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Efficient method for the synthesis of fused benzimidazole–imidazoles via deprotection and cyclization reactions

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ABSTRACT

A fused benzimidazole–imidazole scaffold was designed and synthesized using a facile procedure involving deprotection and cyclization reactions. The acidic conditions and high yields for the benzimidazole ring closure allow potential application of this efficient methodology for the design and synthesis of a range of bioactive compounds.

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1. Introduction

Benzimidazoles are important heterocycles and structurally related to purine bases. They were found in a variety of natural and synthetic products, with numerous biological activities and functions such as antibacterial,[1] anticancer,[2] antihelminthic,[3] antifungal,[4] antiallergic,[5] antimicrobial,[6] antiviral,[7] and antineoplastic activities.[8] The ring system of benzimidazole can be considered as a new device for the target-specific transcription aspect at binding sites related to biological systems. Some representative benzimidazole–imidazole conjugates are shown in Fig. 1.

Compounds **1** and **2**, with modifications to the imidazole ring, have functions as mitochondrial apoptosis inducers and inhibitors of both tubulin polymerization and the PI3K/Akt pathway, respectively.[2c,9] Modification of the benzimidazole group in compounds **4** and **5** gives rise to nitric oxide synthase (NOS) inhibitors and antibacterial agents.[10] Compounds **1**–**5** can be synthesized by the reaction of phenylene-1,2-diamine **3** with aldehydes,[11] and compound **6** can be obtained from a three-component cyclocondensation of a 1,2-diketone, an α-hydroxyketone or α-ketomonoxime with an aldehyde and ammonium acetate, under microwave irradiation.[12] In our previous reports,[13] *N*-Boc-phenylene-1,2-diamine could effect closure of the benzimidazole ring in acidic solvents. The design and synthesis of second-generation oligomeric imidazole-4,5-dicarboxamide (I45DCs) for the

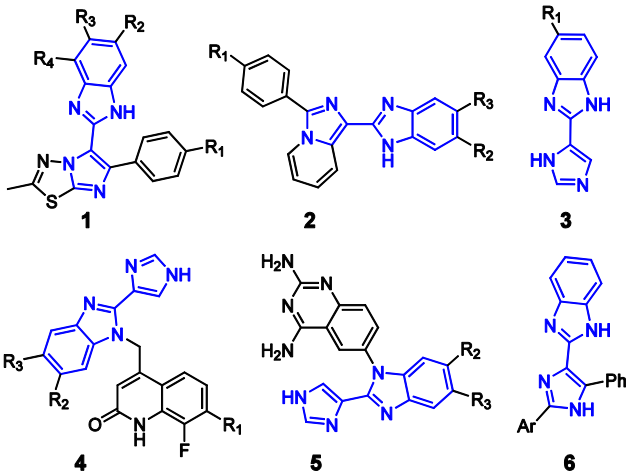

Fig. 1. Bioactive fused benzimidazole–imidazole compounds.

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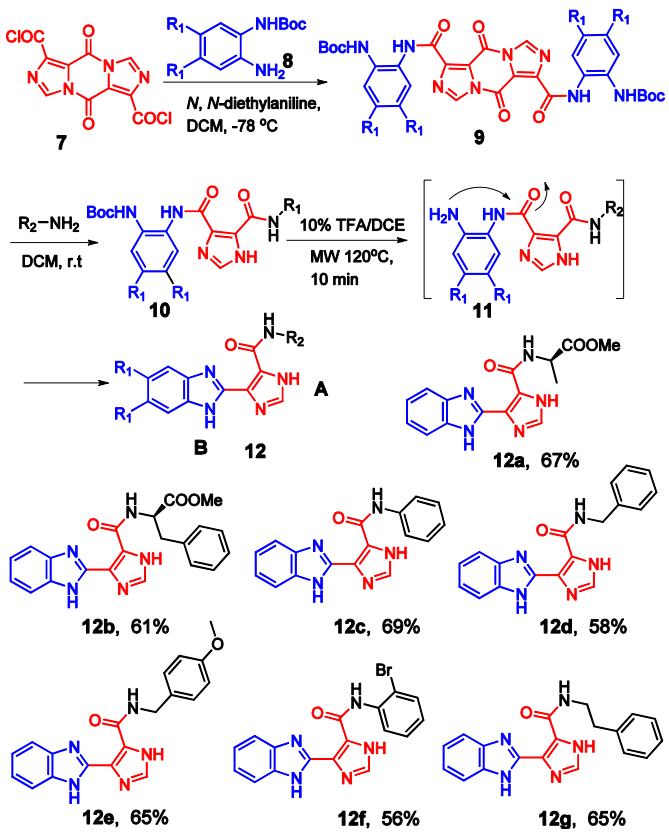
inhibition of protein–protein interactions (PPI) was reported by Dr. Baures.[14] Herein, we describe our most recent work towards the development of a novel strategy for the construction of fused benzimidazole–imidazoles using oligomeric imidazole-4,5-dicarboxamide (I45DCs) as one of the starting materials.

