66.33; H, 5.61; N, 12.31. Found: C, 66.19; H, 5.73; N, 12.42.

Compound 4b. Mp 233.5–234.7 °C (from DMF-H_2O). IR (KBr, cm^{-1}): 3441, 3060, 2923, 2851, 1699, 1655, 1601, 1537; ^1H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H, NH), 9.36 (s, 1H), 8.70 (d, $J = 7.4$ Hz, 1H), 8.63 (d, $J = 8.5$ Hz, 1H), 7.67 (d, $J = 8.3$ Hz, 1H), 7.26–7.65 (m, 10H), 5.38 (s, 2H), 5.10 (s, 2H); ^{13}C NMR (125 MHz): 43.3, 52.3, 110.2, 122.8, 124.0, 126.9, 127.6, 128.0, 128.2, 128.4, 129.1, 129.4, 129.7, 130.6, 131.4, 133.1, 133.7, 137.8, 149.0, 153.1, 162.6, 163.7; MS (ESI) m/z: 436 (M^+–1). Anal. calcd. for $C_{26}H_{19}N_3O_4$: C, 71.39; H, 4.38; N, 9.61. Found: C, 71.25; H, 4.51; N, 9.72.

Compound 4c. Mp 236.5–236.7 °C (from DMF-H_2O). IR (KBr, cm^{-1}): 3462, 3060, 2958, 2929, 2873, 1698, 1649, 1606, 1577, 1538; ^1H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H, NH), 9.32 (s, 1H), 8.68 (dd, $J = 7.4$ and 8.5 Hz, 2H), 7.71 (t, $J = 7.8$ Hz, 1H), 4.18 (t, $J = 7.5$ Hz, 2H), 3.99 (t, $J = 5.5$ Hz, 2H), 1.45–1.88 (m, 8H), 1.00 (s, 6H, CH_3); ^{13}C NMR (125 MHz): 14.0, 14.2, 19.9, 20.2, 30.1, 32.1, 49.2, 110.0, 122.8, 123.8, 126.7, 129.5, 129.8, 131.4, 133.1, 133.5, 149.4, 162.5, 163.5; MS (ESI) m/z: 368 (M^+–1). Anal. calcd. for $C_{20}H_{19}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.16; H, 6.47; N, 11.24.

Compound 4d. Mp 241.4–243 °C (from DMF-H_2O). IR (KBr, cm^{-1}): 3444, 3060, 2943, 2856, 2812, 2787, 2762, 2730, 1697, 1653, 1625, 1590; ^1H NMR (500 MHz, DMSO) δ 9.84 (s, 1H, NH), 8.78 (d, $J = 8.5$ Hz, 1H), 8.70 (s, 1H), 8.43 (d, $J = 7.4$ Hz, 1H), 7.72 (t, $J = 7.9$ Hz, 1H), 5.24 (t, $J = 4.8$ Hz, 1H), 4.78 (t, $J = 6.0$ Hz, 1H), 4.02 (t, $J = 6.7$ Hz, 2H), 3.86 (s, 2H, OH), 3.70–3.73 (dd, $J = 4.9$ and 4.9 Hz, 2H), 3.55–3.57 (m, 2H); ^{13}C NMR (125 MHz): 40.5, 52.2, 58.2, 60.1, 110.1, 122.8, 123.5, 126.4, 129.1, 129.3, 131.8, 133.6, 134.0, 150.5, 162.5, 163.6; MS (ESI) m/z: 344 (M^+–1). Anal. calcd. for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.51; H, 4.51; N, 12.35.

Compound 4e. Mp 245–247 °C (from DMF-H_2O). IR (KBr, cm^{-1}): 3447, 3226, 3060, 2919, 2851, 1705, 1663, 1599, 1575, 1543, 1511; ^1H NMR (500 MHz, $CDCl_3$) δ 10.74 (s, 1H, NH), 9.37 (s, 1H), 8.63 (d, $J = 7.4$ Hz, 1H), 8.24 (d, $J = 8.6$ Hz, 1H), 7.45 (t, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.1$ Hz, Hz, 4H), 7.06 (d, $J = 8.2$ Hz, 2H), 2.47 (s, 3H, CH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (125 MHz): 17.5, 18.5, 108.2, 112.9, 120.0, 122.9, 123.5, 125.0, 126.7, 127.5, 129.0, 129.1, 129.5, 130.9, 131.8, 132.7, 133.7, 135.0, 135.4, 136.1, 140.6, 144.9, 161.1, 162.4, 163.4; MS (ESI) m/z: 436 (M^+–1). Anal. calcd. for $C_{26}H_{19}N_3O_4$: C, 71.39; H, 4.38; N, 9.61. Found: C, 71.51; H, 4.20; N, 9.48.

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