Solution-Phase and Solid-Phase Synthesis of 1-Pyrazol-3-ylbenzimidazoles

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Abstract: The facile solution and solid-phase synthesis of 1-pyrazol-3-ylbenzimidazoles from 4-fluoro-3-nitrobenzoate derivatives and 5(3)-amino-3(5)-subtituted-1*H*-pyrazoles is reported. The key step is the unexpected nucleophilic aromatic displacement of the activated fluorine by the exocyclic amino group of the pyrazole ring leading to 4-pyrazolylamino-3-nitrobenzoate derivatives, which are easily converted into the corresponding 1-pyrazol-3-ylbenzimidazoles in very high isolated yield. These novel methodologies would be very useful for the generation of libraries of diverse 1-heteroaryl derivatives of benzimidazoles.

Key words: solid-phase synthesis, combinatorial chemistry, heterocycles, benzimidazoles, pyrazoles

Combinatorial synthesis of low-molecular-weight structures by either solid- and liquid-phase approaches has emerged in the last few years as an important tool for the discovery and development of novel lead compounds and for the optimization of therapeutic efficacy.[1] Synthesis on a solid support shows a number of advantages over solution chemistry:[2] (i) filtration can be used for rapid purification; (ii) excess of reagents can be used to drive the reaction to completion; (iii) automation is easily accomplished; and (iv) relative site isolation is achieved with the 'pseudo-dilution effect'.[3] However, solid-phase synthesis has some limitations, mainly related to difficult characterization of supported products and the lack of precedent of several organic transformations on solid support. For this reason, synthetic approaches to develop combinatorial libraries are sometime a compromise between solution-phase and solid-phase strategies.

From the realm of organic chemistry, heterocycles are of particular interest in combinatorial synthesis, due to the possible similarities with many natural and synthetic molecules with known biological activity.[4] Benzimidazole is an important heterocycle whose effectiveness has been clearly demonstrated in a number of clinically important therapeutic areas. Apart from the antihistamine Astemizole[5] and the antiulcerative Omeprazol,[6] benzimidazole-based compounds have shown biological activity as, for example, inhibitors of phosphodiesterase IV,[7] antagonists of angiotensin 1,[8] and inhibitors of proton pumps.[9]All these features, together with its close structural relationship to benzodiazepines, place the benzimidazole scaffold among the privileged structures.[10]

As part of our interest in novel biologically active nitrogen-containing heterocyclic scaffolds[11] and the application of solid-phase techniques to their synthesis,[12] we describe herein an efficient synthesis of new 1-pyrazol-3-ylbenzimidazoles (**1**, Figure 1) that could be adapted for the solution or solid-phase parallel or combinatorial synthesis of this significant core skeleton.[13,14]

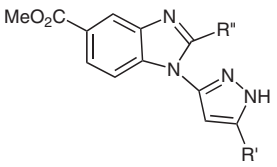

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Figure 1 1-Pyrazol-3-ylbenzimidazoles **1**

Before starting with the development of a solid-phase approach, we decided to test analogous strategies in solution phase in order to obtain models for a subsequent translation to the solid-supported chemistry. In the search of new, biologically promising heterocycle derivatives, we decided to test the reaction between methyl 4-fluoro-3-nitrobenzoate (**2**) and 5(3)-amino-3(5)-phenyl-1*H*-pyrazole (**3a**, R′ = Ph) (Scheme 1). Interestingly, when this reaction was performed in DMSO at room temperature for two hours, the unexpected methyl 4-pyrazolylamino-3-nitrobenzoate (**6a**) was obtained as the sole product in very high yield (90%). Nucleophilic aromatic displacement (S_NAr) of the activated fluorine in **2**[15] was achieved by the amino group of **3a** instead of the expected attack by the more nucleophilic nitrogen of the aromatic ring. The expected methyl 4-(5-amino-3-phenyl-1*H*-pyrazol-1-yl)-3-nitrobenzoate (**4a**) was only obtained when the reaction was heated in an oil bath at 120 °C for 10 minutes, however, the product was mixed with **6a** in a 1:1 proportion.[16,17] Similar results were found for other pyrazoles **3b**,**c** (Table 1). With the 4-pyrazolylamino-3-nitrobenzoates **6a–c** in hand, we investigated the synthesis of the corresponding benzimidazole derivatives. Thus, catalytic reduction of the nitro group in **6a–c** was efficiently

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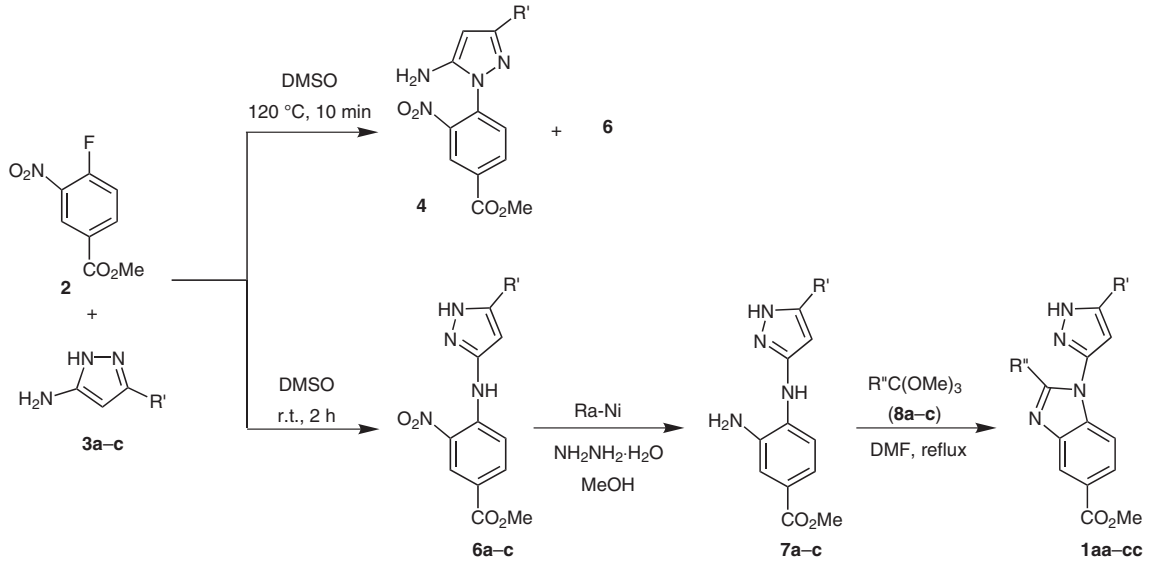


