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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis and evaluation of naphthalimides derivatives as free radical scavengers

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Abstract A facile and efficient microwave-assisted reaction of 1,8-naphthalic anhydride derivatives with primary amines, leading to the synthesis of 1,8-naphthalimides, has been developed. Subsequently, the free radical scavenging properties of the 1,8-naphthalimide derivatives were evaluated against 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$). The results showed that the scavenging activities of compounds **2a**, **NBNA**, **3b**, and **3c** were more efficient than that of the common synthetic antioxidant 2,6-diter-butyl-4-methylphenol (**BHT**), with IC_{50} values of 61.9, 54.0, 42.2, and 43.1 μM, respectively. The imide groups introduced at position 4 as well as the nitro functionality at position 3 of the naphthalene moiety were the major contributors to the free radical scavenging activities.

Keywords Naphthalimides derivatives · Microwave · Radical scavenging capacities

Introduction

It is known that free radicals have an important role in the pathogenesis of aging, many diseases, and cancers (Ames *et al.*, 1995; Halliwell and Grootveld, 1987; McDermott, 2000). The normal metabolic actions in the human body constantly generate free radicals and active oxygen. High levels of the endogenous metabolic products, including hydrogen peroxide (H_2O_2), extremely reactive hydroxyl, and several other free radicals produced by cells, cause damage to lipids, proteins, and DNA (Ames, 1998). Supplementation with radical scavengers could be important to prevent or minimize the damage (Ames, 1998). During the last few years, there has been considerable investment in efforts to develop cost-effective and efficient free radical scavenging agents by our workgroup (Pan *et al.*, 2004, 2007, 2008). Recently, the derivatives of naphthalimides were unexpectedly found to exhibit radical scavenging activities against $DPPH^{\bullet}$ radical in the initial test, and it aroused our interest to design and evaluate the naphthalimides as radical scavengers. The synthetic route was presented in Fig. 1.

Naphthalimides, which are characterized by the presence of a coplanar chromophore and, usually, a π-deficient aromatic system, as well as one or two basic side chains, constitute an important class of prodrugs in anticancer therapy (Kamal *et al.*, 2002; Braña *et al.*, 2003; Malviya *et al.*, 1992). They display high levels of antitumor activity toward multifarious murine and human tumor cells (Malviya *et al.*, 1992; Braña and Ramos, 2001). Two members of this class of compounds, amonifide and mitonafide, are undergoing clinical trials (Malviya *et al.*, 1992). Although the synthesis of 1,8-naphthalimide derivatives has been the object of numerous efforts, to the best of our knowledge, no 1,8-naphthalimide derivatives have been reported as free radical scavengers.

In order to explore the potential utility of naphthalimides as an economical free radical scavengers, the 1,8-naphthalimides (**1–3**) were synthesized using microwave irradiation as the energy source (Fig. 1). Microwave irradiation (Varma, 1999; Nüchter *et al.*, 2004; Kappe, 2004) has been

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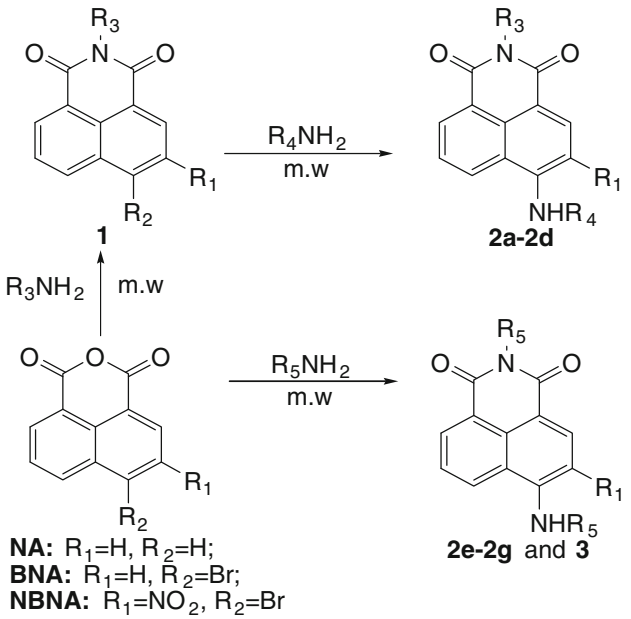


Fig. 1 Synthetic route of compounds **1–3**

considered as a green technology, and its level of energy consumption is low compared with that of most traditional methods. As well as being energy efficient, microwave heating can enhance the rate of chemical reactions and, in many cases, improve product yield. Thus, microwave irradiation was included in the synthesis of 1,8-naphthalimides **1–3**. And their free radical scavenging properties were determined using the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) (Shimada *et al.*, 1992; Lee *et al.*, 2005).

