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Microwave Promoted Simple, Efficient and Regioselective Synthesis of Trisubstituted Imidazo[1,2-*a*]benzimidazoles on Soluble Support

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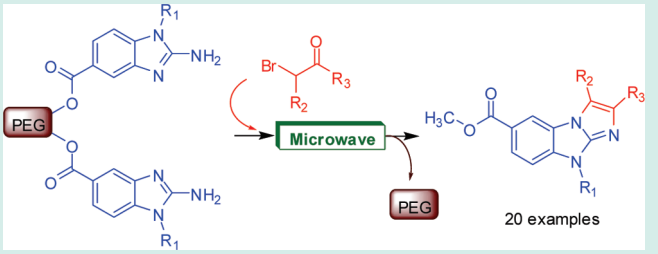
Supporting Information

ABSTRACT: An efficient microwave-assisted and soluble polymer-supported synthesis of medicinally important imidazole-fused benzimidazoles has been developed. The protocol involves the rapid condensation of polymer-bound amino benzimidazoles with various α-bromoketones and subsequent in situ intramolecular cyclization under microwave irradiation resulting in a one pot synthesis of imidazole interlacing benzimidazole polymer conjugates. The condensed product was obtained with excellent regioselectivity. The biologically interesting imidazo[1,2-*a*]benzimidazoles was released from polymer support at ambient temperature. Diversity in the triheterocyclic nucleus was achieved by the different substitutions at its 2, 3, and 9 positions. The new protocol has the advantages of short reaction time, easy workup process, excellent yields, reduced environmental impact, wide substrate scope and convenient procedure.



KEYWORDS: microwave-assisted, polymer-supported, amino benzimidazoles, biologically interesting

INTRODUCTION

As a distinct feature of nature's fundamental amino acid scaffold and emanating from a variety of biogenic processes, the guanidine nucleus has been intimately woven into the diverse and evolving fabric of the natural world. The guanidine-containing derivatives constitute a very important class of therapeutic agents for the treatment of a wide spectrum of diseases.[1] The elaborate interlacing frameworks in which nature has embedded the guanidine core with the two or three heterocyclic fused ring skeleton of the molecule also continues to inspire the development of creative strategies for its construction.[2] One of the guanidine embedded fused ring system, imidazo-benzimidazole, is an important structural subunit and recognition element found in a number of bioactive compounds including small-molecule natural products and related unnatural compounds.[3] The pharmacological properties of imidazole fused benzimidazole derivatives depend both on the type of cycle containing the guanidine pharmacophore group and on the substituent introduced into the nucleus of this tricycle.[4] The combination of diverse biological activity and structural complexity make imidazo[1,2-*a*]-benzimidazoles and its derivatives an attractive scaffold in the heterocyclic community.

There has been an increasing interest in the chemistry of imidazole fused benzimidazoles because of their broad spectrum of biological activity. Many of them show antihistamine, antioxidant, analgetic, hypotensive, anti-inflammatory and potent anesthetic activity.[5] The aminoketone derivatives of imidazo[1,2-*a*]-benzimidazoles are effective adrenoblockers, spasmolytics, antiarrhythmogens, and antimicrobial agents.[6] Some analogs of imidazo-benzimidazoles were prepared and evaluated for anti-anxiety activity[7] **1**, anticancer activity[8] **2**, and neuropsychotropic activity[9] **3** (Figure 1).

Recent advances in high-throughput screening have resulted in fast library collection being a top priority for initial drug discovery. Combinatorial chemistry provided the eminent solution by rapid synthesis of compound libraries to balance this demand. Development of novel synthetic methods for rapid organic synthesis remains central to new compounds with pharmaceutical potential. Thus the technologies that could accelerate and facilitate synthesis of compounds have become highly significant. The advent of microwave technology has enabled organic chemists to dramatically reduce the reaction time of single, as well as multistep, synthesis.[10] In addition, improved yields and cleaner reactions are frequently observed under microwave conditions.[11]

Parallel to the advances in microwave synthesis, the utilization of polymer support to accomplish novel chemistry has allowed for a vast array of compounds to be synthesized and subsequently screened for SAR study.[12] Soluble polymer supported techniques circumvent the tedious chromatographic separation by simple precipitation methods along with advantages of monitoring reaction progress by regular proton NMR techniques. Recent developments in soluble polymer supported synthesis have provided even more expansive ways to create diversified chemical libraries with improved quality and purity. Chemists are increasingly

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looking for the application of advanced techniques in conjunction with soluble polymer support to develop novel strategies that make compound synthesis easier, faster and more practical with an emphasis on quality and high-throughput purification techniques. Consequently, the development of novel methodologies that combine the advantages of microwave heating with soluble polymer supported liquid phase synthesis have become more popular in recent days.[13]

To the best of our knowledge, the synthesis of imidazo[1,2-*a*]-benzimidazole derivatives was mainly reported by the Ugi multicomponent reaction as well as conventional linear protocol.[14] All the reported methods suffered from the drawbacks such as prolonged reaction time, low yields, narrow scope of substrates or tedious workup procedures. Because of the constrains in the available synthetic methods and the broad spectrum of pharmacological applications of the imidazole-fused benzimidazole scaffold, there is an urgent need to develop an alternative, advanced protocol for the simple and rapid synthesis of imidazo-[1,2-*a*]benzimidazole derivatives.