Scheme 1

Table 1 Solution-Phase Synthesis of 1-Pyrazol-3-ylbenzimidazoles **1aa–cc** from Methyl 4-Fluoro-3-nitrobenzoate (**2**)

Entry	R′	Yield (%) of **6**	Yield (%)[a] of **7**	R″	Product	Yield (%)[b] of **1**
1	Ph	–	–	H	**1aa**	65
2	Ph	90	90	Me	**1ab**	66
3	Ph	–	–	Ph	**1ac**	45
4	Me	93	92	H	**1ba**	77
5	Me	–	–	Me	**1bb**	79
6	Me	–	–	H	**1ca**	83
7	*t*-Bu	95	95	Me	**1cb**	84
8	*t*-Bu	–	–	Ph	**1cc**	68

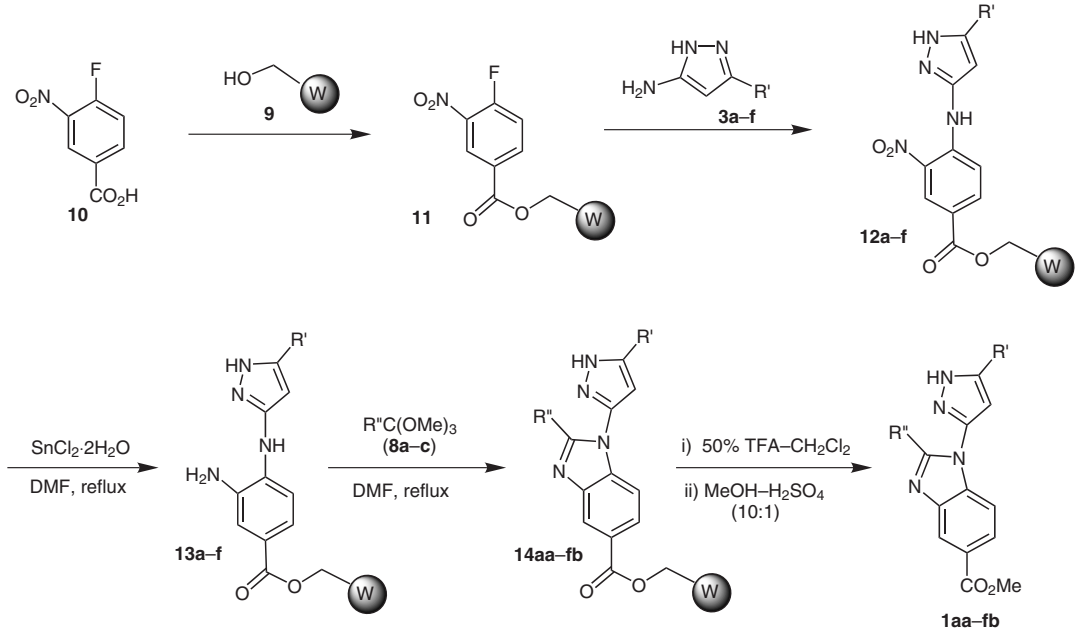
[a] From compound **6**.
[b] Overall isolated yield.

achieved using Raney-Ni and hydrazine hydrate to give the desired amines **7a–c** in yields ranging from 90 to 95%. Further treatment of **7a–c** with the trimethyl orthocarboxylates **8a–c**, afforded the corresponding 1-pyrazol-3-ylbenzimidazoles **1aa–cc**[18] in high isolated yields (Scheme 1 and Table 1).

These results have opened the door to a new solution and solid-phase synthesis of a scarcely reported series of heterocyclic compounds. While the synthesis of 2-pyrazol-3-ylbenzimidazoles is well documented,[19] synthesis of 1-pyrazol-3-ylbenzimidazoles have been only reported through the ring contraction of a benzodiazepine moiety.[13] Our methodology allows the introduction of the pyrazole ring before cyclization to the benzimidazole derivative and, consequently, it could allow the introduction of diverse heterocycles to give libraries of 1-heteroaryl derivatives of benzimidazoles.

Having established the feasibility of the synthetic strategy in solution, we next carried out the synthesis of a solid-phase library of 1-pyrazol-3-ylbenzimidazoles. Commercially available Wang resin **9** was chosen as a proper linker and 4-fluoro-3-nitrobenzoic acid (**10**) was immobilized to that resin using the DIC/DMAP coupling procedure (Scheme 2). Again, as in homogeneous synthesis, treatment of **11** with a series of 5(3)-amino-3(5)-substituted 1*H*-pyrazoles **3a–f** in DMSO at room temperature, afforded the resin-bound 4-pyrazolylamino-3-nitrobenzoates **12a–f** by the attack of the amino group over the activated fluorine. Formation of **12a–c** was corroborated by treatment with TFA and esterification with diazomethane, to yield the already characterized benzoates **6a–c**. Reduction of the nitro group of **12a–f** with Raney-Ni and hydrazine hydrate was inefficient on solid phase and the removal of Raney-Ni residues was problematic. Therefore, this reduction was carried out in the presence of tin(II) chloride dihydrate in DMF (reflux, 5 min) to give the desired *o*-phenylenediamine derivatives **13a–f** tethered to Wang resin. Subsequently, cyclization was achieved by treating **13a–f** with excess of trimethyl orthocarboxylates **8a–c** in DMF at reflux, to afford the resin-bound benzimidazoles **14aa–fb**. Cleavage of **14aa–fb** from the resin was accomplished with 50% TFA–CH_2Cl_2. Finally, esterification with MeOH in the presence of H_2SO_4 gave the 1-pyrazol-3-ylbenzimidazoles **1aa–fb** in very high overall yield after isolation by column chromatography (Table 2).

