Facile Synthesis of New Imidazoles from Direct Reaction of 2,3-Diamino-1,4-naphthoquinone with Aldehydes

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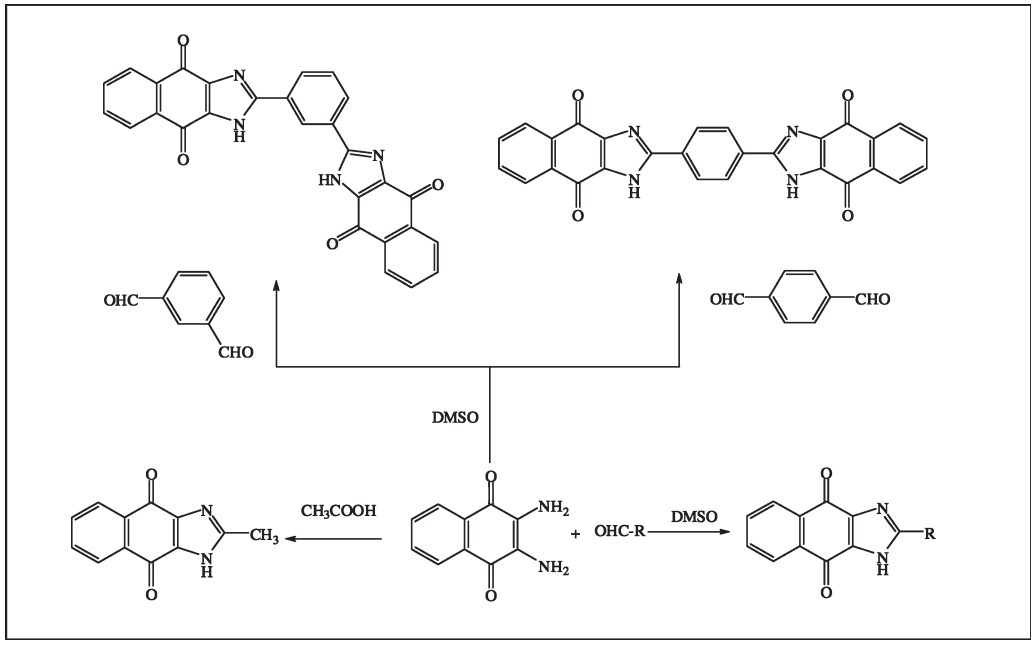

New imidazoles were easily prepared from 2,3-diamino-1,4-naphthoquinone and stoichiometric quantities of the appropriate aldehydes in dimethyl sulfoxide as a solvent. The reaction proceeded for few hours. The procedure can be generalized to different classes of aldehydes. 2-Methyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione was also obtained in good yield during refluxing of 2,3-diaminonaphthoquinone in acetic acid. The structure of the newly synthesized imidazoles was extensively investigated using NMR experiments.