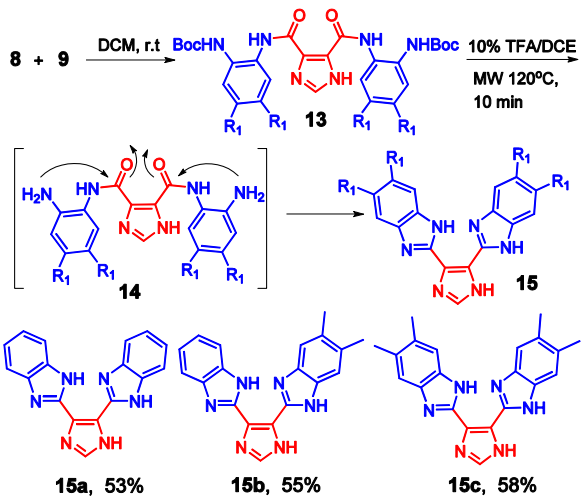
2. Discussion

Acid chloride **7** was treated with Boc-diamine **8** at −78 °C to afford compound **9** in 89% yield (Scheme 1). Compound **9** was then reacted with a range of amines in DCM at room temperature. The solvent was then removed and crude compound **10** was used for the next reaction without further purification. The residue was diluted with 10% TFA/DCE and heated at 120 °C for 10 min under microwave irradiation to afford compound **11** in good yield. Compound **12** contains two imidazole positions (A and B) that could be modified. Position A could also be modified in structure of compound **10**, so these two positions could be selectively functionalized in different steps. A range of amines, including an amino acid ester, was reacted, and gave products **12a**–**g** in 56–69% yield. This facile procedure would be suitable for the synthesis of a range of compounds for use in high-throughput screening.



Scheme 1. Synthesis of fused benzimidazole–imidazoles **12a**–**g**.

Compound **9** was also treated with Boc-diamine **8** in DCM to afford compound **13** (Scheme 2). Following the same procedure as compound **12**, compound **13** was not purified and the solvent was removed to give a residue. The residue was then treated with 10% TFA/DCE to afford intermediate **14**. Following the arrows in structure **14**, two new benzimidazole groups would be formed at the same time to afford compounds **15a**–**c** in over 50% yield for the two steps. This route was designed so that two benzimidazoles could be formed in the same step, and the three imidazole groups present could be modified with different functional groups in different steps.



Scheme 2. Synthesis of compounds **15a**–**c**.

From Scheme 2, the use of Boc-diamine allows the formation of two benzimidazole groups in one step. Based on this idea, diamine **16** was used to link two I45DC functional groups together to afford **17** (Scheme 3). The imidazole group in compound **17** could still be modified in this step. The next deprotection and cyclization steps were carried out under microwave irradiation at 120 °C for 10 min to give **18a**–**f** in 42–65% yield over two steps in a one-pot procedure. These compounds containing four imidazole groups were very polar and purified by recrystallization from ethyl acetate.

3. Discussion

In summary, we have demonstrated a facile and efficient procedure for the synthesis of fused benzimidazole–imidazoles. This procedure provides opportunities for the selective modification of the imidazole groups in two different steps as marked in positions A and B in compound **11**. Biological screening results will provide insights into which way the structures should be modified to improve the bioactivity.