In summary, we have reported an efficient and high-yielding methodology for solution and solid-phase synthesis of 1-pyrazol-3-ylbenzimidazoles. A fourteen-member library of these scarcely reported heterocyclic compounds has been developed by the solid-phase strategy and the products were obtained in very high overall yield for the five reaction steps. We anticipate that this approach should allow the generation of libraries of biologically promising 1-heteroaryl derivatives of benzimidazoles.



Scheme 2

Table 2 Solid-Phase Synthesis of 1-Pyrazol-3-ylbenzimidazoles **1aa–fb**

Entry	Product	R′	R″	Yield of **1** (%)[a]
1	**1aa**	Ph	H	68
2	**1ab**	Ph	Me	70
3	**1ac**	Ph	Ph	65
4	**1ba**	Me	H	75
5	**1bb**	Me	Me	77
6	**1ca**	*t*-Bu	H	80
7	**1cb**	*t*-Bu	Me	81
8	**1cc**	*t*-Bu	Ph	70
9	**1da**	4-MeC_6H_4	H	74
10	**1db**	4-MeC_6H_4	Me	78
11	**1ea**	4-ClC_6H_4	H	76
12	**1eb**	4-ClC_6H_4	Me	79
13	**1fa**	4-BrC_6H_4	H	78
14	**1fb**	4-BrC_6H_4	Me	80

[a] Overall isolated yield after flash column chromatography (based on the initial loading level of Wang resin, five reaction steps).

Chemical reagents were purchased from commercial sources and were used without further purification, unless otherwise noted. Solvents were of analytical grade or purified by standard procedures prior to use. Resins were purchased from Novabiochem (San Diego, CA, USA). IR spectra were recorded on a Shimadzu Prestige 21 spectrophotometer and only partial spectral data are listed. NMR spectra were run on Bruker Avance 300 and Bruker Avance 400 spectrometers using TMS as internal reference. The mass spectra were recorded on a Hewlett-Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 eV. The elemental analyses were obtained using a LECO CHNS-900 elemental analyzer. Analytical TLC was carried out with silica gel 60 F_{254} precoated aluminum sheets (Merck). Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh).

Methyl 4-[(5-Alkyl/aryl-1*H*-pyrazol-3-yl)amino]-3-nitrobenzoates 6a–c; General Procedure

A solution of **3a–c** (2 mmol) and methyl 4-fluoro-3-nitrobenzoate (**2**; 398 mg, 2 mmol) in DMSO (2 mL) was stirred at 25 °C for 2 h. The precipitate was filtered and washed with MeOH (10 mL) to give **6a–c** as orange solids (Table 1).

Methyl 3-Nitro-4-[(5-phenyl-1*H*-pyrazol-3-yl)amino]benzoate (6a)

Orange crystals; mp 257–258 °C.

IR (KBr): 3261 (NH), 1696 (C=O), 1623 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.85 (s, 3 H, OCH_3), 6.73 (s, 1 H, 4-H), 7.38 (t, *J* = 7.93 Hz, 1 H, H_p-C_6H_5), 7.48 (t, *J* = 7.18, 7.93 Hz, 2 H, H_m-C_6H_5), 7.76 (d, *J* = 7.18 Hz, 2 H, H_o-C_6H_5), 8.03 (d, *J* = 9.06 Hz, 1 H, 6-H, Ar), 8.06 (d, *J* = 9.06 Hz, 1 H, 5-H, Ar), 8.66 (s, 1 H, 2-H, Ar), 9.98 (s, 1 H, 5-N*H*Ar), 13.19 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 52.6 (OCH_3), 96.5 (C-4), 117.9 (C-5, Ar), 119.0 (C-1, Ar), 125.6 (C_o-C_6H_5), 128.3 (C-2, Ar), 129.0 (C_p-C_6H_5), 129.3 (C_i-C_6H_5), 129.5 (C_m-C_6H_5), 132.4 (C-4, Ar), 136.1 (C-6, Ar), 143.7 (C-3), 143.4 (C-3, Ar), 148.5 (C-5), 165.2 (C=O).

MS (70 eV): *m*/*z* (%) = 338 (M^+, 100), 307 (12), 292 (40).

HRMS: *m*/*z* calcd for $C_{17}H_{14}N_4O_4$ (M^+): 338.1015; found: 338.1021.

Methyl 4-[(5-Methyl-1*H*-pyrazol-3-yl)amino]-3-nitrobenzoate (6b)

Orange crystals; mp 225–226 °C.

IR (KBr): 3284 (NH), 1698 (C=O), 1621 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 3 H, 3-CH_3), 3.82 (s, 3 H, OCH_3), 6.03 (s, 1 H, 4-H), 7.96 (d, *J* = 9.21 Hz 1 H, 6-H, Ar),

7.99 (d, *J* = 9.21 Hz 1 H, 5-H, Ar), 8.62 (s, 1 H, 2-H, Ar), 9.89 (s, 1 H, 5-N*H*Ar), 12.43 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 11.1 (3-CH_3), 52.6 (OCH_3), 97.8 (C-4), 117.2 (C-5, Ar), 118.6 (C-1, Ar), 128.3 (C-2, Ar), 131.9 (C-4, Ar), 136.0 (C-6, Ar), 140.3 (C-3), 144.4 (C-3, Ar), 147.5 (C-5), 165.2 (C=O).

MS (70 eV): *m*/*z* (%) = 276 (M^+, 100), 245 (12).

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.08; H, 4.67; N, 20.13.

Methyl 4-[(5-*tert*-Butyl-1*H*-pyrazol-3-yl)amino]-3-nitrobenzoate (6c)
Orange crystals; mp 239–240 °C.

