A Convenient Synthesis of Bisbenzimidazoles from Iminoester Hydrochlorides Via Microwave Technique

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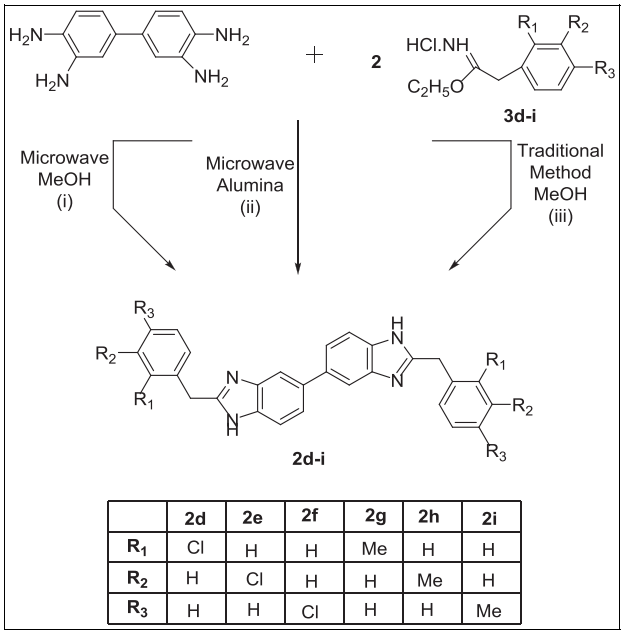

	2d	2e	2f	2g	2h	2i
R_1	Cl	H	H	Me	H	H
R_2	H	Cl	H	H	Me	H
R_3	H	H	Cl	H	H	Me

A simple and practical method has been developed for the synthesis of bisbenzimidazoles. Iminoester hydrochlorides of phenylacetic acids were used as intermediates in this reaction with 3,3′-diaminobenzidine under microwave irradiation leading to the products with good yields and in short reaction times. This method can be a general technique for the synthesis of bisbenzimidazoles.

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INTRODUCTION

The wide range of biological activities of bisbenzimidazole has made it a preferred structure for modern drug discovery [1–4]. The structure of a recent example, Hoechst 33258 [5–7], which is an enzyme inhibitor and antitumor agent, is shown in Figure 1.

There are several methods known for the synthesis of bisbenzimidazole derivatives. The most common protocol involves a cyclocondensation reaction of 3,3′-diaminobenzidine (**1**) with various groups such as ketones [8], ortoesters [9], and 1,3-dicarbonyl compounds [10] (Scheme 1). However, these protocols suffer from one or more disadvantages such as prolonged reaction time, use of special reagents, and vigorous reaction conditions. Therefore, there is a need for a new synthetic method for bisbenzimidazoles (**2**), which is short and economical.

RESULTS AND DISCUSSION

Our studies on bisbenzimidazoles have shown that iminoester hydrochlorides (**3**) could be useful intermediates in the reaction with **1** under microwave irradiation in methanol or under solvent-free conditions. Although the synthesis of (mono) benzimidazoles from phenylendiamine and iminoester hydrochlorides is a known reaction [11–14], this method was used for the first time to prepare bisbenzimidazoles.

The mechanism of reaction between an iminoester hydrochloride and 3,3′-diaminobenzidine has been already proposed in Ref. [15].

In this study, we developed three alternative protocols for the synthesis of symmetric bisbenzimidazoles, which are highly efficient, environmentally friendly, and less time-consuming (Scheme 2). These methods are very suitable for the synthesis of C(2)-substituted bisbenzimidazoles (Table 1).

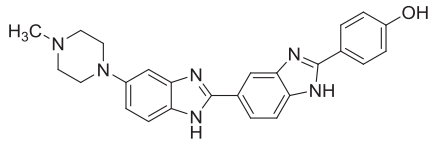


Figure 1. Structure of Hoechst 33258.

Especially, the synthesis via process (ii), which requires no solvents, is more eco-friendly, but the yields of the products are lower.

Having in hand the symmetric bisbenzimidazoles **2d-i**, we synthesized their ester **4d-i** and hydrazide derivatives **5d-i** (Scheme 3) according to the literature [16,17] under microwave irradiation with good yields. Simple alkylation reaction was applied to **2d-i** with methyl α-bromoacetate in acetone and then, the MeO group was displayed by treatment with $NH_2NH_2.H_2O$ in EtOH [18–20].