Materials and methods

Reagents and apparatus

2,6-Diter-butyl-4-methylphenol (BHT) and 1,1-diphenyl-2-picrylhydrazyl (DPPH$^{\bullet}$) were purchased from Sigma Chemicals Co. (St. Louis, MO, USA). Other chemicals were purchased from China National Medicine Group Shanghai Corporation (Shanghai, China). All chemicals and solvents used were of analytical grade. The reactions of 1,8-naphthalic anhydride derivatives with amines were done in WF-4000M microwave oven (Xian DEPA Biology technologies inc, Shanghai, China), and the UV-1100 spectrophotometer (Beijing Rayleigh Analytical Instrument Corporation, Beijing, China) was used to evaluate the radical activity. The NMR study was carried out by the instrument NMR (BRUKER AVANCE 500, BRUKER company, Switzerland), and the mass spectral studies were done using BRUKER ESQUIRE HCT instrument (BRUKER DALTON company, USA). Elemental analyses were determined in the apparatus Carlo Erba model 1106 (Carlo Erba company, Italy).

Synthesis

The reactions of 1,8-naphthalic anhydride (**NA**) or 4-bromo-1,8-naphthalic anhydride (**BNA**) with different amines were done in a sealed and pressurized tube to prepare N-substituted naphthalimides **1** in an ethanol mixture under 450 W of microwave irradiation. The reaction was completed within 5–10 min and the N-substituted products **1** were obtained in 65–92% yield (Table 1). It is important to point out that the work-up after the completion of this reaction is very simple. The mixture was cooled to room temperature, and the deposited product/crystals were obtained by filtration through Buchner funnel and then washed with a small volume of ethanol.

The synthesis of compounds **2a–2d** began with the condensation of naphthalimide **1k** with benzylamine, ethanolamine, propylamine, and butylamine in methoxyethanol, respectively, using microwave irradiation as the energy source. The products were purified by preparative silica gel thin-layer chromatography (TLC) using petroleum ether/ethyl acetate (5:1, v/v) as the eluent. Coupling of 4-bromo-1,8-naphthalic anhydride with benzylamine, butylamine, and propylamine at 850 W in a microwave oven afforded yellow crystals of **2e–2g** in good yield within a few minutes (Table 1).

In DMF, the condensation of 3-nitro-4-bromo-1,8-naphthalic anhydride (**NBNA**) and amines under 850 W microwave irradiation produced 3-nitro-4-amic-alkyl naphthalimides **3** in good yield (82–92%) (Table 1). The presence of the nitro group in 1,8-naphthalic anhydride led to higher yields than those of **2e–2g**. The work-up after the reaction was the same as that described for **1**, and afforded red powder or crystals of **3**.

Scavenging activity on DPPH$^{\bullet}$ radical

To evaluate the free radical scavenging activity, each compound was allowed to react with a stable free radical, 1,1-diphenyl-2-picrylhydrazyl radical (DPPH$^{\bullet}$) according to the method of Shimada *et al.* (1992) and Lee *et al.* (2005) with a little modification. In brief, each scavenger solution (0.1 ml) in DMF at different concentrations was added to solution [3.9 ml, 0.004% (w/v)] of DPPH$^{\bullet}$ in ethanol. The reaction mixture was incubated at 37°C. The scavenging activity on DPPH$^{\bullet}$ radical was determined by measuring the absorbance at 517 nm after 30 min. The scavenging activity was expressed as a percentage of scavenging activity on DPPH$^{\bullet}$ radical: $SC\% = [(A_{control} - A_{test})/A_{control})] \times 100\%$, where $A_{control}$ is the absorbance of the control