IR (KBr): 3370, 3315 (NH), 1705 (C=O), 1625 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.28 (s, 9 H, *t*-C_4H_9), 3.83 (s, 3 H, OCH_3), 6.04 (s, 1 H, 4-H), 8.01 (m, 1 H, 6-H, Ar), 8.00 (m, 1 H, 5-H, Ar), 8.63 (s, 1 H, 2-H, Ar), 9.89 (s, 1 H, 5-N*H*Ar), 12.41 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 30.3 [C(*C*H_3)$_3$], 31.2 [*C*(CH_3)$_3$], 52.6 (OCH_3), 94.8 (C-4), 117.9 (C-5, Ar), 118.7 (C-1, Ar), 128.3 (C-2, Ar), 132.0 (C-4, Ar), 136.0 (C-6, Ar), 144.3 (C-3, Ar), 147.0 (C-5), 154.3 (C-3), 165.2 (C=O).

MS (70 eV): *m*/*z* (%) = 318 (M^+, 100), 287 (15).

HRMS: *m*/*z* calcd for $C_{15}H_{18}N_4O_4$ (M^+): 318.1328; found: 318.1334.

Methyl 3-Amino-4-[(5-Alkyl/aryl-1*H*-pyrazol-3-yl)amino]benzoates 7a–c; General Procedure
A mixture of **6a–c** (1.5 mmol), hydrazine hydrate (225 mg, 4.5 mmol), and Raney-Ni (70 mg) in MeOH (15 mL) was refluxed under magnetic stirring for 15 min. After that, the mixture was filtered to remove the Raney-Ni. The filtrate was cooled and the deposited solid was collected by filtration and crystallized from MeOH to give **7a–c** as white solids.

Methyl 3-Amino-4-[(5-phenyl-1*H*-pyrazol-3-yl)amino]benzoate (7a)
White solid; mp 235–236 °C.

IR (KBr): 3372, 3186 (NH_2), 1683 (C=O), 1597 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (s, 3 H, OCH_3), 5.03 (s, 2 H, ArNH_2), 6.39 (s, 1 H, 4-H), 7.23 (d, *J* = 9.21 Hz, 1 H, 6-H, Ar), 7.32 (s, 1 H, 2-H, Ar), 7.33 (t, *J* = 7.84 Hz, 1 H, H_p-C_6H_5), 7.44 (t, *J* = 7.29, 7.84 Hz, 2 H, H_m-C_6H_5), 7.61 (d, *J* = 9.21 Hz, 1 H, 5-H, Ar), 7.67 (s, 1 H, 5-NH), 7.72 (d, *J* = 7.29 Hz, 2 H, H_o-C_6H_5), 11.94 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 51.8 (OCH_3), 93.0 (C-4), 113.8 (C-5, Ar), 115.7 (C-2, Ar), 120.1 (C-6, Ar), 120.2 (C-1, Ar), 125.5 (C_o-C_6H_5), 128.6 (C_p-C_6H_5), 129.4 (C_m-C_6H_5), 130.1 (C*i*-C_6H_5), 135.6 (C-3, Ar), 135.9 (C-4, Ar), 142.7 (C-3), 151.6 (C-5), 167.1 (C=O).

MS (70 eV): *m*/*z* (%) = 308 (M^+, 100), 297 (10), 277 (20).

Anal. Calcd for $C_{17}H_{16}N_4O_2{\cdot}0.5H_2O$: C, 64.34; H, 5.40; N, 17.66. Found: C, 63.91; H, 5.39; N, 17.82.

Methyl 3-Amino-4-[(5-methyl-1*H*-pyrazol-3-yl)amino]benzoate (7b)
White solid; mp 210–211 °C.

IR (KBr): 3172, 3376 (NH_2), 1716 (C=O), 1649 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.19 (s, 3 H, 3-CH_3), 3.74 (s, 3 H, OCH_3), 4.98 (s, 2 H, ArNH_2), 5.72 (s, 1 H, 4-H), 7.18 (d, *J* = 8.70 Hz, 1 H, 6-H, Ar), 7.26 (s, 1 H, 2-H, Ar), 7.46 (s, 1 H, 5-NH), 7.59 (d, *J* = 8.70 Hz, 1 H, 5-H, Ar), 11.84 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 11.2 (3-CH_3), 51.8 (OCH_3), 94.8 (C-4), 113.5 (C-5, Ar), 115.6 (C-2, Ar), 119.7 (C-1, Ar), 120.1 (C-6, Ar), 135.4 (C-3, Ar), 135.9 (C-4, Ar), 139.6 (C-3), 151.3 (C-5), 167.2 (C=O).

MS (70 eV): *m*/*z* (%) = 246 (M^+, 33), 215 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{14}N_4O_2$ (M^+): 246.1117; found: 246.1119.

Methyl 3-Amino-4-[(5-*tert*-butyl-1*H*-pyrazol-3-yl)amino]benzoate (7c)
White solid; mp 190–191 °C.

IR (KBr): 3303, 3150 (NH_2), 1698 (C=O), 1597 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.26 (s, 9 H, *t*-C_4H_9), 3.74 (s, 3 H, OCH_3), 5.01 (s, 2 H, ArNH_2), 5.71 (s, 1 H, 4-H), 7.20 (d, *J* = 8.50 Hz, 1 H, 6-H, Ar), 7.25 (s, 1 H, 2-H, Ar), 7.44 (s, 1 H, 5-NH), 7.63 (d, *J* = 8.50 Hz, 1 H, 5-H, Ar), 11.84 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 30.4 [C(*C*H_3)$_3$], 31.1 [*C*(CH_3)$_3$], 51.7 (OCH_3), 91.7 (C-4), 113.7 (C-5, Ar), 115.7 (C-2, Ar), 120.0 (C-1, Ar), 120.2 (C-6, Ar), 135.4 (C-3, Ar), 136.1 (C-4, Ar), 150.2 (C-5), 153.6 (C-3), 167.2 (C=O).

MS (70 eV): *m*/*z* (%) = 288 (M^+, 100), 262 (12), 247 (23).

Anal. Calcd for $C_{15}H_{20}N_4O_2{\cdot}0.5H_2O$: C, 60.59; H, 7.12; N, 18.84. Found: C, 60.79; H, 7.10; N, 18.91.