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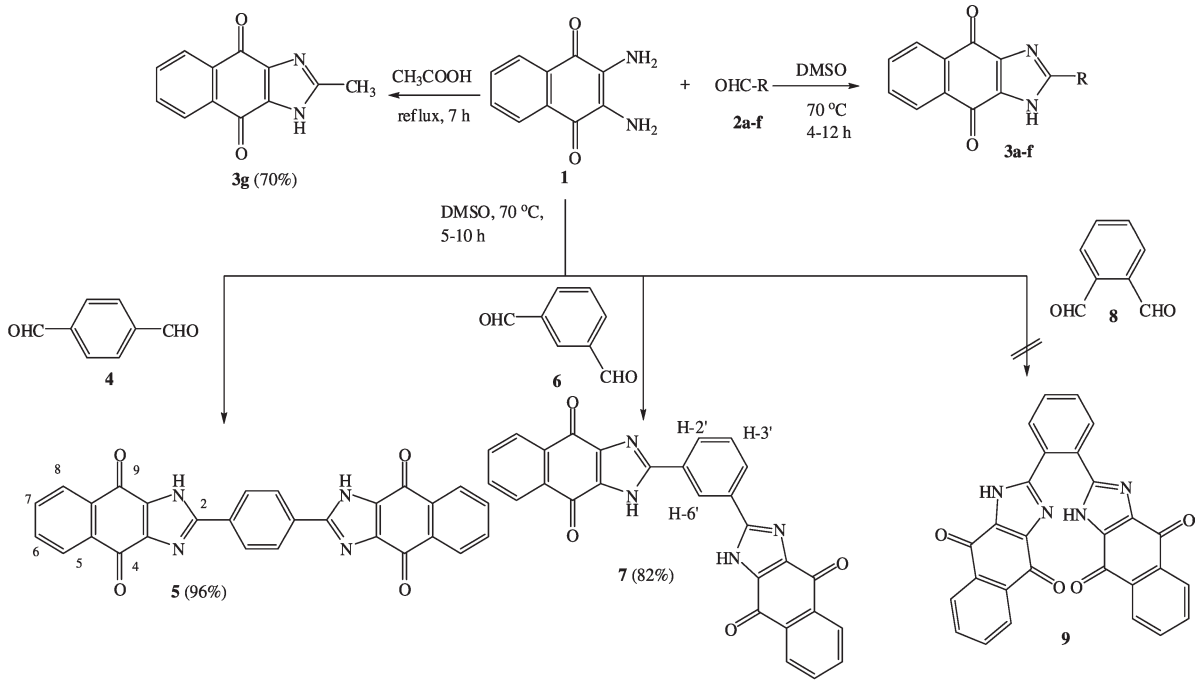
INTRODUCTION

Heterocyclic compounds containing the quinone group represent an important class of biologically active molecules [1]. Some benzimidazole-4,7-dione derivatives have been found to exhibit cytotoxic activity against human lymphoblastic leukemia, non-Hodgkin lymphoma, and other cancer cell lines [2,3]. The compounds also showed antifungal activities [4] and inhibited protozoal purine nucleoside phosphorylase. [5] It was recently reported that some benzimidazoledione derivatives strongly inhibited the proliferation of vascular smooth muscle cells [6] and human umbilical vein endothelial cells. [7] Imidazoles are common scaffolds in many compounds of significant biological activity [8,9] and have attracted the attention of synthetic chemists for over a century. [10] Imidazoles are subunits of highly significant biomolecules, including biotin, the essential amino acid histidine, histamine, the pilocarpine alkaloids [9], and other alkaloids, which have been shown to exhibit interesting biological activities, such as antimicrobial, anticryptococcal, inhibition of nitric oxide synthase, and cytotoxic activities. [11] Imidazole derivatives can be further substituted on the nitrogen atom so that the electron density of the chromophore can be changed. This functionalization will remove the possibility of tautomerism and introduces a new potentially useful chemical variable for the optimization of nonlinear optical (NLO) activity of the

Scheme 1. Synthesis of mono- and bisimidazoles from 2,3-diamino-1,4-naphthoquinone (**1**).



a: R = C_6H_5- (85%); **b**: R = 4-H_3C-OC_6H_4- (90%), **c**: R = 4-Cl-C_6H_4- (80%); **d**: R = 3,4-O-CH_2-OC_6H_3- (94%); **e**: R = 2-Furyl (76%) and **f**: R = 4-[2.2]Paracyclophanyl (74%)