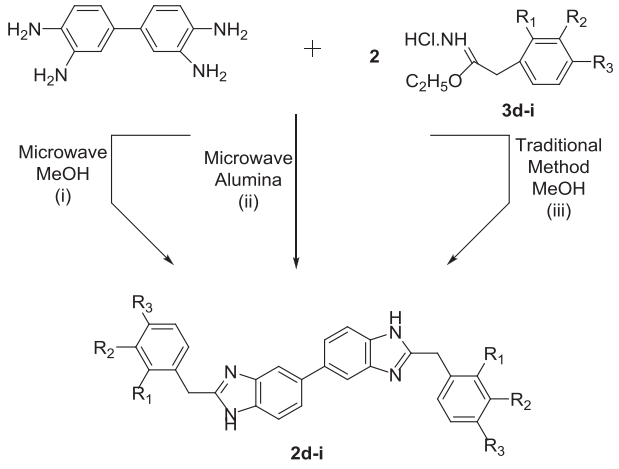
CONCLUSION

In conclusion, we have developed a convenient method for the synthesis of bisbenzimidazole derivatives, which can provide a suitable way of synthesizing potentially bioactive bisbenzimidazoles.

EXPERIMENTAL

All the chemicals were supplied from Merck (Darmstadt, Germany), Aldrich and Fluka (Buchs SG, Switzerland). Melting points were determined on capillary tubes on a Büchi oil heated melting point apparatus (Essen, Germany) and uncorrected. ^{1}H-NMR spectra were performed on Varian-Mercury 400 and 200 MHz spectrophotometer (Varian, Darmstadt, Germany) in DMSO-d_6 using TMS as internal. The IR spectra were recorded on a Perkin-Elmer 100 FTIR spectrophotometer (California, USA) as KBr pellets. The elemental compositions were determined on a Carlo Erba 1106 CHN (Heraeus, Hanau, Germany) analyzer; the experimental values were in agreement (±0.4%) with calculated ones. Mass spectra were recorded on Thermo Scientific Quantum Access max LC-MS spectrophotometer (Thermo-scientific, Florida, USA). A mono-mode CEM-Discover microwave (Linfort, Germany) was used to carry out microwave reactions in 30 mL microwave process vials with temperature control by infrared detection temperature sensor. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

Scheme 2. Synthesis of compound **2d-i**.



	2d	2e	2f	2g	2h	2i
R_1	Cl	H	H	Me	H	H
R_2	H	Cl	H	H	Me	H
R_3	H	H	Cl	H	H	Me

We first synthesized iminoester hydrochlorides (**3d-i**) according to the Pinner method [21,22]. Then, they were reacted with 3,3′-diaminobenzidine (**1**) to obtain the corresponding bisbenzimidazoles.

General procedure for the synthesis of symmetric bisbenzimidazole derivatives, under microwave irradiation in MeOH (method I) (3d-i). A mixture of **1** (0.010 mol) and **3d-i** (0.026 mol) in dry MeOH (15 mL) was irradiated with microwave at 60°C for 10 min at 300 W maximum power. After the completion of the reaction (monitored by TLC, AcOEt/hexane, 3:1), the mixture was poured onto H_2O. The precipitate was collected by filtration and recrystallized from EtOH/H_2O (1:3) to give pure compounds **2d-i**.

Scheme 1. Classical synthetic methods of bisbenzimidazoles.

