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Thiamine hydrochloride (VB_1)-catalyzed one-pot synthesis of (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine derivatives

Fanglei Chen, Min Lei *, Lihong Hu *

Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China

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ABSTRACT

An environmentally benign and efficient method has been developed for the synthesis of (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine derivatives via a four-component reaction of 2-aminobenzimidazole, two molecules of aromatic aldehyde, and trimethylsilanecarbonitrile (TMSCN) in the presence of a catalytic amount of thiamine hydrochloride (VB_1) in EtOH at reflux temperature. The advantages of this method are the use of an inexpensive and readily available catalyst, high yields, simple workup, and easy purification.

1. Introduction

Multi-component reactions (MCRs)[1] have been existed about 160 years since the first MCR was reported in 1850.[2] During this period, a large number of MCRs have been reported, such as Biginelli reaction,[3] Mannich reaction,[4] Passerini reaction,[5] and Ugi reaction.[6] These MCRs have been widely used in modern organic chemistry due to their common advantages, such as convergence, operational simplicity, generally good yield of products, and structural complexity and diversity of products. Because of these valued features, the development of new MCRs has been received much attention in the field of organic synthesis.[7]

2-Aminobenzimidazole is one of important intermediates in organic synthesis. It has been used for the synthesis of a wide diversity of benzimidazole derivatives of pharmacological interest.[8] In addition, it has also been used for the synthesis of organocatalysts,[9] antibiofilm agents,[10] and chemosensors.[11]

In recent years, organocatalysts have been widely used in organic synthesis, such as L-proline,[12] ammonium acetate,[13] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[14] oxalic acid dihydrate,[15] and thiamine hydrochloride (VB_1).[16] Our group has been dedicated to explore new MCRs catalyzed by VB_1.[17–20] It is well known that VB_1 is an inexpensive and eco-friendly reagent. The structure of VB_1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). In the field of organic synthesis, VB_1 and its analogs have been taken as effective catalysts to improve reactions.[21] In continuation of our endeavor to find VB_1 catalyzed new MCRs, we wish to report here a VB_1-catalyzed four-component reaction of 2-aminobenzimidazole, two molecules of aromatic aldehyde, and trimethylsilanecarbonitrile (TMSCN) for the synthesis of (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine derivatives (Scheme 1).

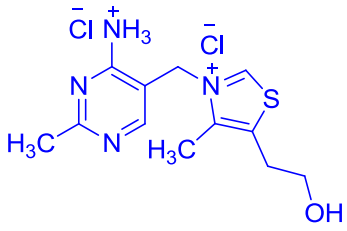

Fig. 1. The structure of thiamine hydrochloride (VB_1).

*Corresponding authors. Tel.: +86 021 2023 1000; fax: +86 021 2023 1965 (M.L.); tel./fax: +86 021 2023 1965 (L.H.); e-mail addresses: mlei@simm.ac.cn (M. Lei), lhhu@simm.ac.cn (L. Hu).

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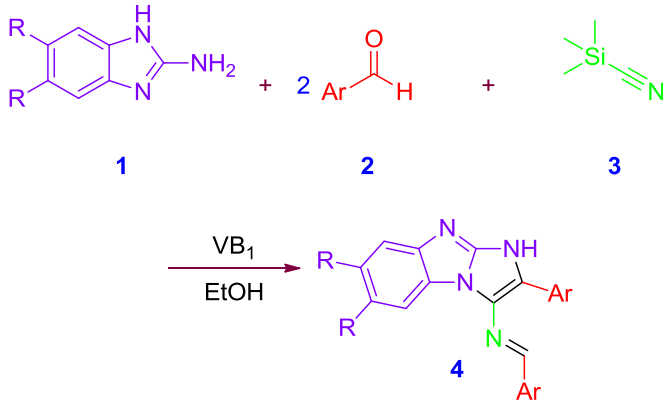
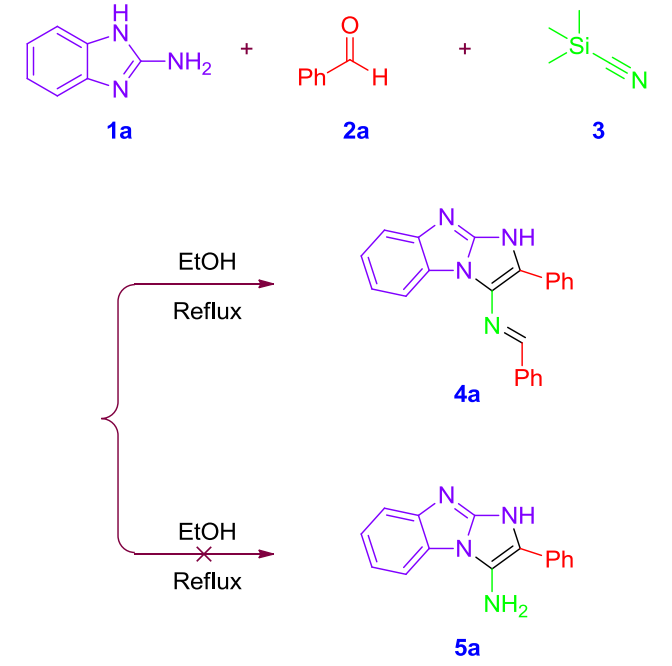


Scheme 1. Synthesis of (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine derivatives **4**.