Table 1 The optimized parameters for synthesis of 1,8-naphthalimides **1–3**

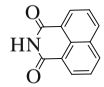
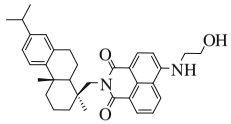
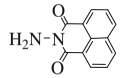
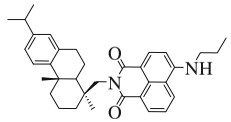
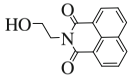
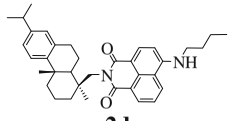
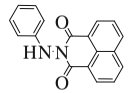
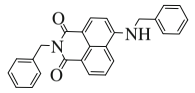
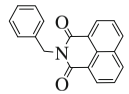
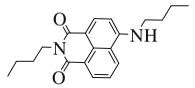
Compounds	Equality of amine[a]	Power (W)	Time (min)	Reaction temperature (°C)	Yields (%)	Compounds	Equality of amine[a]	Power (W)	Time (min)	Reaction temperature (°C)	Yields (%)
 **1a**	1.2	450	8	80	85	 **2b**	1.3	850	10	100	65
 **1b**	1.2	450	8	80	86	 **2c**	1.5	850	10	100	83
 **1c**	1.2	450	5	80	90	 **2d**	1.5	850	10	100	81
 **1d**	1.2	450	8	80	83	 **2e**	2.3	850	10	100	65
 **1e**	1.2	450	5	80	92	 **2f**	2.5	850	8	100	88

Table 1 continued

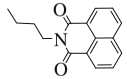
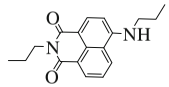
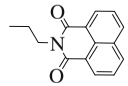
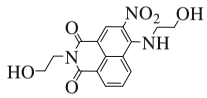
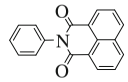
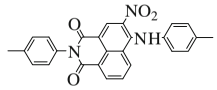
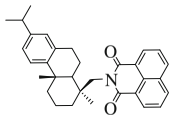
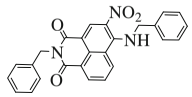
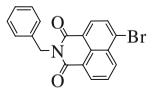
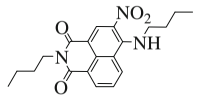
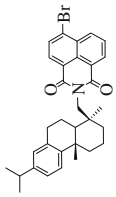
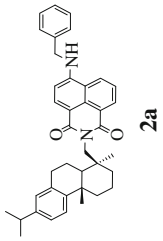
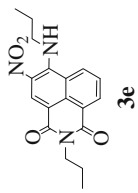
Compounds	Equality of amine[a]	Power (W)	Time (min)	Reaction temperature (°C)	Yields (%)	Compounds	Equality of amine[a]	Power (W)	Time (min)	Reaction temperature (°C)	Yields (%)
 **1f**	1.5	450	8	80	75	 **2g**	2.5	850	8	100	85
 **1g**	1.8	450	8	80	65	 **3a**	2.1	850	8	100	89
 **1h**	1.2	450	8	80	83	 **3b**	2.0	850	10	100	85
 **1i**	1.1	450	10	80	87	 **3c**	2.1	850	8	100	92
 **1j**	1.2	450	8	80	88	 **3d**	2.2	850	10	100	90

Table 1 continued

Compounds	Equality of amine[a]	Power (W)	Time (min)	Reaction temperature (°C)	Yields (%)
 **1k**	1.1	450	10	80	75
 **2a**	1.3	850	10	100	71

Compounds	Equality of amine[a]	Power (W)	Time (min)	Reaction temperature (°C)	Yields (%)
 **3e**	2.2	850	10	100	88

[a] Each dosage of 1,8-naphthalic anhydride, 4-bromo-1,8-naphthalic anhydride, and 3-nitro-4-bromo-1,8-naphthalic anhydride is 1 mmol, as well as that of **1k**

(DPPH$^{\bullet}$ solution without test sample) and A_{test} is the absorbance of the test sample (DPPH$^{\bullet}$ solution plus scavenger). The control contains all reagents except the scavenger. The values of IC_{50} for radical scavengers, the effective concentration at which 50% of DPPH$^{\bullet}$ radicals were scavenged were tested to evaluate the radical activity. All tests were performed in triplicate, and the mean was centered. A blank experiment was also conducted.

Results and discussion

We explored the free radical scavenging ability of the pure compounds **1**–**3**. Each compound was allowed to react with DPPH$^{\bullet}$ essentially as described (Shimada *et al.*, 1992; Lee *et al.*, 2005) but with a little modification. The values of IC_{50} for compounds **1**–**3**, the effective concentration at which 50% of DPPH$^{\bullet}$ radicals were scavenged were tested to evaluate the radical activity (Table 2). The IC_{50} of **BHT** was determined for comparison.