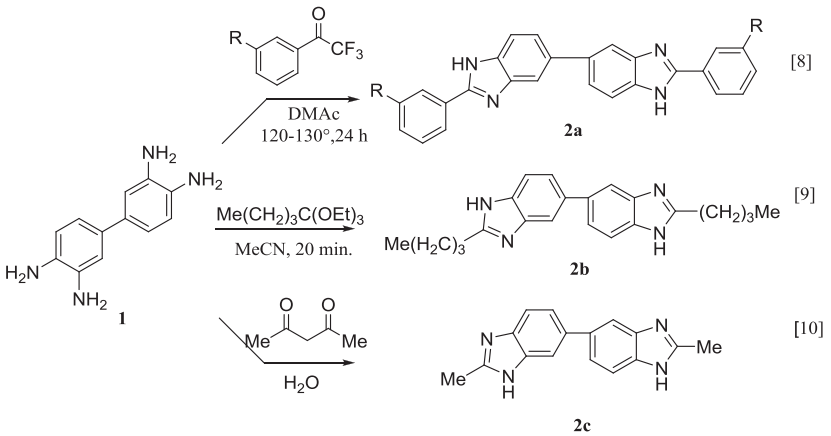


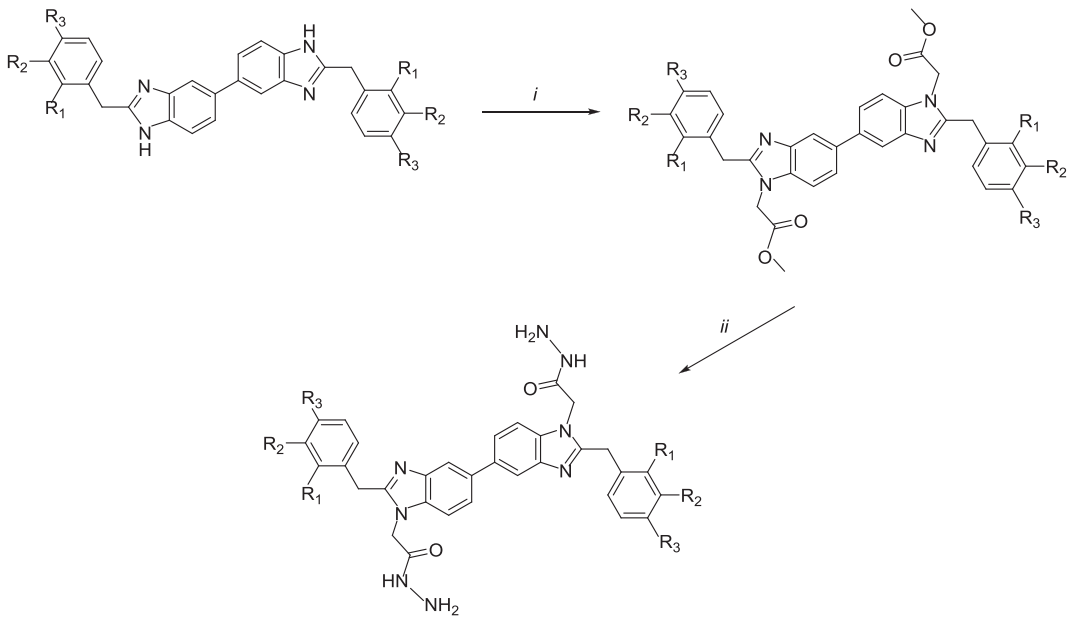
Table 1

Comparation of the yields and reaction times under microwave irradiation and the conventional methods for compounds **2d-i**.

		Method I[a]		Method II[b]		Method III[c]	
Compound no.	Melting point (°C)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (hour)	Yield (%)
2d	265–266	13	93	16	58	13	80
2e	255–256	13	93	16	55	13	65
2f	284–285	13	98	16	63	13	93
2g	291–292	13	90	16	55	13	70
2h	264–265	13	90	16	55	13	68
2i	315–316	13	96	16	65	13	85

[a]MW, MeOH, 60°C, 10 min. [b]MW, Al_2O_3, 85°C, 16 min. [c]RT, MeOH, 13 h.

Scheme 3. Synthesis of compounds **4d-i** and **5d-i**. Reagents and conditions: (i) Acetone, AcOMe, $BrCH_2CO_2Me$, K_2CO_3, MW, 85°C, 7 min; (ii) EtOH, $NH_2NH_2.H_2O$, MW, 120°C, 5 min.



Under microwave irradiation, solvent-free (method II). A mixture of **1** (0.010 mol), **3d-i** (0.026 mol), and acidic alumina oxide (9 g) were taken in a 20 mL round flask and suspended in CH_2Cl_2 (10 mL). The solvent was completely evaporated under reduced pressure. The mixture was microwave irradiated at 85°C for 4 × 4 min at 60 W. After the completion of the reaction (TLC), the mixture was applied to the described way.

Conventional method (method III). A mixture of **1** (0.010 mol) and **3d-i** (0.026 mol) in dry MeOH (30 mL) was stirred for 13 h at r.t. Above purification methods were applied to give pure products **2d-i**.