chromophore (e.g., introduction of groups with suitable electronic properties). For the practical application of second-order NLO materials, not only a high hyperpolarizability but also good thermal stability is required. In this respect, promising candidates are (benz)imidazole derivatives. [11,12] Due to their optoelectronic properties, aryl-imidazophenanthrolines play important roles in materials science and medicinal chemistry [13–15]. 2-Phenyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione was formed as a side product in the reaction of 2,3-diamino-1,4-naphthoquinone (**1**) with diethyl benzylidenemalonate [16]. Recently, Ashraf *et al*. reported the synthesis of biologically active heterocycles such as (*Z*)-methyl 2-[(*Z*)-2-(4-arylimino)-4-oxo-3-phenyl-1,3-thiazolidin-5-ylidene]acetates. One derivative of 1,3-thiazolidine showed moderate antiproliferative *in vitro* activity against hepatocellular carcinoma Hep-G2, whereas another 1,3-thiazolidine exhibited effective antioxidant activity compared to ascorbic acid [17]. Additionally, 4-oxo-3-(propan-2-ylideneamino)-thiazolidine-5-ylidene)acetates have shown antitumor and antioxidant activities [18]. We have recently reported the synthesis of an imidazolone bearing a paracyclophanyl moiety from the reaction of paracyclophanyl nitrone with phenyl isocyanate [19]. To the best of our knowledge, direct preparation of imidazoles derived by 2,3-diaminonaphthoquinone and the corresponding aldehydes has been not reported.

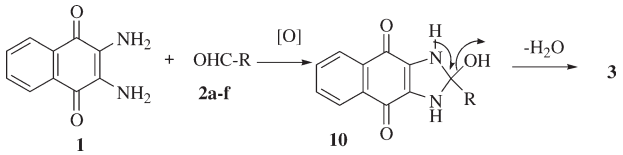
RESULTS AND DISCUSSION

Gentle heating of 2,3-diamino-1,4-naphthoquinone (**1**) and various aromatic aldehydes **2a-f** at 70°C in the minimum amount of DMSO produced the corresponding imidazoles **3a-f** in 74–94% yields (Scheme 1). The yield of **3f** is slightly lower than those of the other products. The role of DMSO is presumably to cosolubilize starting compounds of markedly different polarities, and perhaps also to oxidize an intermediate [9]. In similar fashion, reaction of **1** with terephthalaldehyde (**4**) and isophthalaldehyde (**6**) gave the bisimidazoles **5** and **7**, respectively. The yield of compound **7** is lower than that of **5**, and the reaction required twice as long (10 h) as production of **5** (5 h).

MM2 calculations [20] indicate that the cross-linked compound **7** has a minimum energy of 39.07 Kcal mol^{-1}, whereas the linear bisimidazole **5** has a minimum energy 38.78 Kcal mol^{-1}. Consistent with the thought that rate and yield inversely reflect steric hindrance, reaction of **1** with phthalaldehyde **(8)** did not give the corresponding bisimidazole **9**, even upon prolonged heating. Heating of **1** in glacial acetic acid at reflux afforded 2-methyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (**3g**; Scheme 1).

The IR spectrum of each product showed an NH absorption between 3450–3350 cm^{-1}, two C=O absorptions between 1690–1680 cm^{-1}, and a C=N absorption

Scheme 2. Condensation mechanism of **1** with aldehydes **2a-f**.



between 1630–1610 cm^{-1}. Each assigned molecular formula is supported by a molecular ion in the mass spectrum, and by elemental analysis. NMR signals were assigned with the aid of COSY, HSQC, and HMBC experiments. [21] In the ^{1}H-NMR of each naphthimidazoledione subunit, the imidazole NH gives a broad singlet at δ_H = 14.5–14.1. The naphthimidazoledione subunits appear to have two-fold symmetry; the ^{1}H signals are approximate AA'XX' patterns at δ_H = 8.12–8.08 (H-5,8) and 7.87–7.82 (H-6,7). Such symmetry is only possible if the NH proton exchanges between the two nitrogens; consistent with this idea, the three ^{13}C lines observed for each naphthoquinone part structure are broadened. The aryl groups on C-2 give characteristic NMR signals. For example, the *p*-anisyl group of **3b** has a signal for the methoxyl group, at δ_H = 3.84, to which the other carbons and protons in the *p*-anisyl unit correlate in stepwise fashion. The imino carbon C-2, which resonates at δ_C = 152.5, gives HMBC correlation with H-2′ at δ_H = 8.18. Similarly, the *p*-chloro compound **3c** shows HMBC correlation between its imino carbon (δ_C = 151.3) and H-2′ (δ_H = 8.25). The piperonal derivative **3d** gives a two-proton singlet at δ_H = 6.13 for the methylene protons, and a three-spin aromatic system for the benzodioxole unit.