2. Results and discussion

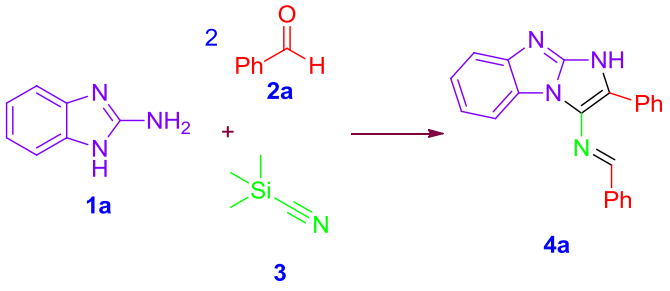
Initially, we explored the multi-component condensation reaction of 2-aminobenzimidazole **1a** (3 mmol) with benzaldehyde **2a** (3 mmol), and TMSCN **3** (3.3 mmol) in 10 mL EtOH at reflux temperature in the presence of VB_1. Curiously, the product (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine **4a**, shown in Scheme 2 and confirmed by NMR and LC-MS, was obtained, while in contrast, the 2-phenyl-1*H*-benzo[*d*]imidazo [1,2-*a*]imidazol-3-amine **5a** was not obtained although only 1 equiv of benzaldehyde **2a** was added (Scheme 2). The probable reason for this phenomenon was that **5a** was easy to react with aldehyde to form **4a** under this reaction conditions. Encouraged by this result, we further optimized the reaction conditions on the model reaction of 2-aminobenzimidazole **1a**, two molecules of benzaldehyde **2a**, and TMSCN **3** (Table 1).



Scheme 2. Condensation of 2-aminobenzimidazole **1a**, benzaldehyde **2a**, and TMSCN **3**.

As shown in Table 1, only 55% yield of the desired product **4a** was obtained under catalyst-free conditions when the condensation of 2-aminobenzimidazole **1** (3 mmol) with benzaldehyde **2a** (6.6 mmol), and TMSCN **3** (3.3 mmol) in 10 mL EtOH at reflux temperature for 10 h (Table 1, entry 1). In contrast, 70% yield of **4a** was obtained when 1 mol % of VB_1 was added to the reaction system (Table 1, entry 2). Further investigation revealed that the yields of **4a** were improved as the amount of VB_1 increased from 1 mol % to 3 mol %. However, an increase in the quantity of VB_1 form 3 mol % to 10 mol % did not improve the yields of **4a** (Table 1, entries 3–5). Hence, 3 mol % of VB_1 was considered to be the most suitable.

Table 1
Optimization of condensation of 2-aminobenzimidazole **1a**, two molecules of benzaldehyde **2a**, and TMSCN **3**[a]



Entry	Cat. (mol %)	Temp (°C)	Time (h)	Yield of **4a** (%)[b]
1	VB_1 (0)	Reflux	10	55
2	VB_1 (1)	Reflux	10	70
3	VB_1 (3)	Reflux	6	90, 89, 87[c]
4	VB_1 (5)	Reflux	6	88
5	VB_1 (10)	Reflux	6	90
6	VB_1 (3)	rt	6	5
7	VB_1 (3)	40	6	10
8	VB_1 (3)	60	6	60

[a] Conditions: 2-aminobenzimidazole **1a** (3 mmol), benzaldehyde **2a** (6.6 mmol), and TMSCN **3** (3.3 mmol), EtOH (10 mL).
[b] Isolated yields.
[c] VB_1 was reused for three times.

To study the relation between the yields of the model reaction and temperature, we performed the reaction at temperature ranging from room to reflux temperature in the presence of 3 mol % VB_1, founding that the yields of product were improved as the temperature was increased (Table 1, entries 3, 6–8). Therefore, the best reaction conditions were obtained by using 3 mol % VB_1 as the catalyst in EtOH at reflux temperature.

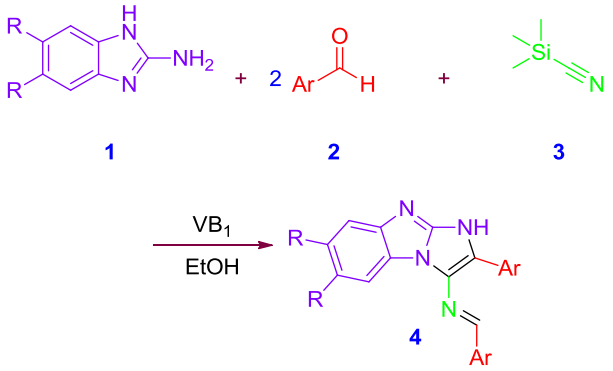
Furthermore, the reusability of VB_1 was also examined with the optimized experiment conditions of the model reaction. After completion of the reaction (TLC), the desired product **4a** was isolated by simple filtration. Then the filtrate containing VB_1 was further used to react with the reactants, affording the product **4a** in 90, 89, 87% yield after 1–3 runs, respectively (Table 1, entry 3). This study demonstrated that VB_1 could be effectively used as a recyclable catalyst for this four-component reaction.

To further explore the scope and limitation of this MCR, a variety of aromatic aldehydes were employed as substrates in this reaction of 2-aminobenzimidazole **1**, aromatic aldehyde **2**, and TMSCN **3** in the presence of 3 mol % VB_1 as the catalyst in EtOH at reflux temperature (Table 2).

As shown in Table 2, the steric hindrance effect from the aromatic aldehydes had no significant impact on the overall yields of the products **4**. For example, aromatic aldehydes carrying substituents (–Me, –Cl, –OMe) at the *ortho*, *meta*, or *para* position could react efficiently to give the corresponding products without significant difference (Table 2, entries 2–4, 5–7, 9–11, 12–13). Furthermore, nicotinaldehyde (Table 2, entry 18) was also selected for this condensation, and 80% yield of the desired product **4r** was obtained under this conditions.