2,2′-Bis(2-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole (2d). White solid, IR (KBr, cm^{-1}): 3382, 3026, 2931, 1626, 1531, 1444, 1278, 852, 803, 742 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.32 (s, 4H, $2CH_2$), 7.29–7.69 (m, 14H, Ar H), 12.34 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 32.65 ($2CH_2$), 113.42, 114.37, 121.50, 127.81, 129.12, 129.75, 131.94, 133.71, 135.03, 135.77, 137.24 (Ar.C), 153.21 (2C═N); *Anal.* Calcd for $C_{28}H_{20}Cl_2N_4$: C, 69.57, H, 4.17, N,11.59; Found: C, 69.60, H, 4.18, N, 11.56. ESI-MS *m/z* calculated $C_{28}H_{20}Cl_2N_4$ $[M+H]^+$ 483.11, 485.10; found 483.22, 485.18 and symmetric division signal 242.23.

2,2′-Bis(3-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole (2e). White solid; IR (KBr, cm^{-1}): 3456, 3021, 2955, 1619, 1597, 1288, 1093, 863, 791 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.20 (s, 4H, $2CH_2$), 7.32–7.8 (m, 14H, Ar H), 12.36 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 35.10 ($2CH_2$), 113.23, 115.82, 121.71, 127.03, 128.02, 128.05, 128.09, 129.11, 129.15, 129.18, 130.78, 130.82, 133.52, 135.84, 140.52 (Ar.C), 154.20 (2C═N); *Anal.* Calcd for $C_{28}H_{20}Cl_2N_4$: C, 69.57, H, 4.17, N,11.59; Found: C, 69.62, H, 4.19, N, 11.62. ESI-MS *m/z* calculated $C_{28}H_{20}Cl_2N_4$ $[M+H]^+$ 483.11, 485.10; found 483.16, 485.12 and symmetric division signal 242.23.

2,2′-Bis(4-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole (2f). White solid; IR (KBr, cm^{-1}): 3336, 3028, 2925, 1630, 1578, 1417, 845, 803, 752, 685 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.20 (s, 4H, $2CH_2$), 7.36–7.70 (m, 14H, Ar H), 12.33 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 34.69 ($2CH_2$), 121.64, 128.81, 128.85, 128.88, 128.98, 131.15, 131.74, 135.79, 137.08 (Ar.C), 154.17 (2C═N); *Anal.* Calcd for $C_{28}H_{20}Cl_2N_4$: C, 69.57, H, 4.17, N,11.59; Found: C, 69.61, H, 4.15, N, 11.58. ESI-MS *m/z* calculated $C_{28}H_{20}Cl_2N_4$ $[M+H]^+$

483.11, 485.10; found 483.26, 485.22 and symmetric division signal 242.30.

2,2′-Bis(2-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole (2g). White solid; IR (KBr, cm^{-1}): 3392, 3026, 2972, 1626, 1536, 1281, 853, 802, 664 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.70 (d, J = 6.6 Hz, 6H, $2CH_3$), 4.35 (q, J = 6.6 Hz, 4H, $2CH_2$), 7.22–7.78 (m, 14H, Ar H), 12.22 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.13 ($2CH_3$), 38.90 ($2CH_2$), 121.80, 127.05, 127.27, 127.72, 127.85, 128.10, 128.89, 128.96, 129.21, 135.10, 144.39 (Ar.C), 158.65 (2C═N); *Anal*. Calcd for $C_{30}H_{26}N_4$: C, 81.42, H, 5.92, N,12.66; Found: C, 81.40, H, 5.94, N, 12.66. ESI-MS *m/z* calculated $C_{30}H_{26}N_4$ $[M+H]^+$ 443.22; found 443.34 and symmetric division signal 222.28.

2,2′-Bis(3-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole (2h). White solid; IR (KBr, cm^{-1}): 3442, 3016, 2915, 1629, 1524, 1273, 850, 803, 696 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 6H, $2CH_3$), 4.13 (s, 4H, $2CH_2$), 7.02–7.67 (m, 14H, Ar H), 12.28 (bs, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.65 ($2CH_3$), 34.68 ($2CH_2$), 113.10, 115.47, 122.88, 126.66, 128.14, 129.20, 130.14, 136.40, 136.68, 137.21, 137.84, 138.40 (Ar.C), 154.74 (2C═N); *Anal*. Calcd for $C_{30}H_{26}N_4$: C, 81.42, H, 5.92, N,12.66; Found: C, 81.41, H, 5.90, N, 12.65. ESI-MS *m/z* calculated $C_{30}H_{26}N_4$ $[M+H]^+$ 443.22; found 443.27 and symmetric division signal 222.35.