4. Experimental section

4.1. General procedures for compound 12

To a suspension of acid chloride **7** (1.56 g, 5.0 mmol) and *N*,*N*-diethylaniline (1.60 mL, 10 mmol) in DCM (40 mL), *N*-Boc-1,2-phenylenediamine **8** (1.04 g, 5.0 mmol) was added at −78 °C. The reaction was kept for 1 h at this temperature and then warmed to room temperature. After stirring 5 h, the yellow solid was precipitated from the solvent and filtered to give compound **9** in 92% yield.

To a suspension of compound **9** (66 mg, 0.1 mmol) in DCM (3 mL), amine (0.21 mmol) was added and stirred at room temperature overnight. Then, the solvent was removed and 10% TFA/DCE (3 mL) was added to the residue. The mixture was treated with microwave at 120 °C for 10 min. After the microwave vial was cooled to room temperature, the solvent was removed under reduced pressure and then diluted with EtOAc (15 mL) and washed with satd Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (20–100%) to afford the relative targeted product **12**.

*4.1.1. Methyl (4-(1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carbonyl)-D-alaninate (Compound **12a**).* White solid, yield 67%. ^{1}H

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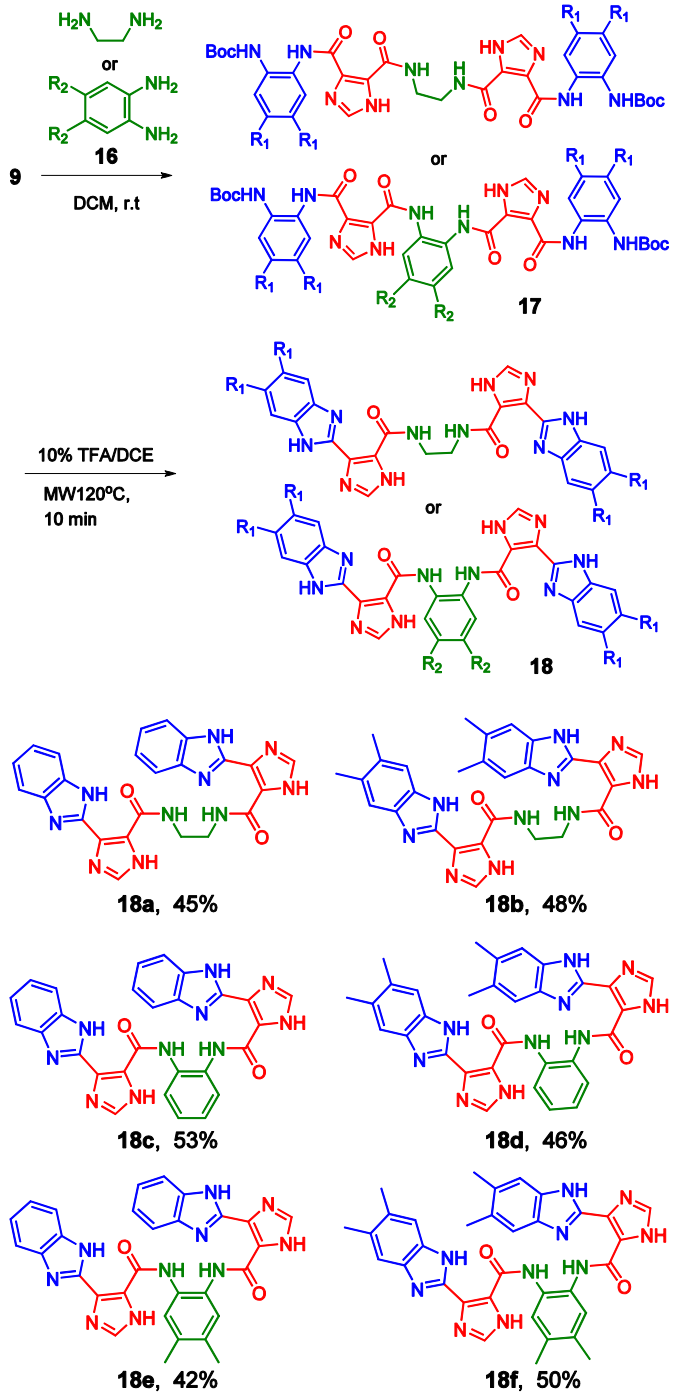

Scheme 3. Synthesis of compounds **18a**–**f**.