Table 2 shows that the radical scavenging ability of compounds **1** was less than that of **BHT**. The IC_{50} values were: **BHT**, 65.8 μM; **1a**, 149.4 μM; **1c**, 154.8 μM; **1g**, 179.2 μM; and **1f**, 182.6 μM. On the basis of this observation, it can be suggested that the presence of N-substituent groups in the imide segment had an important influence on the free radical scavenging ability. Neither the introduction of bromine at position 4 on the naphthalene moiety nor the chiral dehydroabiatyl substituent in the imide moiety improved their DPPH$^{\bullet}$ scavenging activity.

Table 2 Scavenging activity of compounds **1**–**3** against DPPH

Compounds	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]
NA	1773.8	**2b**	221.3
1a	149.4	**2c**	209.9
1b	186.7	**2d**	205.9
1c	154.8	**2e**	84.6
1d	147.1	**2f**	320.1
1e	142.6	**2g**	351.1
1f	182.6	**NBNA**	54.0
1g	179.2	**3a**	230.7
1h	129.5	**3b**	42.2
1i	165.6	**3c**	43.1
1j	237.8	**3d**	214.7
1k	208.1	**3e**	231.1
BNA	na	**BHT**	65.8
2a	61.9		

[a] IC_{50} = the effective concentration at which 50% of DPPH$^{\bullet}$ radicals were scavenged. Each experiment was done in duplicate at least three times, and the data presented are the average values (*na* not active)

The presence of an electron-donating substituent in position 4 of naphthalimides is known to increase both the electronic mobility (Bojinov *et al.*, 2003) and the electron densities and, hence, the stability of the radical. This would also contribute to their radical scavenging ability. On the basis of these hypotheses, some alkyl-amino groups were designed to inject into the naphthalene section to afford **2a**–**2g**. We expected compounds **2** to advance the scavenging ability against DPPH$^{\bullet}$. However, the scavenging activity was clearly weakened, except **2a** and **2e**, which were shown to be as potent as **BHT**, with IC_{50} 61.9 and 84.6 μM, respectively, implying the importance of the 4-substituent in the naphthalene moiety for the scavenging activity against DPPH$^{\bullet}$. Since all of the **2** compounds, except **2a** and **2e**, contain one or two soft side chains, we conclude that the flexibility of these side chains in naphthalimides should reduce the structural rigidity of the compounds and, consequently, their scavenging activity. In contrast, rigid groups in the naphthalene moiety, e.g., benzylamino, would lead to a favorable scavenging activity, such as that of **2a** and **2e**.

Nitryl was a good electron-withdrawal group, and it would damage the stabilization of DPPH$^{\bullet}$ for its capability of absorbing electron or radicals. In the presence of nitro group at 3-position of naphthalene portion, the scavenging activities of compounds **NBNA**, **3b**, and **3c** were found to be more efficient than that of **BHT**, with respective IC_{50} 54.0, 42.2, and 43.1 μM, indicating the importance of nitro functionality for the radical scavenging activities. Complexes **3a**, **3d**, and **3e** showed weaker activities for the presence of tender chain sides, which reduced their structural rigidity and then their free scavenging activities.

Based on the above observation, the groups introduced in imide and 4-position of naphthalene moiety, as well as nitro functionality appeared to be major contributors to the radical scavenging activity. The order was nitro functionality > the substituents introduced in 4-position of naphthalene moiety > the groups in imide.

Conclusions

In conclusion, we have demonstrated a rapid, simple, clean, and efficient method for the synthesis of 1,8-naphthalimides under microwave irradiation, and evaluated their scavenging ability against the free radical DPPH$^{\bullet}$. To our knowledge, this synthesis has not been described before, and it is very simple and useful. All of the synthetic 1,8-naphthalimide derivatives presented good free radical scavenging activity against DPPH$^{\bullet}$. Especially **2a**, **NBNA**, **3b**, and **3c** are more potent than the common synthetic antioxidant **BHT**. Besides, the production costs will be very low and that is of great importance for the production of radical scavengers. More work is in progress to evaluate the intrinsic toxicities of compounds **1**–**3**.

Synthesis of the derivatives

Synthesis

(a) General procedure for the preparation of **1**: The mixture of primary amine (1.1–1.8 mmol), ethanol (10 ml), and 1,8-naphthalic anhydride (or 4-bromo-1,8-naphthalic anhydride) (1.0 mmol) was blended together in a sealed and pressurized tube and reacted at 80°C and 450 W under microwave irradiation for a few minutes. Once cooled to room temperature, pale powder or crystals of **1** were obtained.