2,2′-Bis(4-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole (2i). White solid; IR (KBr, cm^{-1}): 3340, 3007, 2918, 1628, 1577, 1273, 850, 808, 767, 673 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 6H, $2CH_3$), 4.13 (s, 4H, $2CH_2$), 7.10–7.67 (m, 14H, Ar H), 12.29 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.33 ($2CH_3$), 35.30 ($2CH_2$), 121.51, 129.02, 129.06, 129.12, 129.43, 129.54, 135.04, 135.73, 136.01 (Ar.C), 154.80 (2C═N); *Anal*. Calcd for $C_{30}H_{26}N_4$: C, 81.42, H, 5.92, N,12.66; Found: C, 81.38, H, 5.95, N, 12.62.ESI-MS *m/z* calculated $C_{30}H_{26}N_4$ $[M+H]^+$ 443.22; found 443.27 and symmetric division signal 222.35.

General procedure for the synthesis of dimethyl 2,2′-[2,2′-bis (substitetudbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetates (4d-i). A mixture of compounds **2a-i** (0.01 mol), methyl α-bromoacetate (0.02 mol) and K_2CO_3 (0.05 mol) in acetone (15 mL) was irradiated with microwave at 85°C for 7 min, at 300 W maximum power. After the completion of the reaction (monitored by TLC, AcOEt/hexane, 3:1), the mixture was pured into H_2O. The precipitate was collected by filtration and recrystallized from acetone/water (1:3) to give pure **4d-i**.

Dimethyl 2,2′-[2,2′-bis(2-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetate (4d). White solid; Yield: 94%; IR (KBr, cm^{-1}): 3058, 2951, 1741, 1621, 1210, 1036, 749 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 3.63 (s, 6H, $2OCH_3$), 4.34 (s, 4H, $2CH_2$), 5.30 (s, 4H, 2 N—CH_2), 7.32–7.88 (m, 14H, Ar H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 31.57 ($2CH_2$), 45.20 (2 N—CH_2), 53.10 ($2OCH_3$), 108.88, 108,98, 110.75, 110.80, 117.39, 117.50, 119.27, 121.58, 121.88, 122.20, 122.32, 127.71, 129.10, 129.71, 132.04, 133.85, 134.81, 136.00, 136.88, 141.02, 141.96, 143.33, 143.37 (Ar.C), 153.70, 153.93 (2C═N), 168.90, 168.95 (C═O); *Anal*. Calcd for $C_{34}H_{28}Cl_2N_4O_4$: C, 65.07, H, 4.53, N,8.95; Found: C, 65.08, H, 4.50, N,8.93.ESI-MS *m/z* calculated $C_{34}H_{28}Cl_2N_4O_4$ $[M+H]^+$ 627.15, 629.15; found 627.12, 629.22 and symmetric division signal 314.25.

Dimethyl 2,2′-[2,2′-bis(3-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetate (4e). White solid; Yield: 95%; IR (KBr, cm^{-1}): 3055, 2953, 1737, 1597, 1216, 1077, 786 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.54 (s, 6H, $2OCH_3$), 4.30 (s, 4H, $2CH_2$), 5.28 (s, 4H, 2 N—CH_2), 7.31–7.92 (m, 14H, Ar H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 32.07 ($2CH_2$), 44.99 (2 N—CH_2), 52.69 ($2OCH_3$), 109.09, 110.91, 117.43, 119.26, 122.39, 127.05, 128.21, 129.25, 130.69, 133.43, 135.47, 135.69, 136.03, 136.87, 139.43, 141.76, 143.28 (Ar.C), 154.24, 154.39 (C═N), 168.75, 168.81 (C═O); *Anal*. Calcd for $C_{34}H_{28}Cl_2N_4O_4$: C, 65.08, H, 4.50, N,8.93; Found: C, 65.04, H, 4.52, N,8.90. ESI-MS *m/z* calculated $C_{34}H_{28}Cl_2N_4O_4$ $[M+H]^+$ 627.15, 629.15; found 627.15, 629.25 and symmetric division signal 314.24.