NMR (400 MHz, $CDCl_3$) δ 14.70 (s, 1H), 8.17 (s, 1H), 7.78–7.67 (m, 3H), 7.40 (s, 2H), 4.95–4.71 (m, 1H), 3.83 (s, 3H), 1.62 (d, J=6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 163.3, 142.1, 137.8, 134.6, 124.6, 122.7, 118.1, 117.0, 112.9, 52.7, 48.4, 18.2. LC/MS calculated for $C_{15}H_{16}N_5O_3$ $[M+H]^+$, 314; found 314.

4.1.2. Methyl (4-(1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carbonyl)-D-phenylalaninate (Compound ***12b****).* White solid, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.22 (s, 1H), 8.20 (d, J=6.6 Hz, 1H), 7.85 (s, 2H), 7.67 (s, 1H), 7.47 (s, 2H), 7.31 (d, J=6.4 Hz, 2H), 7.22 (d, J=6.2 Hz, 2H), 5.05 (d, J=6.2 Hz, 1H), 3.78 (s, 3H), 3.29 (dt, J=20.0, 11.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 163.2, 140.9, 138.8, 135.8, 135.5, 129.2, 128.8, 127.4, 125.9, 120.6, 116.1, 113.2, 53.8, 52.7, 38.1. LC/MS calculated for $C_{21}H_{20}N_5O_3$ $[M+H]^+$, 390; found 390.

4.1.3. 4-(1H-Benzo[d]imidazol-2-yl)-N-phenyl-1H-imidazole-5-carboxamide (Compound ***12c****).* White solid, yield 69%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.65 (s, 1H), 13.45 (s, 1H), 13.22 (s, 1H), 8.08 (s, 1H), 7.98 (d, J=7.6 Hz, 2H), 7.86 (s, 1H), 7.60 (s, 1H), 7.48 (t, J=7.1 Hz, 2H), 7.32 (s, 2H), 7.17 (t, J=7.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.2, 148.3, 142.1, 139.9, 138.6, 134.1, 130.6, 129.7, 126.8, 124.1, 123.8, 123.0, 119.8, 118.5, 112.6. LC/MS calculated for $C_{17}H_{14}N_5O$ $[M+H]^+$, 304; found 304.

4.1.4. 4-(1H-Benzo[d]imidazol-2-yl)-N-benzyl-1H-imidazole-5-carboxamide (Compound ***12d****).* White solid, yield 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 13.04 (s, 1H), 12.70 (s, 1H), 7.99 (s, 1H), 7.51 (s, 3H), 7.40 (s, 4H), 7.22 (s, 2H), 4.67 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.8, 148.2, 142.2, 139.1, 138.0, 134.1, 130.5, 128.9, 128.3, 127.5, 126.3, 123.5, 122.6, 118.4, 112.3, 43.6. LC/MS calculated for $C_{18}H_{16}N_5O$ $[M+H]^+$, 318; found 318.

4.1.5. 4-(1H-Benzo[d]imidazol-2-yl)-N-(4-methoxybenzyl)-1H-imidazole-5-carboxamide (Compound ***12e****).* White solid, yield 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.69–11.93 (m, 3H), 7.98 (s, 1H), 7.78–7.35 (m, 4H), 7.23 (s, 2H), 6.95 (d, J=7.4 Hz, 2H), 4.57 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.9, 137.9, 131.2, 129.6, 123.0, 114.4, 55.6, 42.9. LC/MS calculated for $C_{19}H_{18}N_5O_2$ $[M+H]^+$, 348; found 348.