However, the electronic effect from the aromatic aldehydes had significance impact on the yields of the products **4**. As shown in Table 2, the aromatic aldehydes with either electron-donating (–Me, –OMe, –OH) or weak electron-withdrawing groups (–Cl,

Table 2
Synthesis of (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine derivatives catalyzed by VB_1[a]



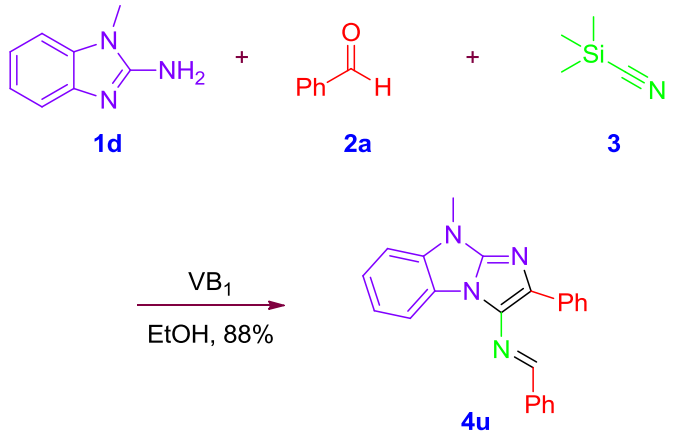
Entry	1	Ar	Product 4	Time (h)	Yield of 4 (%)[b]
1	**1a**	C_6H_5	**4a**	6	90
2	**1a**	2-MeC_6H_4	**4b**	6	86
3	**1a**	3-MeC_6H_4	**4c**	6	89
4	**1a**	4-MeC_6H_4	**4d**	6	90
5	**1a**	2-ClC_6H_4	**4e**	8	83
6	**1a**	3-ClC_6H_4	**4f**	8	87
7	**1a**	4-ClC_6H_4	**4g**	8	85
8	**1a**	4-FC_6H_4	**4h**	8	80
9	**1a**	2-$MeOC_6H_4$	**4i**	6	90
10	**1a**	3-$MeOC_6H_4$	**4j**	6	91
11	**1a**	4-$MeOC_6H_4$	**4k**	6	92
12	**1a**	3-HOC_6H_4	**4l**	6	87
13	**1a**	4-HOC_6H_4	**4m**	6	88
14	**1a**	4-NCC_6H_4	**4n**	12	0
15	**1a**	4- $O_2NC_6H_4$	**4o**	12	0
16	**1a**	3,4-$(MeO)_2C_6H_3$	**4p**	6	92
17	**1a**	3,4,5-$(MeO)_3C_6H_2$	**4q**	6	93
18	**1a**	3-Pyridyl	**4r**	6	80
19	**1b**	C_6H_5	**4s**	8	85
20	**1c**	C_6H_5	**4t**	6	91

[a] Conditions: 2-aminobenzimidazole **1** (3 mmol), aromatic aldehyde **2** (6.6 mmol), TMSCN **3** (3.3 mmol), VB_1 (0.09 mmol, 3 mol %), EtOH (10 mL), reflux.
[b] Isolated yields.

–F) afforded the corresponding products **4** in 80–93% yields (Table 2, entries 1–12, 16–17). Whereas, no desired products were observed when using aromatic aldehydes with strong electron-withdrawing groups (–NO_2, –CN) as the substrates under the same reaction conditions for 12 h (Table 2, entries 14 and 15), and only some byproducts were detected by LC-MS (See in the Supplementary data).

Moreover, substituted 2-aminobenzimidazole, such as 5,6-dichloro-1*H*-benzo[d]imidazol-2-amine **1b** and 5*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*d*]imidazol-6-amine **1c** were used as the substrates, finding the reaction can proceed smoothly to obtain the corresponding products in good yields (Table 2, entries 19, 20). In addition, we also used 1-methyl-2-aminobenzimidazole **1d** as the substrate to replace 2-aminobenzimidazole **1a** in EtOH as solvent under reflux temperature for 8 h, and the product (*E*)-*N*-benzylidene-9-methyl-2-phenyl-9*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine **4u** was obtained in 88% yield (Scheme 3).

Although the mechanism of this reaction has not been established experimentally, the proposed mechanism for the formation of **4** is illustrated (Scheme 4). TMSCN **3** reacts with EtOH to release the NC^-,



Scheme 3. Condensation of 1-methyl-2-aminobenzimidazole **1d**, benzaldehyde **2a**, and TMSCN **3**.

which is captured by VB_1 to generate intermediate **6**. Intermediate **6** reacts with the corresponding aromatic aldehyde **2** to give intermediate **7**, then **7** reacts with another molecule of **3** to generate intermediate **8** and NC^-, and NC^- participates next reaction cycle. Next, intermediate **8** reacts with 2-aminobenzimidazole **1** to yield intermediate **9**, which is cyclized to form **10**. Next, intermediate **10** is isomerized to **11**, which reacts with another molecule of aromatic aldehyde **2** to form product **4**.

3. Conclusion

In conclusion, we have developed a novel and convenient method for the synthesis of (*E*)-*N*-benzylidene-2-phenyl-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazol-3-amine derivatives via the four-component reaction of 2-aminobenzimidazole **1**, two molecules of aromatic aldehyde **2**, and TMSCN **3** catalyzed by VB_1 in EtOH. The use of inexpensive and eco-friendly catalyst VB_1, mild reaction condition, high yields, and easy workup procedure, make this method attractive to synthesize a variety of these derivatives.