Dimethyl 2,2′-[2,2′-bis(4-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetate (4f). White solid; Yield: 97 %; IR (KBr, cm^{-1}): 3047, 2950, 1738, 1623, 1221, 844, 799 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.54 (s, 6H, $2OCH_3$), 4.28 (s, 4H, $2CH_2$), 5.24 (s, 4H, 2 N—CH_2), 7.31–7.91 (m, 14H, Ar H);^{13}C-NMR (100 MHz, DMSO-d_6): δ32.55, 32.66 (CH_2), 44.97, 45.01 (N—CH_2), 52.61, 52.67 (OCH_3), 109.00, 110.77, 110.85, 117.34, 117.46, 117.50, 121.87, 122.23, 122.33, 128.79, 129.03, 131.31, 131.50, 131.57, 131.63, 131.67, 131.75, 131.85, 135.08, 136.05, 136.13 (Ar.C), 154.53, 154.57 (C═N), 168.75, 168.75 (C═O); *Anal*. Calcd for $C_{34}H_{28}Cl_2N_4O_4$: C, 65.08, H, 4.50, N,8.93; Found: C, 65.06, H, 4.53, N,8.91. ESI-MS *m/z* calculated $C_{34}H_{28}Cl_2N_4O_4$ $[M+H]^+$ 627.15, 629.15; found 627.15, 629.18 and symmetric division signal 314.10.

Dimethyl 2,2′-[2,2′-bis(2-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetate (4g). White solid; Yield: 94 %; IR (KBr, cm^{-1}): 3024, 2932, 1742, 1621, 1455, 1207, 699 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.68 (d, J = 6.8 Hz, 6H, $2CH_3$), 3.41 (s, 6H, $2OCH_3$), 4.52 (q, J = 6.8 Hz, 4H, $2CH_2$), 5.16 (s, 4H, 2 N—CH_2), 7.26–7.98 (m, 14H, Ar H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.39 ($2CH_3$), 35.22 ($2CH_2$), 46.42 (2 N—CH_2), 52.02 ($2OCH_3$), 108.85, 109.03, 110.76, 112.16, 117.10, 118.13, 124.21, 125.13, 126.63, 127.44, 128.91, 135.51, 135.62, 136.53, 136.96, 137.07, 140.22, 141.59, 142.08 (Ar.C), 157.83, 157.95 (C═N), 168.43, 168.46 (C═O); *Anal*. Calcd for $C_{36}H_{34}N_4O_4$: C, 73.70, H, 5.84, N,9.55; Found: C, 73.75, H, 5.85, N,9.53. ESI-MS *m/z* calculated $C_{36}H_{34}N_4O_4$ $[M+H]^+$ 587.26; found 587.33 and symmetric division signal 294.30.

Dimethyl2,2′-[2,2′-bis(3-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetate (4h). White solid; Yield: 94%; IR (KBr, cm^{-1}): 3020, 2950, 1742, 1607, 1513, 1209, 1092, 796 cm^{-1}; 1H-NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 6H, $2CH_3$), 3.52 (s, 6H, $2OCH_3$), 4.23 (s, 4H, $2CH_2$), 5.20 (s, 4H, 2 N—CH_2), 7.28–7.83 (m, 14H, Ar H); ^{13}C–NMR (100 MHz, DMSO-d_6): δ 21.45 ($2CH_3$), 33.40 ($2CH_2$), 44.92, 45.02 (N—CH_2), 52.61 ($2OCH_3$), 109.03, 110.85, 117.36, 119.20, 121.79, 126.43, 127.68, 128.80, 129.89, 135.43, 135.88, 135.96, 136.72, 136.88, 137.98, 141.91, 143.32 (Ar.C), 154.82 (2C═N), 168.69 (2C═O); *Anal*. Calcd for $C_{36}H_{34}N_4O_4$: C, 73.70, H, 5.84, N,9.55; Found: C, 73.72, H, 5.84, N,9.51. ESI-MS *m/z* calculated $C_{36}H_{34}N_4O_4$ $[M+H]^+$ 587.26; found 587.33 and symmetric division signal 294.30.