4.1.6. 4-(1H-Benzo[d]imidazol-2-yl)-N-(2-bromophenyl)-1H-imidazole-5-carboxamide (Compound ***12f****).* White solid, yield 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, broad, 1H), 11.76 (s, broad, 2H), 8.14–8.12 (m, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.84–7.74 (m, 1H), 7.67 (d, J=2.9 Hz, 2H), 7.47 (t, J=7.7 Hz, 1H), 7.30–7.28 (m, 2H), 7.20 (t, J=7.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.5, 146.6, 138.9, 136.8, 133.4, 130.1, 128.5, 127.2, 126.9, 123.5, 117.0, 115.5, 114.3. ^{1}H NMR (400 MHz, DMSO-d_6+D_2O) δ 8.16 (s, 1H), 7.97 (s, 1H), 7.79 (d, J=7.8 Hz, 1H), 7.73 (s, 2H), 7.50 (t, J=7.5 Hz, 1H), 7.36 (dd, J=5.8, 2.9 Hz, 2H), 7.24 (t, J=7.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6+D_2O) δ 158.4, 145.8, 138.9, 136.8, 136.2, 133.4, 129.4, 128.6, 127.7, 127.4, 127.0, 124.1, 117.6, 117.2, 115.6, 114.7. LC/MS calculated for $C_{17}H_{13}BrN_5O$ $[M+H]^+$, 382; found 382.

4.1.7. 4-(1H-Benzo[d]imidazol-2-yl)-N-phenethyl-1H-imidazole-5-carboxamide (Compound ***12g****).* White solid, yield 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18–12.22 (m, 3H), 7.97 (s, 1H), 7.60 (s, 2H), 7.43–7.12 (m, 7H), 3.71 (d, J=4.7 Hz, 2H), 3.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.9, 137.8, 129.1, 128.8, 126.6, 123.1, 35.5. LC/MS calculated for $C_{19}H_{18}N_5O$ $[M+H]^+$, 332; found 332.

4.2. General procedures for compound 15

With the same procedure for compound **12**.

4.2.1. 2,2′-(1H-Imidazole-4,5-diyl)bis(1H-benzo[d]imidazole) (Compound ***15a****).* White solid, yield 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.84 (s, 3H), 8.12 (s, 1H), 7.83 (s, 4H), 7.32 (d, J=2.3 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.9, 123.0, 115.8. ^{1}H NMR (400 MHz, DMSO-d_6+CD_3OD) δ 8.09–8.05 (m, 1H), 7.80 (s, 4H), 7.40–7.22 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6+CD_3OD) δ 138.6, 122.9, 115.1. LC/MS calculated for $C_{17}H_{13}N_6$ $[M+H]^+$, 301; found 301.

4.2.2. 2-(4-(1H-Benzo[d]imidazol-2-yl)-1H-imidazol-5-yl)-5,6-dimethyl-1H-benzo[d]imidazole (Compound ***15b****).* White solid, yield 55%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.88 (dd, J=5.6, 2.9 Hz, 2H), 7.62 (s, 2H), 7.41 (dd, J=5.9, 3.0 Hz, 2H), 2.37 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.5, 140.0, 136.6, 133.8, 125.8, 124.3,

115.6, 115.1, 20.4. ^{1}H NMR (400 MHz, DMSO-d_6+CD_3OD) δ 8.30 (d, J=7.2 Hz, 1H), 7.89 (dd, J=6.0, 3.1 Hz, 2H), 7.63 (s, 2H), 7.43 (dd, J=6.0, 3.1 Hz, 2H), 2.38 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6+CD_3OD) δ 139.8, 136.2, 134.2, 133.1, 125.5, 124.4, 115.4, 114.8, 20.1. LC/MS calculated for $C_{19}H_{17}N_6$ $[M+H]^+$, 329; found 329.

*4.2.3. 2,2′-(1H-Imidazole-4,5-diyl)bis(5,6-dimethyl-1H-benzo[d] imidazole) (Compound **15c**).* White solid, yield 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.52 (s, 4H), 2.34 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.5, 139.9, 133.6, 115.3, 20.5. ^{1}H NMR (400 MHz, DMSO-d_6+CD_3OD) δ 8.31 (d, J=6.4 Hz, 1H), 7.68 (d, J=8.0 Hz, 4H), 2.42 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6+CD_3OD) δ 139.7, 134.2, 114.9, 20.0. LC/MS calculated for $C_{21}H_{21}N_6$ $[M+H]^+$, 357; found 357.