In compound **3f**, the ^{1}H-NMR revealed eight proton signals for the ethano-bridges, between δ_H = 2.80–3.32. The seven paracyclophane aromatic protons appeared between δ_H = 6.35–7.08. Compound **3g** gave a methyl singlet at δ_H = 2.45, in addition to the usual signals for the naphthimidazoledione substructure.

The NMR spectra of compounds **5** and **7** indicated their symmetry: each structure showed a single set of naphthimidazoledione signals, with integrals requiring two naphthimidazolediones and a single central phenylene unit. The *p*-phenylene protons of **5** appeared as a singlet at δ_H = 7.85, whereas the *m*-phenylene group of **7** showed three types of protons as expected. The signal at δ_C = 151.91 is assigned as C-2 (C=N) not C-1′, based on its HMBC correlations with H-6′ and H-2′ (δ_H = 9.10 and 8.32, respectively), both of which are three bonds away.

The mechanism of the reaction can be described as due to condensation reaction between **1** and **2**, with partial oxidation, to form intermediate **10**. Elimination of water from **10** would produce imidazoles **3** (Scheme 2). Dehydration might also occur before oxidation.

CONCLUSION

The reaction of aldehydes with 2,3-diamino-1,4-naphthoquinone (**1**) in DMSO constitutes a facile synthesis of imidazoles, and reaction of dialdehydes with **1** permits synthesis of symmetrical bisimidazolonaphthoquinones. Compound **3g**, formally derived from **1** and acetaldehyde, is instead prepared by heating **1** in acetic acid.

EXPERIMENTAL

Melting points were determined on using open capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded with Shimadzu 408 instrument using potassium bromide pellets. NMR spectra were recorded on a Bruker AV-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts are expressed as δ (ppm) with DMSO-d_6 as a solvent, b = broad, s = singlet, and m = multiplet. Coupling constants *(J)* are expressed in Hz. The mass spectra (70 eV, electron impact mode) were recorded on Varian MAT 312 instruments. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt. TLC was performed on analytical Merck 9385 Silica aluminum sheets (Kieselgel 60) with PF_{254} indicator. TLC's were viewed λ_{max} = 254 nm UV.

Starting materials. 2,3-Diamino-1,4-naphthoquinone (**1**) was prepared according to literature [16].

General procedure: Reactions of 2,3-diaminonaphthalene-1,4-dione (1) with aldehydes 1a-f; synthesis of 2-(substituted)-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones. Equimolar amounts of 2,3-diaminonaphthalene-1,4-dione (**1**, 0.188 g, 1 mmol) and the appropriate aldehyde (1 mmol) in DMSO (5–10 mL) was heated at 70°C for 4–12 h. The reaction was followed by TLC analysis The reaction mixture was cooled and the precipitate obtained was filtered, washed with cold ethanol, and recrystallized from appropriate solvents.

2-Phenyl-1H-naphtho[2,3-d]imidazole-4,9-dione (3a). Yield 0.233 g (85%), m.p. = 340–341°C (339–342°C) [16].