4. Experimental section

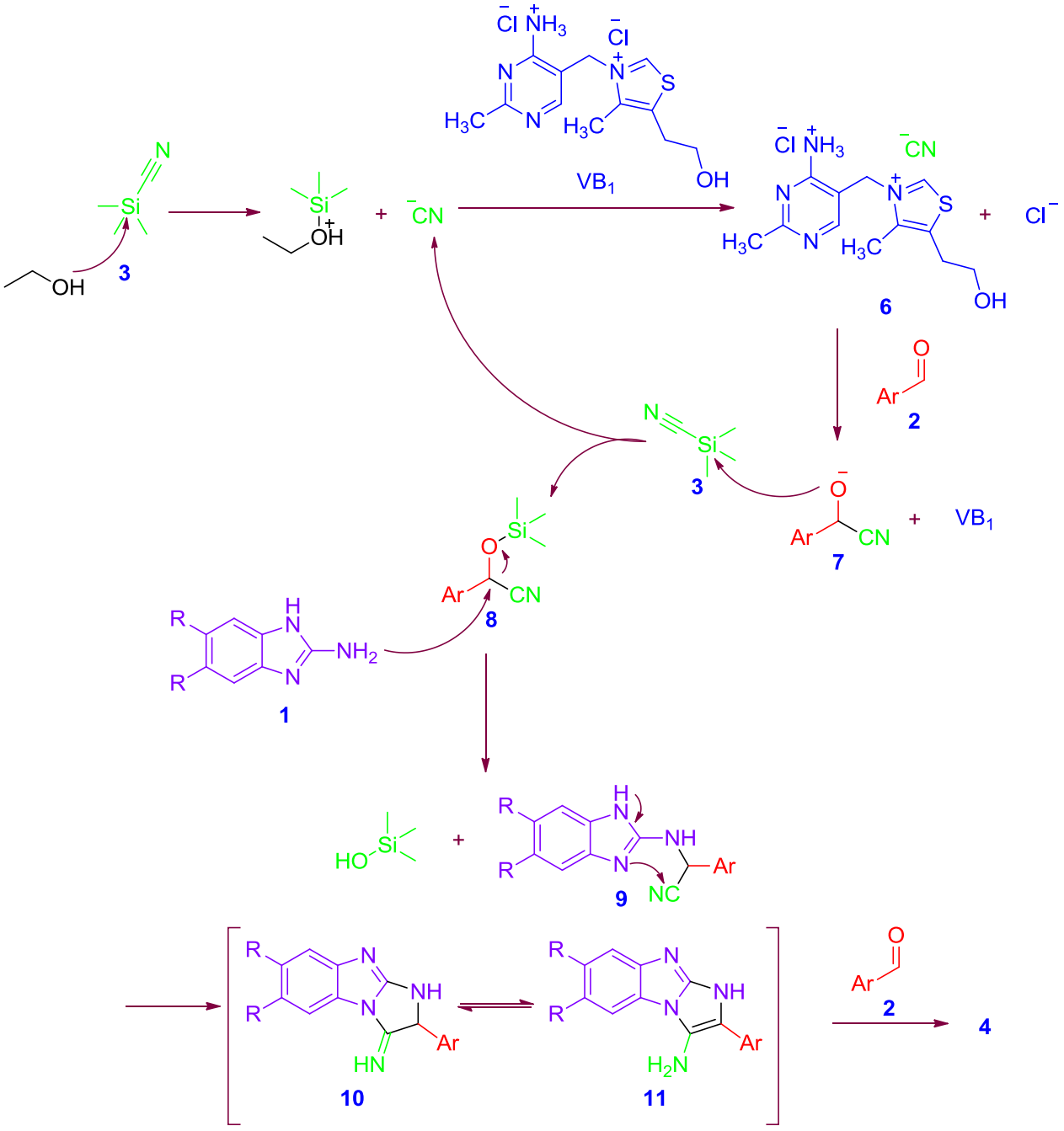
4.1. General

Melting points were measured by a WRS-1B micromelting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 400 and Bruker Avance III/500 instruments using solvent peaks as DMSO-d_6 solutions. HRESIMS were determined on a Micromass Q-Tof Global mass spectrometer and ESIMS were run on a Bruker Esquire 3000 Plus Spectrometer. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China). The chemicals used in this work were obtained from commercial channels and were used without purification.

4.2. Experimental procedure for the condensation of 2-aminobenzimidazole 1, aromatic aldehyde 2, and TMSCN 3

A mixture of 2-aminobenzimidazole **1** (3 mmol), aromatic aldehyde **2** (6.6 mmol), TMSCN **3** (3.3 mmol) and VB_1 (0.09 mmol, 3 mol %) in 10 mL EtOH was heated to reflux for 6–12 h (Table 2). After completion of the reaction (TLC), the solid was filtered off and washed with ethanol to yield the pure products **4**.

*4.2.1. (E)-N-Benzylidene-2-phenyl-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4a**).* Isolated as a yellow powder; mp 266.4–270.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.11 (br s, 1H, NH), 8.92 (s, 1H, CH), 8.20 (d, *J*=7.6 Hz, 2H, ArH), 8.02 (d, *J*=7.6 Hz, 2H, ArH), 7.75 (d,



Scheme 4. A plausible mechanistic pathway to explain the formation of compounds **4**.