Dimethyl2,2′-[2,2′-bis(4-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetate (4i). White solid; Yield: 94%; IR (KBr, cm^{-1}): 3015, 2950, 1742, 1621, 1513, 1209, 802, 766 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.45 (s, 6H, $2CH_3$), 3.51 (s, 6H, $2OCH_3$), 4.20 (s, 4H, $2CH_2$), 5.18 (s, 4H, 2 N—CH_2), 7.11–7.88 (m, 14H, Ar H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.71 ($2CH_3$), 35.28 ($2CH_2$), 44.87, 44.98 (N—CH_2), 52.64 ($2OCH_3$), 108.84, 108.99, 110.80, 117.30, 117.35, 119.18, 121.56, 121.77,

122,11, 122.22, 129.11, 129.20, 129.43, 133.74, 135.56, 135.87, 136.07, 136.96, 141.79, 141.91, 143.33 (Ar.C), 154.90, 155.06 (C═N), 168.71 (2C═O); *Anal*. Calcd for $C_{36}H_{34}N_4O_4$: C, 73.70, H, 5.84, N,9.55; Found: C, 73.73, H, 5.86, N,9.56. ESI-MS *m/z* calculated $C_{36}H_{34}N_4O_4$ $[M+H]^+$ 587.26; found 587.40 and symmetric division signal 294.30.

General procedure for the synthesis of 2,2′-[2,2′-bis (substitutedbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl] diacetohydrazides (5d-i). A mixture of compounds **4d-i** (0.01 mol) and $NH_2NH_2.H_2O$ (0.05 mol) in abs. EtOH (15 mL) was irradiated with microwave at 120°C for 5 min, at 300 W maximum power. After the completion of the reaction (monitored by TLC, AcOEt/hexane, 3:1), the mixture was cooled to RT. The precipitate was washed with EtOH dried over $CaCl_2$ to give pure **5d-i**.

2,2′-[2,2′-Bis(2-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetohydrazide (5d). White solid; Yield: 82%; IR (KBr, cm^{-1}): 3281, 3195, 1662, 1588 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.29 (s, 4H, $2CH_2$), 4.40 (s, 8H, $2NH_2 + 2CH_2$), 4.91 (d, $J = 7$, 4H, 2 N—CH_2), 7.31–7.77 (m, 14H, Ar H), 9.59 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 31.49 ($2CH_2$), 45.08 (2 N—CH_2), 108.71, 108.82, 110.65, 117.23, 119.17, 121.39, 121.71, 121.89, 122.04, 127.73, 129.03, 129.66, 131.99, 133.83, 135.21, 135.39, 135.81, 135.96, 136.70, 143.32 (Ar.C), 153.99, 154.25 (C═N), 166.39 (2C═O); *Anal*. Calcd for $C_{32}H_{28}Cl_2N_8O_2$: C, 61.25, H, 4.50, N,17.86; Found: C, 61.28, H, 4.51, N,17.83. ESI-MS *m/z* calculated $C_{32}H_{28}Cl_2N_8O_2$ $[M+H]^+$ 627.17, 629.17; found 627.33, 629.21 and symmetric division signal 313.12.

2,2′-[2,2′-Bis(3-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetohydrazide (5e). White solid; Yield: 82%; IR (KBr, cm^{-1}): 3277, 3202, 1659, 1597 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.15 (s, 4H, $2CH_2$), 4.39 (s, 4H, $2NH_2$), 4.85 (s, 4H, 2 N—CH_2), 7.27–7.81 (m, 14H, Ar H), 9.48 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 32.24 ($2CH_2$), 44.86 (2 N—CH_2), 108.30, 110.22, 116.66, 118.62, 120.96, 121.55, 126.44, 127.77, 128.81, 130.10, 130.48, 132.81, 134.60, 134.76, 134.97, 135.31, 136.07, 139.18, 139.36, 141.23, 142.75 (Ar.C), 154.01, 154.19 (C═N), 165.86 (2C═O); *Anal*. Calcd for $C_{32}H_{28}Cl_2N_8O_2$: C, 61.25, H, 4.50, N,17.86; Found: C, 61.23, H, 4.52, N,17.86. ESI-MS *m/z* calculated $C_{32}H_{28}Cl_2N_8O_2$ $[M+H]^+$ 627.17, 629.17; found 627.12, 629.22 and symmetric division signal 314.18.