2-(4′-Methoxyphenyl)-1H-naphtho[2,3-d]imidazole-4,9-dione (3b). Orange crystals (acetonitrile), 0.274 g (90%), mp 320–322°C (dec). IR: 3400 (NH), 2110 (Ar—CH), 2920 (Ali—CH), 1690, 1685 (CO), 1630 (C=N), 1610, 1580 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 14.14 (bs, 1H; NH), 8.18 (d, *J* = 8.7, 2H; H-2′), 8.08 (m, 2H; H-5,8). 7.83 (m, 2H; H-6,7), 7.09 (d, *J* = 8.7, 2H; H-3′), 3.84 (s, 3H; OCH_3). ^{13}C-NMR: 161.1 (C-4′), 152.5 (C-2), 133.7 (C-6,7), 132.7 (C-4a,8a), 128.5 (C-2′), 126.2 (C-5,8), 121.0 (C-1′), 114.4 (C-3′), 55.3 (CH_3). C-3a,9a and C-4,9 were not observed. MS: m/z: 304 (M^+, 100), 289 (22), 275 (14), 261 (17), 233 (6), 171 (8), 134 (26), 130 (13), 104 (10), 88 (6), 76 (16). *Anal. Calcd.* for $C_{18}H_{12}N_2O_3$ (304.30): C, 71.05; H, 3.97; N, 9.21. Found: C, 70.90; H, 4.03; N, 9.15.

2-(4′-Chlorophenyl)-1H-naphtho[2,3-d]imidazole-4,9-dione (3c). Violet crystals (ethanol), 0.246 g (80%), mp 300–302°C. IR: 3450 (NH), 3115 (Ar—CH), 2950 (Ali—CH), 1690, 1684 (CO), 1628 (C=N), 1594, 1580 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 14.46 (bs, 1H; NH), 8.25 (d, *J* = 7.9, 2H; H-2′), 8.12 (m, 2H; H-5,8), 7.87 (m, 2H; H-6,7), 7.64 (d, *J* = 7.9, 2H; H-3′). ^{13}C-NMR: 151.3 (C-2), 135.3 (C-4′), 133.9 (C-6,7), 132.8

(C-4a,8a), 129.1 (C-3′), 128.6 (C-2′), 127.5 (C-1′), 126.3 (C-5,8). C-3a,9a and C-4,9 were not observed. MS (FAB): m/z: 309 (M + 1, 30), 308 (M^+, 100). *Anal. Calcd.* for $C_{17}H_9ClN_2O_2$ (308.72): C, 66.14; H, 2.94; Cl, 11.48; N, 9.07. Found: C, 66.00; H, 2.86; Cl, 11.38; N. 9.07.

2-(Benzo[d][1,3]dioxol-5-yl)-1H-naphtho[2,3-d]imidazole-4,9-dione (3d). Violet crystals (ethanol), 0.299 g (94%), mp 230°C (dec). IR: 3450 (NH), 3090 (Ar—CH), 3080 (Ali—CH), 1685, 1680 (CO), 1625 (C=N), 1592, 1580 (Ar and C=C) $cm^{-1.}$ ^{1}H-NMR: 14.16 (bs, 1H; NH), 8.09 (m, 2H; H-5,8), 7.84 (m, 2H; H-6,7), 7.80 (dd, J = 8.6, 1H; H-6′), 7.75 (d, J, 1H; H-2′), 7.09 (d, J = 8.6, 1H; H-5′), 6.13 (s, 2H; CH_2). ^{13}C-NMR: 147.8 (C-3′,4′), 133.8 (C-6,7), 132. (C-4a,8a), 126.2 (C-5,8), 123. (C-1′), 121.7 (C-6′), 108.8 (C-5′), 106.6 (C-2′), 101.7 (CH_2). C-4a,8a and C-1′ were observed *via* HMBC correlations; C-2, C-3a,9a, and C-4,9 were not observed. MS: m/z: 318 (M^+, 100), 290 (4), 261 (4), 232 (5), 204 (14), 171 (19), 159 (16), 148 (20), 130 (12), 104 (20), 88 (16), 76 (13), 50 (14), 40 (10). *Anal. Calcd.* for $C_{18}H_{10}N_2O_4$ (318.28): C, 67.92; H, 3.17; N, 8.80. Found: C, 67.80; H, 3.10; N. 8.72.