J=8.0 Hz, 1H, ArH), 7.61–7.52 (m, 3H, ArH), 7.49–7.43 (m, 3H, ArH), 7.34 (t, *J*=7.6 Hz, 1H, ArH), 7.29 (t, *J*=7.2 Hz, 1H, ArH), 7.22 (t, *J*=7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 152.03, 148.19, 136.64, 134.67, 130.60, 130.60, 128.99, 128.99, 128.24, 128.24, 127.88, 127.88, 127.76, 127.34, 127.34, 126.76, 125.09, 123.63, 123.63, 119.86, 112.32, 112.22. ESI-MS *m*/*z* 337 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}N_4$ $[M+H]^+$ 337.1448, found 337.1440.

*4.2.2. (E)-N-(2-Methylbenzylidene)-2-(o-tolyl)-1H-benzo[d]imidazo [1,2-a]imidazol-3-amine (**4b**).* Isolated as a yellow powder; mp 266.0–267.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 11.94 (br s, 1H, NH), 8.46 (s, 1H, CH), 8.10–8.03 (m, 1H, ArH), 7.96 (d, *J*=7.8 Hz, 1H, ArH), 7.47 (d, *J*=8.1 Hz, 2H, ArH), 7.39–7.28 (m, 6H, ArH), 7.25 (t, *J*=7.6 Hz, 1H, ArH), 7.21–7.15 (m, 1H, ArH), 2.28 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 150.15, 146.88, 137.38, 136.31, 134.17, 130.94, 130.94, 130.30, 130.23, 130.23, 128.37, 128.11, 126.40, 126.40, 126.12, 125.48, 124.79, 123.39, 123.39, 120.17, 112.33, 111.76, 19.53, 18.14; ESI-MS *m*/*z* 365 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N_4$ $[M+H]^+$ 365.1761, found 365.1768.

*4.2.3. (E)-N-(3-Methylbenzylidene)-2-(m-tolyl)-1H-benzo[d]imidazo [1,2-a]imidazol-3-amine (**4c**).* Isolated as a yellow powder; mp 237.0–237.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.10 (br s, 1H, NH), 8.84 (s, 1H, CH), 8.06 (s, 1H, ArH), 7.97 (d, *J*=8.0 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.79 (d, *J*=8.0 Hz, 1H, ArH), 7.73 (d, *J*=8.1 Hz, 1H, ArH), 7.47–7.41 (m, 2H, ArH), 7.35–7.30 (m, 3H, ArH), 7.21 (t, *J*=7.8 Hz, 1H, ArH), 7.10 (d, *J*=7.4 Hz, 1H, ArH), 2.42 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 153.48, 150.03, 140.06, 138.91,

138.62, 136.41, 133.14, 130.77, 130.77, 130.18, 130.01, 130.01, 129.47, 129.29, 126.97, 126.97, 126.37, 125.47, 125.47, 121.72, 114.21, 114.17, 23.18, 22.88; ESI-MS *m/z* 365 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N_4$ $[M+H]^+$ 365.1761, found 365.1752.

*4.2.4. (E)-N-(4-Methylbenzylidene)-2-(p-tolyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4d**).* Isolated as a yellow powder; mp 279.9–281.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.05 (br s, 1H, NH), 8.86 (s, 1H, CH), 8.06 (d, *J*=8.0 Hz, 2H, ArH), 7.89 (d, *J*=8.0 Hz, 2H, ArH), 7.71 (d, *J*=7.9 Hz, 1H, ArH), 7.45 (d, *J*=7.9 Hz, 1H, ArH), 7.38 (d, *J*=8.1 Hz, 2H, ArH), 7.32 (t, *J*=7.8 Hz, 1H, ArH), 7.26 (d, *J*=8.1 Hz, 2H, ArH), 7.20 (t, *J*=7.8 Hz, 1H, ArH), 2.41 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 151.83, 148.09, 140.56, 135.94, 134.12, 131.82, 129.60, 129.60, 129.28, 129.06, 128.85, 128.85, 127.84, 127.84, 127.44, 127.23, 127.23, 125.19, 123.46, 119.72, 112.30, 112.18, 21.16, 20.83; ESI-MS *m/z* 365 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N_4$ $[M+H]^+$ 365.1761, found 365.1770.

*4.2.5. (E)-N-(2-Chlorobenzylidene)-2-(2-chlorophenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4e**).* Isolated as a yellow powder; mp 280.5–282.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.09 (br s, 1H, NH), 8.47 (s, 1H, CH), 8.28 (d, *J*=7.4 Hz, 1H, ArH), 8.05 (d, *J*=7.4 Hz, 1H, ArH), 7.70–7.65 (m, 1H, ArH), 7.64–7.58 (m, 1H, ArH), 7.52–7.43 (m, 6H, ArH), 7.36 (t, *J*=7.8 Hz, 1H, ArH), 7.29 (t, *J*=7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 147.06, 146.83, 135.11, 134.26, 133.91, 133.32, 132.44, 132.36, 131.76, 130.32, 129.91, 129.91, 129.70, 128.46, 127.71, 127.53, 126.89, 124.45, 123.81, 120.61, 112.12, 112.12; ESI-MS *m/z* 405 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{14}Cl_2N_4$ $[M+H]^+$ 405.0668, found 405.0664.