2,2′-[2,2′-Bis(4-chlorobenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetohydrazide (5f). White solid; Yield: 83%; IR (KBr, cm^{-1}): 3288, 3207, 3049, 1655, 1581 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.27 (s, 4H, $2CH_2$), 4.46 (s, 4H, $2NH_2$), 4.85 (s, 4H, 2 N—CH_2), 7.36–7.79 (m, 14H, Ar H), 9.56 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 32.07 ($2CH_2$), 45.47 (2 N—CH_2), 108.27, 110.15, 116.63, 118.58, 121.17, 121.38, 128.21, 130.81, 131.01, 134.65, 134.94, 135.31, 135.40, 135.79, 136.12, 141.34, 142.74 (Ar.C), 154.17, 154.35 (C═N), 165.83 (2C═O); *Anal*. Calcd for $C_{32}H_{28}Cl_2N_8O_2$: C, 61.25, H, 4.50, N,17.86; Found: C, 61.30, H, 4.55, N,17.88. ESI-MS *m/z* calculated $C_{32}H_{28}Cl_2N_8O_2$ $[M+H]^+$ 627.17, 629.17; found 627.22, 629.18 and symmetric division signal 314.24.

2,2′-[2,2′-Bis(2-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetohydrazide (5g). White solid; Yield: 80%; IR (KBr, cm^{-1}): 3295, 3144, 1659, 1597 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.49 (s, 6H, $2CH_3$), 4.21 (s, 4H, $2CH_2$), 4.33 (s, 4H, $2NH_2$), 4.88 (s, 4H, 2 N—CH_2), 7.31–7.91 (m, 14H, Ar H), 9.55 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 22.32 ($2CH_3$), 37.57 ($2CH_2$), 44.77 (2 N—CH_2), 110.72, 117.41, 122.12, 127.12, 127.87, 129.10, 135.33, 135.91, 143.19, 143.44 (Ar.C), 158.49 (2C═N), 166.31 (2C═O); *Anal*. Calcd for $C_{34}H_{34}N_8O_2$: C, 69.61, H, 5.84, N,19.10; Found: C, 69.66, H, 5.87, N,19.13. ESI-MS *m/z* calculated $C_{34}H_{34}N_8O_2$ $[M+H]^+$ 587.29; found 587.33 and symmetric division signal 294.20.

2,2′-[2,2′-Bis(3-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetohydrazide (5h). White solid; Yield: 80%; IR (KBr, cm^{-1}): 3304, 3136, 1659, 1507 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 6H, $2CH_3$), 4.22 (s, 4H, $2CH_2$), 4.33 (s, 4H, $2NH_2$), 4.84 (s, 4H, 2 N—CH_2), 7.06–7.72 (m, 14H, Ar H), 9.53 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.48 ($2CH_3$), 33.44, 33.48 (CH_2), 45.00, 45.08 (N—CH_2), 108.88, 110.72, 117.20, 117.26, 119.13, 121.43, 121.97, 126.44, 127.67, 128.82, 129.93, 135.85, 135.89, 136.81, 137.14, 137.17, 138.01, 141.87, 143.41 (Ar.C), 155.08, 155.24 (C═N), 166.38 (2C═O); *Anal*. Calcd for $C_{34}H_{34}N_8O_2$: C, 69.61, H, 5.84, N,19.10; Found: C, 69.62, H, 5.88, N,19.15. ESI-MS *m/z* calculated $C_{34}H_{34}N_8O_2$ $[M+H]^+$ 587.29; found 587.30 and symmetric division signal 294.00.

2,2′-[2,2′-Bis(4-methylbenzyl)-1H,1′H-5,5′-bisbenzimidazole-1,1′-diyl]diacetohydrazide (5i). White solid; Yield: 81%; IR (KBr, cm^{-1}): 3298, 3151, 1659, 1512 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 6H, $2CH_3$), 4.20 (s, 4H, $2CH_2$), 4.30 (s, 4H, $2NH_2$), 4.83 (s, 4H, 2 N—CH_2), 7.17–7.83 (m, 14H, Ar H), 9.51 (s, 2H, 2NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.55 ($2CH_3$), 32.49 ($2CH_2$), 44.41 (2 N—CH_2), 108.18, 110.10, 116.60, 118.53, 120.84, 121.28, 128.64, 128.91, 133.59, 134.70, 134.86, 134.92, 135.24, 135.35, 135.44, 136.19, 141.23, 142.77 (Ar.C), 154.64, 154.86 (C═N), 165.84 (2C═O). *Anal*. Calcd for $C_{34}H_{34}N_8O_2$: C, 69.61, H, 5.84, N,19.10; Found: C, 69.65, H, 5.83, N,19.16. ESI-MS *m/z* calculated $C_{34}H_{34}N_8O_2$ $[M+H]^+$ 587.29; found 587.30 and symmetric division signal 294.30.

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