1-Pyrazol-3-ylbenzimidazoles 1aa–cc; General Procedure
The *o*-phenylenediamine derivatives **7a–c** (1 mmol) and an excess of the corresponding trimethyl orthocarboxylate **8a–c** (1 mL) were mixed in DMF (1 mL). The resulting mixture was refluxed under magnetic stirring for 5 h and then cooled to r.t. The precipitate obtained was isolated by filtration, washed with MeOH (5 mL) and the residue was crystallized from DMSO to give **1aa–cc** as white crystals.

Methyl 1-(5-Phenyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate (1aa)
White solid; mp 257–258 °C.

IR (KBr): 3199 (NH), 1722 (C=O), 1622 cm^{-1} (C=N).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.98 (s, 3 H, OCH_3), 7.35 (s, 1 H, H-4′), 7.52 (t, *J* = 7.35 Hz, 1 H, H_p-C_6H_5), 7.62 (t, *J* = 6.87, 7.35 Hz, 2 H, H_m-C_6H_5), 7.94 (d, *J* = 6.87 Hz, 2 H, H_o-C_6H_5), 8.12 (d, *J* = 8.93 Hz, 1 H, H-6), 8.28 (d, *J* = 8.93 Hz, 1 H, H-7), 8.45 (s, 1 H, H-4), 8.98 (s, 1 H, H-2), 13.73 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 52.6 (OCH_3), 94.4 (C-4′), 113.3 (C-7), 121.8 (C-4), 124.8 (C-5), 125.3 (C-6), 125.8 (C_o-C_6H_5), 129.0 (C_i-C_6H_5), 129.4 (C_p-C_6H_5), 129.6 (C_m-C_6H_5), 135.7 (C-7a), 144.5 (C-5′), 143.6 (C-3a), 144.6 (C-2), 146.4 (C-3′), 167.0 (C=O).

MS (70 eV): *m*/*z* (%) = 318 (M^+, 88), 287 (100), 197 (24).

Anal. Calcd for $C_{18}H_{14}N_4O_2{\cdot}0.5H_2O$: C, 66.05; H, 4.62; N, 17.12. Found: C, 66.30; H, 4.57; N, 16.96.

Methyl 2-Methyl-1-(5-phenyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate (1ab)
White solid; mp 231–233 °C.

IR (KBr): 3197 (NH), 1709 (C=O), 1615 cm^{-1} (C=N).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.65 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 6.53 (s, 1 H, H-4′), 7.53 (m, 1 H, H_p-C_6H_5), 7.58 (m, 2 H, H_m-C_6H_5), 7.90 (d, *J* = 6.82 Hz, 2 H, H_o-C_6H_5), 7.46 (d, *J* = 8.48 Hz, 1 H, H-7), 7.76 (d, *J* = 8.48 Hz, 1 H, H-6), 8.24 (s, 1 H, H-4), 12.83 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 51.9 (OCH_3), 98.1 (C-4′), 111.0 (C-7), 120.0 (C-4), 123.7 (C-5), 123.8 (C-6), 125.3

(C_o-C_6H_5), 134.4 (C_i-C_6H_5), 128.0 (C_p-C_6H_5), 129.0 (C_m-C_6H_5), 138.6 (C-7a), 144.1 (C-5′), 141.9 (C-3a), 153.7 (C-2), 144.3 (C-3′), 166.7 (C=O).

MS (70 eV): *m*/*z* (%) = 332 (M^+, 95), 301 (100), 273 (15).

Anal. Calcd for $C_{19}H_{16}N_4O_2·H_2O$: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.18; H, 5.17; N, 16.31.

Methyl 2-Phenyl-1-(5-phenyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate (1ac)
White solid; mp 296–298 °C.

IR (KBr): 3263 (NH), 1680 (C=O), 1612 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 3.74 (s, 3 H, OCH_3), 6.40 (s, 1 H, H-4′), 7.41 (m, 1 H, H_p-C_6H_5), 7.46 (m, 2 H, H_m-C_6H_5), 7.51 (d, *J* = 8.62 Hz, 1 H, H-7), 7.54 (m, 1 H, $H_{p'}$-C_6H_5), 7.72 (m, 2 H, $H_{m'}$-C_6H_5), 7.78 (d, *J* = 7.36 Hz, 2 H, H_o-C_6H_5), 7.84 (d, *J* = 8.59 Hz, 1 H, H-6), 7.98 (d, *J* = 7.43 Hz, 2 H, $H_{o'}$-C_6H_5), 8.26 (s, 1 H, H-4), 12.68 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.2 (OCH_3), 97.9 (C-4′), 111.2 (C-7), 120.8 (C-4), 124.3 (C-5), 124.4 (C-6), 128.1 (C_p-C_6H_5), 128.2 (C_m-C_6H_5), 128.8 (C_o-C_6H_5), 129.3 (C_i-C_6H_5), 127.1 ($C_{o'}$-C_6H_5), 128.8 ($C_{m'}$-C_6H_5), 129.0 ($C_{p'}$-C_6H_5), 132.3 ($C_{i'}$-C_6H_5), 140.1 (C-7a), 141.9 (C-3a), 143.3 (C-3′), 153.9 (C-2), 154.8 (C-5′), 166.5 (C=O).

MS (70 eV): *m*/*z* (%) = 394 (M^+, 93), 363 (100), 220 (35).

Anal. Calcd for $C_{24}H_{18}N_4O_2·0.33H_2O$: C, 71.99; H, 4.70; N, 13.99. Found: C, 72.11; H, 4.68; N, 14.03.

Methyl 1-(5-Methyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate (1ba)
White solid; mp 245–246 °C.

IR (KBr): 3276 (NH), 1705 (C=O), 1609 cm^{-1} (C=N).