*4.2.6. (E)-N-(3-Chlorobenzylidene)-2-(3-chlorophenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4f**).* Isolated as a yellow powder; mp 292.8–293.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.27 (br s, 1H, NH), 8.88 (s, 1H, CH), 8.31 (t, *J*=1.8 Hz, 1H, ArH), 8.17 (d, *J*=7.9 Hz, 1H, ArH), 8.07 (s, 1H, ArH), 8.00 (d, *J*=7.8 Hz, 1H, ArH), 7.82 (d, *J*=7.8 Hz, 1H, ArH), 7.63–7.57 (m, 2H, ArH), 7.52–7.45 (m, 2H, ArH), 7.40–7.34 (m, 2H, ArH), 7.25 (t, *J*=7.5 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 149.62, 148.49, 138.92, 133.89, 133.89, 133.02, 130.87, 130.87, 130.19, 130.14, 127.85, 127.38, 127.07, 126.51, 126.34, 126.34, 125.74, 124.84, 124.06, 120.22, 113.01, 112.07; ESI-MS *m/z* 405 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{14}Cl_2N_4$ $[M+H]^+$ 405.0668, found 405.0663.

*4.2.7. (E)-N-(4-Chlorobenzylidene)-2-(4-chlorophenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4g**).* Isolated as a yellow powder; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.16 (br s, 1H, NH), 8.88 (s, 1H, CH), 8.21 (d, *J*=8.4 Hz, 2H, ArH), 8.03 (d, *J*=8.4 Hz, 2H, ArH), 7.76 (d, *J*=8.0 Hz, 1H, ArH), 7.62 (d, *J*=8.2 Hz, 2H, ArH), 7.50 (d, *J*=8.2 Hz, 2H, ArH), 7.45 (d, *J*=8.0 Hz, 1H, ArH), 7.35 (t, *J*=7.8 Hz, 1H, ArH), 7.22 (t, *J*=7.8 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 150.88, 148.83, 136.05, 135.54, 131.82, 130.07, 130.07, 129.60, 129.60, 129.47, 129.47, 128.83, 128.83, 128.34, 128.24, 125.42, 125.39, 124.41, 124.36, 120.58, 113.19, 113.19; ESI-MS *m/z* 405 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{14}Cl_2N_4$ $[M+H]^+$ 405.0668, found 405.0677.

*4.2.8. (E)-N-(4-Fluorobenzylidene)-2-(4-fluorophenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4h**).* Isolated as a yellow powder; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.14 (br s, 1H, NH), 8.87 (s, 1H, CH), 8.21 (dd, *J*=8.6, 5.8 Hz, 2H, ArH), 8.06 (dd, *J*=8.6, 5.8 Hz, 2H, ArH), 7.72 (d, *J*=8.1 Hz, 1H, ArH), 7.46–7.18 (m, 7H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 164.50 and 162.52 ($^1J_{CF}$=247.4 Hz), 162.15 and 160.21 ($^1J_{CF}$=243.0 Hz), 150.57, 148.15, 135.77 and 135.75 ($^4J_{CF}$=2.8 Hz), 135.33, 133.35 and 133.32 ($^4J_{CF}$=2.6 Hz), 131.27, 130.16 and 130.09 ($^3J_{CF}$=8.6 Hz), 129.26 and 129.20 ($^3J_{CF}$=7.8 Hz), 127.45, 125.01, 123.72, 119.94, 116.18 and 116.01 ($^2J_{CF}$=21.9 Hz), 115.24 and 115.08 ($^2J_{CF}$=21.2 Hz), 112.49, 112.10; ESI-MS *m/z* 373 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{14}F_2N_4$ $[M+H]^+$ 373.1259, found 373.1256.

*4.2.9. (E)-N-(2-Methoxybenzylidene)-2-(2-methoxyphenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4i**).* Isolated as a yellow powder; mp 251.0–251.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 11.82 (br s, 1H, NH), 8.50 (s, 1H, CH), 8.15 (dd, *J*=7.6, 1.7 Hz, 1H, ArH), 8.02 (d, *J*=7.2 Hz, 1H, ArH), 7.60 (dd, *J*=7.6, 1.7 Hz, 1H, ArH), 7.47–7.40 (m, 3H, ArH), 7.31 (td, *J*=7.7, 1.2 Hz, 1H, ArH), 7.24 (td, *J*=7.7, 1.2 Hz, 1H, ArH), 7.16–7.06 (m, 4H, ArH), 3.74 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 158.49, 156.09, 148.42, 146.60, 131.85, 131.57, 129.24, 129.20, 125.42, 125.04, 124.94, 123.96, 123.20, 120.88, 120.88, 120.39, 120.39, 120.02, 112.33, 111.83, 111.81, 110.98, 55.56, 55.00; ESI-MS *m/z* 397 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N_4O_2$ $[M+H]^+$ 397.1659, found 397.1650.

*4.2.10. (E)-N-(3-Methoxybenzylidene)-2-(3-methoxyphenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4j**).* Isolated as a yellow powder; mp 220.8–221.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.13 (br s, 1H, NH), 8.86 (s, 1H, CH), 7.85 (s, 1H, ArH), 7.80 (d, *J*=7.9 Hz, 1H, ArH), 7.73 (d, *J*=7.9 Hz, 1H, ArH), 7.61–7.56 (m, 2H, ArH), 7.50–7.44 (m, 2H, ArH), 7.37–7.32 (m, 2H, ArH), 7.22 (t, *J*=7.7 Hz, 1H, ArH), 7.09 (dd, *J*=8.2, 2.2 Hz, 1H, ArH), 6.86 (dd, *J*=8.2, 2.2 Hz, 1H, ArH), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 159.72, 159.14, 151.57, 148.21, 138.19, 135.97, 130.08, 129.24, 127.71, 125.07, 123.70, 120.86, 120.86, 119.92, 119.79, 116.75, 116.75, 112.69, 112.54, 112.44, 112.24, 111.87, 55.16, 54.92; ESI-MS *m/z* 397 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N_4O_2$ $[M+H]^+$ 397.1659, found 397.1662.