4.3. General procedures for compound 18

To a suspension of compound **9** (66 mg, 0.1 mmol) in DCM (3 mL), diamine **16** (0.1 mmol) was added and stirred at room temperature overnight. Then, the solvent was removed and 10% TFA/DCE (3 mL) was added to the residue. The mixture was treated in microwave at 120 °C for 10 min. After the microwave vial was cooled to room temperature, the solvent was removed under reduced pressure and then diluted with EtOAc (15 mL) and washed with satd Na_2CO_3 and brine. The organic layer was dried over $MgSO_4$ and concentrated. The products were purified by recrystallization from ethyl acetate to afford compound **18** with white solid.

*4.3.1. N,N′-(Ethane-1,2-diyl)bis(4-(1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carboxamide) (Compound **18a**).* White solid, yield 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 2H), 11.45 (s, 2H), 7.95 (s, 2H), 7.51 (s, 4H), 7.19 (s, 4H), 3.77 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 146.9, 138.0, 128.6, 123.3, 115.7, 46.1. LC/MS calculated for $C_{24}H_{21}N_{10}O_2$ $[M+H]^+$, 481; found 481.

*4.3.2. N,N′-(Ethane-1,2-diyl)bis(4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carboxamide) (Compound **18b**).* White solid, yield 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 3H), 7.98 (s, 2H), 7.26 (s, 4H), 3.73 (s, 4H), 2.26 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 145.2, 138.2, 132.7, 127.8, 115.0, 46.0, 20.3. LC/MS calculated for $C_{28}H_{29}N_{10}O_2$ $[M+H]^+$, 537; found 537.

*4.3.3. N,N′-(1,2-Phenylene)bis(4-(1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carboxamide) (Compound **18c**).* White solid, yield 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.83 (s, 1H), 7.93 (s, 1H), 7.80 (s, 1H), 7.34 (s, 3H), 7.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3, 146.9, 138.1, 131.3, 130.2, 127.2, 125.9, 125.5, 122.9, 115.1. LC/MS calculated for $C_{28}H_{21}N_{10}O_2$ $[M+H]^+$, 529; found 529.

*4.3.4. N,N′-(1,2-Phenylene)bis(4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carboxamide) (Compound **18d**).* White solid, yield 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.99 (s, 4H), 7.95 (dd, J=5.9, 3.6 Hz, 2H), 7.79 (s, 2H), 7.32 (dd, J=6.0, 3.5 Hz, 2H), 7.02 (s, 4H), 2.13 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 145.9, 137.8, 131.5, 131.1, 130.5, 126.7, 125.7, 125.3, 114.5, 20.4. LC/MS calculated for $C_{32}H_{29}N_{10}O_2$ $[M+H]^+$, 585; found 585.

*4.3.5. N,N′-(4,5-Dimethyl-1,2-phenylene)bis(4-(1H-benzo[d]imidazol-2-yl)-1H-imidazole-5-carboxamide) (Compound **18e**).* White solid, yield 42%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 2H), 7.85 (s, 2H), 7.67 (s, 2H), 7.39 (s, 4H), 7.05 (s, 4H), 2.33 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 146.6, 138.1, 133.8, 129.7, 128.8, 127.6, 126.8, 123.1, 115.0, 19.7. LC/MS calculated for $C_{30}H_{25}N_{10}O_2$ $[M+H]^+$, 557; found 557.

*4.3.6. N,N′-(4,5-Dimethyl-1,2-phenylene)bis(4-(5,6-dimethyl-1H-benzo [d]imidazol-2-yl)-1H-imidazole-5-carboxamide) (Compound **18f**).* White solid, yield 50%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 7.87 (s, 2H), 7.68 (s, 2H), 7.12 (s, 4H), 2.31 (s, 6H), 2.13 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3, 145.2, 138.1, 133.6, 132.3, 129.7, 128.6, 127.3, 126.7, 114.8, 21.1, 19.7. LC/MS calculated for $C_{34}H_{23}N_{10}O_2$ $[M+H]^+$, 613; found 613.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.09.008.

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