^1H NMR (300 MHz, DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 6.61 (s, 1 H, H-4′), 8.06 (d, *J* = 8.47 Hz, 1 H, H-6), 8.17 (d, *J* = 8.47 Hz, 1 H, H-7), 8.41 (s, 1 H, H-4), 8.87 (s, 1 H, H-2), 13.70 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, DMSO-d_6): δ = 11.1 (CH_3), 52.6 (OCH_3), 95.8 (C-4′), 113.3 (C-7), 121.7 (C-4), 124.7 (C-5), 125.2 (C-6), 135.7 (C-7a), 141.3 (C-5′), 143.4 (C-3a), 144.6 (C-2), 145.6 (C-3′), 167.0 (C=O).

MS (70 eV): *m*/*z* (%) = 256 (M^+, 93), 225 (100), 197 (24).

Anal. Calcd for $C_{13}H_{12}N_4O_2·0.25H_2O$: C, 59.88; H, 4.83; N, 21.43. Found: C, 59.78; H, 4.87; N, 21.77.

Methyl 2-Methyl-1-(5-methyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate (1bb)
White solid; mp 228–229 °C.

IR (KBr): 3194 (NH), 1710 (C=O), 1612 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, 5′-CH_3), 2.57 (s, 3 H, 2-CH_3), 3.88 (s, 3 H, OCH_3), 6.38 (s, 1 H, H-4′), 7.48 (d, *J* = 8.48 Hz, 1 H, H-7), 7.87 (d, *J* = 8.48 Hz, 1 H, H-6), 8.20 (s, 1 H, H-4), 13.00 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.7 (5′-CH_3), 14.4 (2-CH_3), 51.9 (OCH_3), 94.4 (C-4′), 110.8 (C-7), 119.9 (C-4), 123.7 (C-5), 123.6 (C-6), 138.6 (C-7a), 140.6 (C-5′), 141.8 (C-3a), 143.6 (C-3′), 153.7 (C-2), 166.7 (C=O).

MS (70 eV): *m*/*z* (%) = 270 (M^+, 77), 239 (100), 211 (26), 42 (26).

Anal. Calcd for $C_{14}H_{14}N_4O_2·2H_2O$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.01; H, 5.87; N, 18.34.

Methyl 1-(5-*tert*-Butyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate (1ca)
White solid; mp 200–201 °C.

IR (KBr): 3327 (NH), 1704 (C=O), 1615 cm^{-1} (C=N).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-C_4H_9), 3.97 (s, 3 H, OCH_3), 6.27 (s, 1 H, H-4′), 8.01 (d, *J* = 7.65 Hz, 1 H, H-7), 8.18 (d, *J* = 7.65 Hz, 1 H, H-6), 8.59 (s, 1 H, H-4), 8.50 (s, 1 H, H-2), 13.71 (s, 1 H, NH).

^{13}C NMR (75.6 MHz, $CDCl_3$): δ = 30.1 [C(*C*H_3)$_3$], 31.4 [*C*(CH_3)$_3$], 52.2 (OCH_3), 93.2 (C-4′), 112.4 (C-7), 122.3 (C-4), 125.3 (C-5), 125.7 (C-6), 135.8 (C-7a), 155.5 (C-5′), 142.5 (C-3a), 143.0 (C-2), 145.4 (C-3′), 167.6 (C=O).

MS (70 eV): *m*/*z* (%) = 298 (M^+, 80), 283 (15), 267 (100), 197 (24).

HRMS: *m*/*z* calcd for $C_{16}H_{18}N_4O_2$ (M^+): 298.1430; found: 298.1426.

Methyl (5-*tert*-Butyl-1*H*-pyrazol-3-yl)-2-methyl-1*H*-benzimidazole-5-carboxylate (1cb)
White solid; mp 190–192 °C.

IR (KBr): 3203 (NH), 1705 (C=O), 1621 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 1.37 (s, 9 H, *t*-C_4H_9), 2.59 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 6.41 (s, 1 H, H-4′), 7.52 (d, *J* = 6.82 Hz, 1 H, H-7), 7.87 (d, *J* = 6.82 Hz, 1 H, H-6), 8.21 (s, 1 H, H-4), 13.03 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5 (CH_3), 29.8 [C(*C*H_3)$_3$], 31.0 [*C*(CH_3)$_3$], 52.2 (OCH_3), 96.4 (C-4′), 110.9 (C-7), 119.9 (C-4), 123.6 (C-5), 123.7 (C-6), 138.5 (C-7a), 143.1 (C-3′), 141.8 (C-3a), 153.7 (C-2), 154.5 (C-5′), 166.7 (C=O).

MS (70 eV): *m*/*z* (%) = 312 (M^+, 71), 281 (100), 253 (12).

HRMS: *m*/*z* calcd for $C_{17}H_{20}N_4O_2$ (M^+): 312.1586; found: 312.1601.

Methyl 1-(5-*tert*-Butyl-1*H*-pyrazol-3-yl)-2-phenyl-1*H*-benzimidazole-5-carboxylate (1cc)
White solid; mp 202–204 °C.

IR (KBr): 3188 (NH), 1714 (C=O), 1616 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 1.32 (s, 9 H, *t*-C_4H_9), 3.90 (s, 3 H, OCH_3), 6.15 (s, 1 H, H-4′), 7.42 (m, 1 H, H_p-C_6H_5), 7.44 (m, 2 H, H_m-C_6H_5), 7.52 (d, *J* = 8.06 Hz, 1 H, H-7), 7.65 (d, *J* = 7.24 Hz, 2 H, H_o-C_6H_5), 7.92 (d, *J* = 8.06 Hz, 1 H, H-6), 8.37 (s, 1 H, H-4), 13.09 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.7 [C(*C*H_3)$_3$], 30.9 [*C*(CH_3)$_3$], 52.2 (OCH_3), 97.9 (C-4′), 111.2 (C-7), 120.8 (C-4), 124.3 (C-5), 124.4 (C-6), 128.1 (C_p-C_6H_5), 128.2 (C_m-C_6H_5), 128.8 (C_o-C_6H_5), 129.3 (C_i-C_6H_5), 140.1 (C-7a), 141.9 (C-3a), 143.3 (C-3′), 153.9 (C-2), 154.8 (C-5′), 166.5 (C=O).