*4.2.11. (E)-N-(4-Methoxybenzylidene)-2-(4-methoxyphenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4k**).* Isolated as a yellow powder; mp 285.9–286.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.01 (br s, 1H, NH), 8.82 (s, 1H, CH), 8.12 (d, *J*=8.8 Hz, 2H, ArH), 7.95 (d, *J*=8.8 Hz, 2H, ArH), 7.68 (d, *J*=8.0 Hz, 1H, ArH), 7.44 (d, *J*=8.0 Hz, 1H, ArH), 7.30 (t, *J*=7.8 Hz, 1H, ArH), 7.19 (t, *J*=7.8 Hz, 1H, ArH), 7.12 (d, *J*=8.7 Hz, 2H, ArH), 7.02 (d, *J*=8.7 Hz, 2H, ArH), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 161.36, 158.19, 158.19, 151.49, 148.01, 129.55, 129.55, 128.48, 128.48, 127.20, 127.06, 125.31, 123.32, 123.32, 119.61, 119.61, 114.55, 114.55, 113.77, 113.77, 112.39, 112.10, 55.42, 55.07; ESI-MS *m/z* 397 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{20}N_4O_2$ $[M+H]^+$ 397.1659, found 397.1655.

*4.2.12. (E)-3-(3-((3-Hydroxybenzylidene)amino)-1H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenol (**4l**).* Isolated as a yellow powder; mp 247.1–247.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.06 (br s, 1H, NH), 9.76 (br s, 1H, OH), 9.43 (br s, 1H, OH), 8.82 (s, 1H, CH), 7.68 (d, *J*=8.0 Hz, 1H, ArH), 7.63 (d, *J*=8.0 Hz, 1H, ArH), 7.61–7.57 (m, 1H, ArH), 7.47–7.40 (m, 3H, ArH), 7.39–7.30 (m, 2H, ArH), 7.26–7.16 (m, 2H, ArH), 6.96–6.91 (m, 1H, ArH), 6.72–6.67 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 157.84, 157.21, 152.89, 147.98, 137.95, 135.89, 130.03, 130.03, 129.16, 127.81, 125.15, 123.60, 119.79, 119.60, 118.39, 118.07, 114.23, 113.93, 113.70, 113.70, 112.30, 112.11; ESI-MS *m/z* 369 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}N_4O_2$ $[M+H]^+$ 369.1346, found 369.1355.

*4.2.13. (E)-4-(3-((4-Hydroxybenzylidene)amino)-1H-benzo[d]imidazo[1,2-a]imidazol-2-yl)phenol (**4m**).* Isolated as a yellow powder; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 11.90 (br s, 1H, NH), 10.12 (br s, 1H, OH), 9.54 (br s, 1H, OH), 8.77 (s, 1H, CH), 7.97 (d, *J*=8.6 Hz, 2H, ArH), 7.84 (d, *J*=8.6 Hz, 2H, ArH), 7.66 (d, *J*=8.0 Hz, 1H, ArH), 7.43 (d, *J*=8.0 Hz, 1H, ArH), 7.28 (t, *J*=7.6 Hz, 1H, ArH), 7.16 (t, *J*=7.6 Hz, 1H, ArH), 6.94 (d, *J*=8.6 Hz, 2H, ArH), 6.84 (d, *J*=8.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 160.08, 156.42, 152.06, 147.91, 129.77, 129.77, 128.56, 128.56, 128.07, 126.77, 125.45, 125.45, 123.14, 119.44, 115.96, 115.96, 115.84, 115.18, 115.18, 112.60, 111.92, 111.92;

ESI-MS *m/z* 369 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}N_4O_2$ $[M+H]^+$ 369.1346, found 369.1343.

*4.2.14. (E)-N-(3,4-Dimethoxybenzylidene)-2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4p**).* Isolated as a yellow powder; mp 271.1–273.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 11.99 (br s, 1H, NH), 8.82 (s, 1H, CH), 7.87 (d, *J*=1.9 Hz, 1H, ArH), 7.73 (dd, *J*=8.4, 1.9 Hz, 1H, ArH), 7.68–7.64 (m, 2H, ArH), 7.53 (dd, *J*=8.4, 1.9 Hz, 1H, ArH), 7.45 (d, *J*=7.6 Hz, 1H, ArH), 7.31 (t, *J*=7.4 Hz, 1H, ArH), 7.19 (t, *J*=7.4 Hz, 1H, ArH), 7.13 (d, *J*=8.4 Hz, 1H, ArH), 7.04 (d, *J*=8.4 Hz, 1H, ArH), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 152.07, 151.36, 149.26, 148.37, 147.98, 147.86, 129.64, 129.64, 127.35, 127.12, 125.31, 123.34, 122.86, 119.75, 119.62, 112.45, 112.05, 111.66, 111.66, 110.74, 108.89, 108.89, 55.69, 55.48, 55.46, 55.27; ESI-MS *m/z* 457 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{24}N_4O_4$ $[M+H]^+$ 457.1870, found 457.1864.