2-(Furan-2-yl)-1H-naphtho[2,3-d]imidazole-4,9-dione (3e). Brick red crystals (methanol), 0.307 g, (76%), mp 340–342°C (dec). IR: 3420 (NH), 3080 (Ar—CH), 3065 (Ali—CH), 1690, 1685 (CO), 1615 (C=N), 1590, 1560 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 14.5 (bs, 1H; NH), 8.10 (m, 2H; H-5,8), 7.98 (m, 1H; H-5′), 7.86 (m, 2H; H-6,7), 7.36 (m, 1H; H-3′), 6.75 (m, 1H; H-4′). MS (FAB): m/z: 264 (M^+, 100). *Anal. Calcd.* for $C_{15}H_8N_2O_3$ (264.24): C, 68.18; H, 3.05; N, 10.60. Found: C, 68.00; H, 3.00; N. 10.50.

2-(4′-[2.2]Paracyclophanyl)-1H-naphtho[2,3-d]imidazole-4,9-dione (3f). Orange crystals (ethanol), 0.195 g (74%), mp 330°C. IR: 3350 (NH), 3075 (Ar—CH), 3060 (Ali—CH), 1684, 1680 (CO), 1620 (C=N), 1590, 1584 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 8.34–8.40 (m, 2H; H-5,8); 8.13–8.18 (m, 2H; H-6,7), 7.03–7.08 (m, 1H, 8′-H; PC-H), 6.85 (d, 1H; 5′-H, PC-H), 6.73 (dd, 1H; 16′-H, PC-H), 6.60 (m, 2H; 7′-, 15′-H, PC-H), 6.52 (dd, 1H; 13′-H, PC-H), 6.35 (dd, 1H; 12′-H, PC-H), 3.32 (ddd, 1H; 2-H_s, ethano bridge), 3.22–3.24 (m, 1H; 9-H_a, ethano bridge), 3.13 (ddd, 1H; 10′-H_s, ethano bridge), 3.10–3.14 (ddd, 1H; 1-H_s, ethano bridge), 3.20 (ddd, 1H; 10-H_a, ethano bridge), 2.92 (ddd, 1H; 9′-H_s, ethano bridge), 2.85 (ddd, 1H; 1-H_a, ethano bridge), 2.80 (ddd, 1H; 2′-H_a, ethano bridge). NH was not observed. ^{13}C-NMR: 179.2 (CO), 178.7 (CO), 153.4 (C=N), 138.6, 137.6, 138.2, 135.3, 134.2, 134.1, 133.6, 133.4, 133.1, 132.9, 132.8, 132.7, 132.5, 131.3, 129.0, 128.7, 127.6, 127.4, 126.5 (PC—C, Ar—C), 124.0 (PC-C-5) 36.3 (CH_2-1), 35.3 (CH_2-9), 35.0 (CH_2-1), 33.8 (CH_2-2). MS: m/z: 404 (40), 300 (100), 273 (14), 242 (18), 228 (4), 105 (24), 77 (10). *Anal. Calcd.* for $C_{27}H_{20}N_2O_2$ (404.46): C, 80.18; H, 4.98; N, 6.93. Found: C, 80.00; H, 5.00; N. 6.90.