(b) General procedure for the preparation of **2a**–**2d**: The mixture of amines (2.3–2.5 mmol), methoxyethanol (10 ml), and **1k** (1.0 mmol) was blended together in a sealed and pressurized tube and reacted at 100°C and 850 W 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. Yellow powders of **2a**–**2d** were obtained.

(c) General procedure for the preparation of **2e**–**2g**: The mixture of amines (2.3–2.5 mmol), methoxyethanol (10 ml), and 4-bromo-1,8-naphthalic anhydride (1.0 mmol) was blended together in a sealed and pressurized tube and reacted at 100°C and 850 W under microwave irradiation for a few minutes. Once cooled to the room temperature, yellow crystals of **2e**–**2g** were obtained.

(d) General procedure for the preparation of **3**: The mixture of amines (2.0–2.3 mmol), DMF (10 ml), and 4-bromo-3 nitro-1,8-naphthalic anhydride (1.0 mmol) was blended together in a sealed and pressurized tube and reacted at 100°C and 850 W under microwave irradiation for a few minutes. Once cooled to room temperature, red crystals of **3** were obtained.

Spectra data for representative compounds

(a) Compound **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, $J = 7.3$ Hz, 1H), 8.44 (d, $J = 8.4$ Hz, 1H), 8.11 (d, $J = 8.1$ Hz, 1H), 7.62 (t, $J = 7.9$ Hz, 1H), 7.37–7.45 (m, 5H), 7.14 (t, $J = 8.1$ Hz, 2H), 6.94 (t, $J = 8.02$ Hz, 2H), 6.78 (d, $J = 8.3$ Hz, 1H), 5.56 (s, 1H, NH), 4.6 (d, $J = 5.0$ Hz, 2H), 4.20–4.33 (dd, $J = 13.2$ Hz, 2H), 3.01 (d, $J = 5.6$ Hz, 2H), 2.80 (t, $J = 5.4$ Hz, 2H), 2.22 (m, 2H), 1.61 (m, 1H), 1.1.36–1.47 (m, 7H), 1.45 (m, 3H), 1.29 (m, 10H), 1.24 (s, 3H), 1.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 148.8, 147.7, 145.4, 135.2, 134.4, 131.3, 129.5, 126.9, 125.8, 124.7, 123.9, 123.6, 123.1, 120.2,

110.7, 104.4, 60.5, 49.6, 46.6, 45.5, 39.9, 38.2, 37.8, 37.5, 33.4, 30.5, 26.0, 24.0, 19.9, 19.2, 18.7; MS (ESI) *m/z*: 569 (M–H); Anal. calcd for $C_{34}H_{40}N_2O_3$: C, 82.07; H, 7.42; N, 4.91. Found: C, 82.21; H, 7.26; N, 4.86.

(b) Compound **2b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, $J = 7.3$ Hz, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 8.1$ Hz, 1H), 7.48 (t, $J = 7.9$ Hz, 1H), 7.13 (d, $J = 8.2$ Hz, 1H), 6.94 (t, $J = 8.02$ Hz, 2H), 6.61 (d, $J = 8.3$ Hz, 1H), 5.76 (s, 1H, NH), 4.15–4.29 (d, $J = 5.0$ Hz, 2H), 4.05 (m, $J = 13.2$ Hz, 2H), 3.52 (dd, $J = 13.2$ Hz, 2H), 3.01 (d, $J = 5.6$ Hz, 2H), 2.22 (m, 2H), 1.61 (m, 1H), 1.1.36–1.47 (m, 7H), 1.45 (m, 3H), 1.29 (m, 10H), 1.24 (s, 3H), 1.10 (s, 1H), 1.07 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 165.6, 165.2, 149.3, 147.6, 145.4, 135.1, 134.4, 131.2, 129.6, 126.9, 125.8, 124.7, 123.9, 123.6, 123.1, 120.2, 110.7, 104.4, 60.5, 49.6, 46.6, 45.5, 39.9, 38.2, 37.8, 37.5, 33.4, 30.5, 26.0, 24.0, 19.9, 19.2, 18.6; MS (ESI) *m/z*: 523 (M–H); Anal. calcd for $C_{34}H_{40}N_2O_3$: C, 77.83; H, 7.68; N, 5.34. Found: C, 73.94; H, 7.30; N, 5.07.