MS (70 eV): *m*/*z* (%) = 374 (M^+, 100), 359 (37), 343 (31), 77 (26), 41 (20).

Anal. Calcd for $C_{22}H_{22}N_4O_2·0.67H_2O$: C, 68.38; H, 6.09; N, 14.50. Found: C, 68.41; H, 5.99; N, 14.62.

Solid-Phase Synthesis of 1-Pyrazol-3-ylbenzimidazoles 1aa–fb; General Procedure
To a suspension of Wang resin **9** (1 g, 1.1 mmol, 1.1 mmol/g loading) in DMF (8 mL) was added successively 4-fluoro-3-nitrobenzoic acid (**10**; 815 mg, 4.4 mmol), DIC (0.75 mL, 2.2 mmol), and DMAP (14 mg, 0.11 mmol). The suspension was stirred for 15 h at r.t., and the yellow solid-supported 4-fluoro-3-nitrobenzoate **11** resin formed was then filtered and washed with DMF (2 × 6 mL), MeOH (2 × 6 mL), and CH_2Cl_2 (2 × 6 mL), and dried under high

vacuum. An aliquot of resin **11** (250 mg, 0.23 mmol) was then treated with **3a–f** (1.15 mmol) in DMSO (3 mL) at r.t. for 20 h to afford the resin-bound aminoarylpyrazoles **12a–f**. The orange resin was washed with DMF (3 × 3 mL), MeOH (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL), and dried under high vacuum. Each immobilized 3-nitrobenzoate **12a–f** (0.21 mmol) was treated with a suspension of 2.0 M solution of $SnCl_2·2H_2O$ in DMF (1 mL, 2.0 mmol) in DMF (3 mL) at reflux for 5 min. The resulting white resin was washed with DMF (3 × 3 mL), 20% H_2O–THF (at 60 °C, 3 × 3 mL), MeOH (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL), and dried under high vacuum. The resin-bound *o*-phenylenediamine derivatives **13a–f** (0.19 mmol) were then treated with the corresponding orthoesters **8a–c** (0.5 mL) in DMF (2 mL) at reflux for 5 h. The resin-bound 1-pyrazol-3-ylbenzimidazoles **14aa–fb** obtained were then washed with DMF (3 × 3 mL), MeOH (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL), and dried under high vacuum. For releasing the product from the solid phase, each benzimidazole resin (0.17 mmol) was treated with 50% TFA (2 mL) in CH_2Cl_2 (2 mL) for 2 h at r.t. The mixture was filtered and the filtrate was evaporated under reduced pressure. Esterification with MeOH in the presence of H_2SO_4 (in a ratio of 10:1, respectively) by heating at reflux for 2 h, afforded the crude product, which was then purified by column chromatography (MeOH–CH_2Cl_2, 1:30) to give the desired 1-pyrazol-3-ylbenzimidazoles **1aa–fb** in high overall yields (65–81%), based on the initial loading level of the Wang resin.

For the analytical and spectral properties of **1aa–1cc**, see above.

Methyl 1-[5-(4-Methylphenyl)-1*H*-pyrazol-3-yl]-1*H*-benzimidazole-5-carboxylate (1da)
Yellow solid; mp 219–220 °C.

IR (KBr): 3271 (NH), 1713 (C=O), 1613 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, ArCH_3), 3.91 (s, 3 H, OCH_3), 7.23 (s, 1 H, H-4′), 7.60 (t, *J* = 7.85 Hz, 2 H, H_m-C_6H_5), 7.75 (d, *J* = 7.85 Hz, 2 H, H_o-C_6H_5), 8.05 (d, *J* = 8.66 Hz, 1 H, H-6), 8.19 (d, *J* = 8.66 Hz, 1 H, H-7), 8.37 (s, 1 H, H-4), 8.90 (s, 1 H, H-2), 13.54 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.7 (ArCH_3), 52.1 (OCH_3), 93.5 (C-4′), 112.9 (C-7), 121.4 (C-4), 124.8 (C-5), 125.8 (C-6), 125.3 (C_o-C_6H_5), 126.9 (C_i-C_6H_5), 130.7 (C_m-C_6H_5), 138.4 (C_p-C_6H_5), 135.3 (C-7a), 144.0 (C-5′), 143.2 (C-3a), 144.1 (C-2), 146.0 (C-3′), 166.6 (C=O).

MS (70 eV): *m*/*z* (%) = 332 (M^+, 100), 301 (86).

Anal. Calcd for $C_{19}H_{16}N_4O_2·2H_2O$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.01; H, 5.41; N, 15.39.

Methyl 2-Methyl-1-[5-(4-methylphenyl)-1*H*-pyrazol-3-yl]-1*H*-benzimidazole-3-carboxylate (1db)
Yellow solid; mp 225–226 °C.

IR (KBr): 3287 (NH), 1723 (C=O), 1619 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, ArCH_3), 2.65 (s, 3 H, 2-CH_3), 3.89 (s, 3 H, OCH_3), 7.07 (s, 1 H, H-4′), 7.33 (t, *J* = 8.06 Hz, 2 H, H_m-C_6H_5), 7.77 (d, *J* = 8.06 Hz, 2 H, H_o-C_6H_5), 7.60 (d, *J* = 8.48 Hz, 1 H, H-7), 7.90 (d, *J* = 8.48 Hz, 1 H, H-6), 8.24 (s, 1 H, H-4), 13.72 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.0 (CH_3), 52.6 (OCH_3), 98.9 (C-4′), 111.4 (C-7), 120.5 (C-4), 124.4 (C-5), 125.0 (C-6), 127.5 (C_m-C_6H_5), 129.6 (C_o-C_6H_5), 138.3 (C_p-C_6H_5), 126.5 (C_i-C_6H_5), 138.5 (C-7a), 144.5 (C-5′), 141.9 (C-3a), 144.1 (C-3′), 153.7 (C-2), 166.6 (C=O).

MS (70 eV): *m*/*z* (%) = 346 (M^+, 100), 315 (90).

Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.34; H, 5.40; N, 15.97.