*4.2.15. (E)-N-(3,4,5-Trimethoxybenzylidene)-2-(3,4,5-trimethoxyphenyl)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4q**).* Isolated as a yellow powder; mp 252.1–252.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 12.04 (br s, 1H, NH), 8.85 (s, 1H, CH), 7.65 (d, *J*=8.0 Hz, 1H, ArH), 7.56 (s, 2H, ArH), 7.46 (d, *J*=8.0 Hz, 1H, ArH), 7.37 (s, 2H, ArH), 7.33 (t, *J*=7.8 Hz, 1H, ArH), 7.21 (t, *J*=7.8 Hz, 1H, ArH), 3.88 (s, 6H, OCH_3), 3.85 (s, 6H, OCH_3), 3.76 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 153.41, 153.41, 152.86, 152.71, 152.71, 147.98, 140.06, 136.64, 132.08, 132.08, 127.64, 125.15, 123.60, 123.60, 119.86, 112.32, 112.19, 112.19, 105.16, 105.16, 104.52, 104.52, 60.23, 60.13, 56.00, 56.00, 55.71, 55.71; ESI-MS *m/z* 517 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{28}N_4O_6$ $[M+H]^+$ 517.2082, found 517.2087.

*4.2.16. (E)-2-(Pyridin-3-yl)-N-(pyridin-3-ylmethylene)-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4r**).* Isolated as a yellow powder; mp 257.2–258.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.21 (br s, 1H, NH), 9.36 (s, 1H, ArH), 9.15 (s, 1H, ArH), 8.92 (s, 1H, CH), 8.67 (d, *J*=4.5 Hz, 1H, ArH), 8.51 (d, *J*=8.0 Hz, 1H, ArH), 8.48 (d, *J*=4.5 Hz, 1H, ArH), 8.37 (d, *J*=8.0 Hz, 1H, ArH), 7.85 (d, *J*=8.3 Hz, 1H, ArH), 7.62–7.55 (m, 1H, ArH), 7.52–7.42 (m, 2H, ArH), 7.36 (t, *J*=7.7 Hz, 1H, ArH), 7.24 (t, *J*=7.7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 151.34, 150.24, 149.17, 149.10, 148.84, 148.00, 135.86, 135.82, 134.75, 134.56, 132.78, 130.98, 128.69, 125.25, 124.57, 124.48, 123.91, 120.65, 113.45, 112.48; ESI-MS *m/z* 339 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{14}N_6$ $[M+H]^+$ 339.1353, found 369.1340.

*4.2.17. (E)-N-Benzylidene-6,7-dichloro-2-phenyl-1H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4s**).* Isolated as a yellow powder; mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 12.50 (br s, 1H, NH), 8.95 (s, 1H, CH), 8.09 (d, *J*=7.6 Hz, 2H, ArH), 8.01 (d, *J*=7.6 Hz, 2H, ArH), 7.83 (s, 1H, ArH), 7.74 (s, 1H, ArH), 7.62–7.55 (m, 3H, ArH), 7.49 (t, *J*=7.5 Hz, 2H, ArH), 7.35 (t, *J*=7.5 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 155.45, 149.95, 136.72, 136.72, 131.72, 131.72, 129.63, 129.63, 129.03, 129.03, 128.65, 128.65, 127.97, 127.82, 127.82, 127.73, 125.94, 125.70, 121.13, 121.06, 113.97, 113.97; ESI-MS *m/z* 405 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{14}Cl_2N_4$ $[M+H]^+$ 405.0668, found 405.0679.

*4.2.18. (E)-N-Benzylidene-7-phenyl-6H-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-d]imidazo[1,2-a]imidazol-8-amine (**4t**).* Isolated as a yellow powder; mp 287.1–287.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 11.96 (br s, 1H, NH), 8.79 (s, 1H, CH), 8.12 (d, *J*=7.2 Hz, 2H, ArH), 7.98 (d, *J*=7.2 Hz, 2H, ArH), 7.58–7.50 (m, 3H, ArH), 7.44 (t, *J*=7.6 Hz, 2H, ArH), 7.28 (t, *J*=7.6 Hz, 1H, ArH), 7.26 (s, 1H, ArH), 7.08 (s, 1H, ArH), 6.07 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 152.38, 148.79, 144.64, 144.64, 141.64, 137.12, 137.12, 131.03, 129.46, 129.46, 128.76, 128.76, 128.32, 128.32, 127.74, 127.74, 127.48, 127.24, 127.24, 119.08, 101.66, 101.66, 94.96; ESI-MS *m/z* 381 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{16}N_4O_2$ $[M+H]^+$ 381.1346, found 381.1334.

*4.2.19. (E)-N-Benzylidene-9-methyl-2-phenyl-9H-benzo[d]imidazo[1,2-a]imidazol-3-amine (**4u**).* Isolated as a yellow powder; mp 130.0–131.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 8.85 (s, 1H, CH), 8.22 (dd, *J*=8.0, 1.2 Hz, 2H, ArH), 7.99 (dd, *J*=8.0, 1.2 Hz, 2H, ArH), 7.73 (d, *J*=8.1 Hz, 1H, ArH), 7.60–7.51 (m, 4H, ArH), 7.44 (t, *J*=7.8 Hz, 2H, ArH), 7.39 (t, *J*=7.8 Hz, 1H, ArH), 7.29 (d, *J*=7.4 Hz, 1H, ArH), 7.25 (d, *J*=7.4 Hz, 1H, ArH), 3.76 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 152.14, 148.73, 137.18, 137.13, 136.57, 135.39, 131.09, 129.48, 129.48, 128.94, 128.72, 128.72, 128.40, 128.40, 127.92, 127.92, 127.27, 124.86, 124.14, 120.67, 112.90, 110.74, 29.16; ESI-MS *m/z* 351 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{18}N_4$ $[M+H]^+$ 351.1604, found 351.1615.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.022.

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