(c) Compound **2c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, $J = 7.2$ Hz, 1H), 8.43 (1H, d, $J = 8.4$ Hz), 8.08 (1H, d, $J = 8.3$ Hz), 7.57 (1H, t, $J = 7.9$ Hz), 7.15 (1H, d, $J = 8.1$ Hz), 6.96 (2H, t, $J = 8.1$ Hz), 6.71 (1H, d, $J = 8.4$ Hz), 5.33 (1H, s, NH), 4.20–4.32 (2H, dd, $J = 13.2$ Hz), 3.37 (2H, m), 2.84–3.04 (3H, m), 2.21–2.25 (2H, m), 1.75 (1H, m), 1.36–1.47 (6H, m), 1.45 (2H, m), 1.29 (4H, m), 1.31 (3H, s), 1.24 (6H, s), 1.10 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 165.7, 165.1, 149.3, 147.7, 145.4, 135.2, 134.5, 131.2, 129.7, 126.9, 125.6, 124.6, 123.9, 123.4, 120.1, 110.5, 104.4, 49.6, 46.6, 39.9, 38.2, 37.9, 37.5, 33.5, 30.6, 26.0, 24.0, 22.8, 19.9, 19.2, 18.7, 11.6; MS (ESI) *m/z*: 521 (M–H); Anal. calcd for $C_{35}H_{42}N_2O_2$: C, 80.42; H, 8.10; N, 5.36. Found: C, 80.59; H, 8.14; N, 5.28.

(d) Compound **2d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, $J = 7.2$ Hz, 1H), 8.43 (d, $J = 8.3$ Hz, 1H), 8.07 (d, $J = 8.3$ Hz, 1H), 7.57 (t, $J = 7.9$ Hz, 1H), 7.15 (d, $J = 8.1$ Hz, 1H), 6.95 (t, $J = 8.1$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 1H), 5.30 (s, 1H, NH), 4.20–4.34 (dd, $J = 13.2$ Hz, 2H), 3.39 (m, 2H), 2.84–3.04 (m, 3H), 2.21–2.25 (m, 2H), 1.75 (m, 1H), 1.36–1.47 (m, 6H), 1.45 (m, 2H), 1.29 (m, 4H), 1.31 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 165.7, 165.1, 149.3, 147.7, 145.4, 135.2, 134.5, 131.2, 129.7, 126.9, 125.6, 124.6, 123.9, 123.6, 123.4, 120.1, 110.4, 104.3, 49.5, 46.6, 43.4, 39.9, 38.2, 37.8, 37.5, 33.5, 31.1, 30.6, 26.1, 24.0, 20.3, 19.9, 19.2, 18.7, 13.8; MS (ESI) *m/z*: 535 (M–H); Anal. calcd for $C_{36}H_{44}N_2O_2$: C, 80.56; H, 8.26; N, 5.22. Found: C, 80.44; H, 8.38; N, 5.11.

(e) Compound **2e**: ^{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, 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); MS (ESI) *m/z*: 436 (M–H); 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.

(f) *Compound* **2f**: ^{1}H 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, 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), 1.86 (m, 2H), 1.60 (m, 2H), 1.45–1.48 (m, 4H), 1.01–1.06 (m, 6H, CH_3); MS (ESI) *m/z*: 323 (M–H); 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.

(g) Compound **2g**: ^{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 (dd, 2H), 1.81 (dd, 2H), 1.74 (dd, 2H), 1.14 (t, $J = 7.4$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H); MS (ESI) *m/z*: 295 (M–H); 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.

(h) Compound **3a**: ^{1}H 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), 3.73 (dd, $J = 4.9$ Hz, 2H), 3.56 (m, 2H); MS (ESI) *m/z*: 344 (M–H); 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.

(i) Compound **3b**: ^{1}H 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, 4H), 7.06 (d, $J = 8.2$ Hz, 2H), 2.47 (s, 3H, CH_3), 2.41 (s, 3H, CH_3); MS (ESI) *m/z*: 436 (M–H); 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.

(j) Compound **3c**: ^{1}H 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); MS (ESI) *m/z*: 436 (M–H); 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.

(k) Compound **3d**: ^{1}H 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), 4.16–4.19 (t, $J = 7.5$ Hz, 2H), 3.97–4.00 (t, $J = 5.5$ Hz, 2H), 1.45–1.88 (m, 8H), 1.00 (s, 6H, CH_3); MS (ESI) *m/z*: 368 (M–H); 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.

(l) Compound **3e**: ^{1}H 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); MS (ESI) *m/z*:340 (M–H); 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.

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