Methyl 1-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-1*H*-benzimidazole-5-carboxylate (1ea)
White solid; mp 296–297 °C.

IR (KBr): 3289 (NH), 1704 (C=O), 1612 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3 H, OCH_3), 7.22 (s, 1 H, H-4′), 7.56 (t, *J* = 7.78 Hz, 2 H, H_m-C_6H_5), 7.84 (d, *J* = 7.78 Hz, 2 H, H_o-C_6H_5), 8.00 (d, *J* = 8.78 Hz, 1 H, H-6), 8.12 (d, *J* = 8.78 Hz, 1 H, H-7), 8.34 (s, 1 H, H-4), 8.82 (s, 1 H, H-2), 13.38 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.5 (OCH_3), 94.9 (C-4′), 112.9 (C-7), 121.8 (C-4), 124.9 (C-5), 125.2 (C-6), 127.6 (C_o-C_6H_5), 128.9 (C_i-C_6H_5), 129.6 (C_m-C_6H_5), 131.3 (C_p-C_6H_5), 135.9 (C-7a), 144.8 (C-5′), 143.7 (C-3a), 145.1 (C-2), 147.0 (C-3′), 167.4 (C=O).

MS (70 eV): *m*/*z* (%) = 354/352 (M^+, 29/85), 323/321 (36/100).

Anal. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.33; H, 3.68; N, 15.96.

Methyl 1-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-2-methyl-1*H*-benzimidazole-5-carboxylate (1eb)
White solid; mp 276–277 °C.

IR (KBr): 3289 (NH), 1704 (C=O), 1612 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 2.60 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 7.10 (s, 1 H, H-4′), 7.54 (t, *J* = 8.03 Hz, 2 H, H_m-C_6H_5), 7.84 (d, *J* = 8.03 Hz, 2 H, H_o-C_6H_5), 7.56 (d, *J* = 8.29 Hz, 1 H, H-7), 7.87 (d, *J* = 8.29 Hz, 1 H, H-6), 8.20 (s, 1 H, H-4), 13.85 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.0 (CH_3), 52.6 (OCH_3), 98.9 (C-4′), 111.4 (C-7), 120.5 (C-4), 124.4 (C-5), 125.0 (C-6), 127.5 (C_m-C_6H_5), 129.6 (C_o-C_6H_5), 131.0 (C_p-C_6H_5), 134.4 (C_i-C_6H_5), 138.9 (C-7a), 143.2 (C-5′), 141.6 (C-3a), 144.9 (C-3′), 152.1 (C-2), 167.3 (C=O).

MS (70 eV): *m*/*z* (%) = 368/366 (M^+, 36/100), 337/335 (35/99).

Anal. Calcd for $C_{19}H_{15}ClN_4O_2$: C, 62.22; H, 4.12; N, 15.27. Found: C, 62.27; H, 4.11; N, 15.39.

Methyl 1-[5-(4-Bromophenyl)-1*H*-pyrazol-3-yl]-1*H*-benzimidazole-3-carboxylate (1fa)
White solid; mp 294–295 °C.

IR (KBr): 3275 (NH), 1716 (C=O), 1614 cm^{-1} (C=N).

^1H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3 H, OCH_3), 7.21 (s, 1 H, H-4′), 7.68 (t, *J* = 7.89 Hz, 2 H, H_m-C_6H_5), 7.73 (d, *J* = 7.89 Hz, 2 H, H_o-C_6H_5), 7.97 (d, *J* = 8.29 Hz, 1 H, H-6), 8.11 (d, *J* = 8.29 Hz, 1 H, H-7), 8.30 (s, 1 H, H-4), 8.81 (s, 1 H, H-2), 13.63 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.5 (OCH_3), 94.6 (C-4′), 113.2 (C-7), 121.8 (C-4), 124.7 (C-5), 125.2 (C-6), 127.7 (C_o-C_6H_5), 122.4 (C_i-C_6H_5), 132.5 (C_m-C_6H_5), 128.1 (C_p-C_6H_5), 135.6 (C-7a), 143.3 (C-5′), 143.3 (C-3a), 144.4 (C-2), 146.5 (C-3′), 166.9 (C=O).

MS (70 eV): *m*/*z* (%) = 398/396 (M^+, 98/100), 367/365 (99/98).

Anal. Calcd for $C_{18}H_{13}BrN_4O_2·H_2O$: C, 52.07; H, 3.64; N, 13.49. Found: C, 52.12; H, 3.75; N, 14.01.

Methyl 1-[5-(4-Bromophenyl)-1*H*-pyrazol-3-yl]-2-methyl-1*H*-benzimidazole-3-carboxylate (1fb)
White solid; mp 280–281 °C.

IR (KBr): 3285 (NH), 1721 (C=O), 1614 cm^{-1} (C=N).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.60 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 7.12 (s, 1 H, H-4′), 7.58 (d, *J* = 8.03 Hz, 1 H, H-7), 7.69 (t, *J* = 7.78 Hz, 2 H, H_m-C_6H_5), 7.79 (d, *J* = 7.78 Hz, 2 H, H_o-C_6H_5), 7.86 (d, *J* = 8.03 Hz, 1 H, H-6), 8.19 (s, 1 H, H-4), 13.86 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.0 (CH_3), 52.5 (OCH_3), 99.0 (C-4′), 111.4 (C-7), 120.4 (C-4), 121.6 (C_i-C_6H_5), 122.4 (C-5), 124.4 (C-6), 127.8 (C_m-C_6H_5), 132.1 (C_p-C_6H_5), 132.5 (C_o-C_6H_5), 138.9 (C-7a), 142.4 (C-5′), 142.0 (C-3a), 143.4 (C-3′), 154.3 (C-2), 167.1 (C=O).

MS (70 eV): *m*/*z* (%) = 412/410 (M^+, 100/98), 379/381 (90/91).

Anal. Calcd for $C_{19}H_{15}BrN_4O_2$: C, 55.49; H, 3.68; N, 13.62. Found: C, 55.51; H, 3.67; N, 13.79.

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