2-Methyl-1H-naphtho[2,3-d]imidazole-4,9-dione (3g). A solution of 1 (0.188 g, 1 mmol) in glacial acetic acid (30 mL) was heated at reflux for 7 h. The reaction mixture was cooled and the precipitate obtained was filtered and washed with acetic acid. The product obtained was dissolved in acetone (5 mL) and applied on PLC by silica gel (Toluene: ethyl acetate: 10:1). The product was recrystallized from ethanol to give gray crystals, 0.148 g (70%), mp = 350 dec. IR: 3430 (NH), 3112 (Ar—CH), 2940 (Ali—CH), 1686, 1682 (CO), 1620 (C=N), 1580 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 13.72 (bs, 1H; NH), 8.06 (m, 2H; H-5,8), 7.83 (m, 2H; H-6,7), 2.46 (s, 3H; CH_3). ^{13}C-NMR: 152.6 (C-2), 133.7 (C-6,7), 132.5 (C-4a,8a), 126.1 (C-5,8), 14.0 (CH_3). C-3a,9a and C-4,9 were not observed. MS: m/z: 212 (M^+, 100), 198 (16), 184 (24), 171 (32), 155 (10), 143 (6), 130 (22), 115 (16), 103 (22), 97 (7), 88 (10), 76 (22), 69 (10), 55 (14), 44 (54). *Anal. Calcd.* $C_{12}H_8N_2O_2$ (212.20): C, 67.92; H, 3.80; N, 13.20. Found: C, 67.80; H, 3.84; N, 13.10.

Reactions of 2,3-diaminonaphthalene-1,4-dione (1) with dialdehydes 4 and 6. A mixture of 2,3-diamino-1,4-naphthoquinone (1, 0.376 g, 2 mmol) and bisaldehyde (0.134 mg, 1 mmol) in DMSO (5–10 mL) was heated at 70°C for 5 h (for compound **5**) and 10 h (for compound **7**). The reaction was followed by TLC analysis. The reaction mixture was cooled and the precipitate obtained was filtered and recrystallized from DMF to give pure products **5** or **7**.

2,2′-(1,4-Phenylene)bis(1H-naphtho[2,3-d]imidazole-4,9-dione) (5). Orange crystals, (0.451 g, 96%), mp 350–352°C (dec). IR: 3450 (NH), 3100–3060 (Ar—CH), 2980–2860 (Ali—CH), 1686, 1680 (CO), 1610 (C=N), 1592, 1570 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 14.40 (s, 2H; NH), 8.10 (m, 4H; H-5,8), 7.85 (s, 4H; H-2′), 7.82 (m, 4H; H-6,7). ^{13}C-NMR: 186.8 (C-4,9), 161.2 (C-2), 152.1 (C-1′), 133.7 (C-6,7), 132.9 (C-4a, 8a), 128.3 (C-2′), 126.4 (C-5,8). C-3a,9a were not observed. MS: m/z: 470 (M^+, 100), 442 (14), 300 (30), 235 (6), 207 (10), 171 (10), 130 (14), 115 (18), 91 (19). *Anal. Calcd.* for $C_{28}H_{14}N_4O_4$ (470.44): C, 71.49; H, 3.00; N, 11.91 Found: C, 71.30; H, 3.00; N. 11.80.

2,2′-(1,3-Phenylene)bis(1H-naphtho[2,3-d]imidazole-4,9-dione) (7). Obtained as orange crystals, 0.385 g (82%), mp 350–352°C (dec). IR: 3400 (NH), 3106–3070 (Ar—CH), 2970–2830 (Ali—CH), 1685, 1680 (CO), 1613 (C=N), 1590, 1574 (Ar and C=C) cm^{-1}. ^{1}H-NMR: 14.58 (b, 1H; NH), 9.10 (bs, 1H; H-6′), 8.32 (dd, J = 7.8, 1.3, 2H; H-2′), 8.09 (m, 4H; H-5,8), 7.83 (m, 4H; H-6,7), 7.69 (t, J = 7.8, 1H; H-3′). ^{13}C-NMR: 151.9 (C-2), 133.8 (C-6,7), 132.8 (C-4a,8a), 129.6 (C-3′), 128.3 (C-2′), 126.3 (C-5,8), 125.5 (C-6′). C-1′, C-3a,9a, and C-4,9 were not observed. MS (FAB): m/z: 470 (M^+, 100). *Anal. Calcd.* for $C_{28}H_{14}N_4O_4$ (470.44): C, 71.49; H, 3.00; N, 11.91. Found: C, 71.34; H, 3.06; N. 11.84.

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