In continuing with our ongoing work on the development of multidisciplinary synergetic approaches[15] for the rapid access to biologically active small heterocyclic molecules, we herein demonstrate that using soluble support in conjunction with microwave irradiation could facilitate the synthesis of imidazo[1,2-a]-benzimidazoles. In addition, as shown in our previous reports,[16] such a procedure also results in an easy workup process.

RESULTS AND DISCUSSIONS

By considering the solubility profile and loading capacity of the polymer derivatives, polyethylene glycol (PEG) of average molecular weight 4000 was chosen as the polymer support for the synthetic protocol. The requisite PEG supported 2-amino-benzimidazole **5** with diversity through *N*-substitution was prepared from immobilized *ortho*-fluoronitrobenzene by microwave assisted protocol. Accordingly, 4-fluoro-3-nitrobenzoic acid **4** was attached to polyethylene glycol by esterification followed by coupling with various amines through *ipso*-fluoro-nucleophilic substitution. The nitro-group of the polymer bound nitroaniline was reduced using ammonium formate and zinc. Subsequently, cyclization with cyanogen bromide furnished the requisite PEG bound benzimidazole derivatives **5**.

For the preliminary evaluation of polymer supported one pot condensation, we have carried out the investigation under microwave irradiations at 150 °C with PEG bound 2-amino-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate **5a** (**5**: R_1 = 2-methoxy ethyl) and 2-bromo-1-*p*-tolylethanone as a representative example. It was observed that the desired condensed product was not obtained when the model reaction was carried out in acetone. Attempts to use methanol as a solvent for the reaction (as its microwave coefficient was much higher) resulted in very low yield (18%) of the desired PEG bound 9-(2-methoxyethyl)-2-(4-methylphenyl)-9*H*-imidazo[1,2-*a*]-benzoimidazole-6-carboxylate **6a** (**6** R_1 = 2-methoxy ethyl, R_2 = H, R_3 = 4-methyl phenyl). After a few trials as well as analysis of earlier studies,[17] we decided to carry out the reaction in a binary solvent mixture. Surprisingly in our first attempt of the reaction in 1:1 (*v*/*v*) mixture of methanol and acetone under microwave irradiation at 150 °C (15 bar), the desired condensed product was obtained in 60% yield within 20 min. Consequently the proportion of solvents was optimized and set to 1:3 (*v*/*v*) mixture of methanol and acetone, in order to improve the yields (72%) and also to reduce the time (15 min) required for complete conversion. The temperature of the reaction was also investigated for better results; the most suitable temperature remains at 150 °C. The reaction involves the rapid condensation of PEG attached 2-amino-benzimidazole **5a** with α-bromoketones and subsequent in situ intramolecular cyclization under microwave irradiation leading to one pot synthesis of imidazole fused benzimidazole polymer conjugates **6a**. Excellent regioselectivity was observed during the condensation reaction. Finally, the polymer support was removed by treating the PEG bound imidazo[1,2-*a*]benzimidazoles **6a** with one molar solution of potassium cyanide in methanol at room temperature for 12 h. This furnished the desired imidazo[1,2-*a*]benzimidazoles **7a** in quantitative yields.

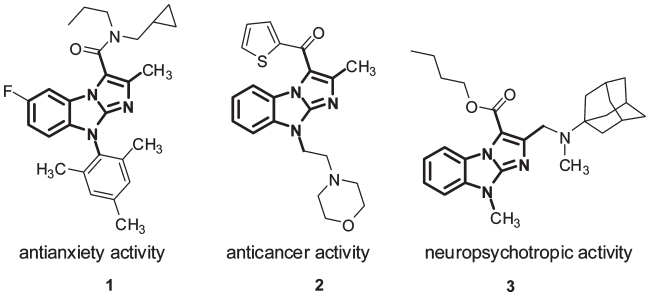

Figure 1. Representative bioactive imidazo[1,2-*a*]benzimidazole derivatives.

Scheme 1. General Synthetic Strategy Towards Imidazo[1,2-*a*]benzimidazoles

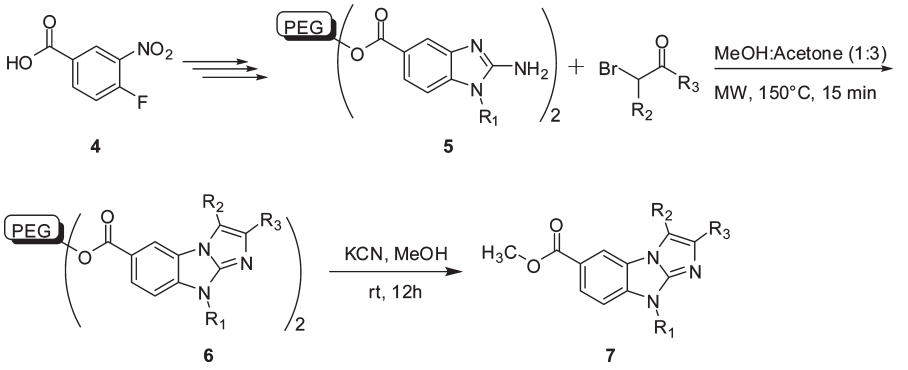

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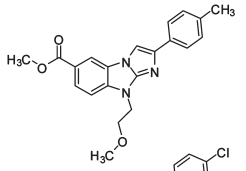
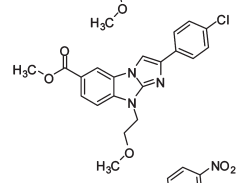
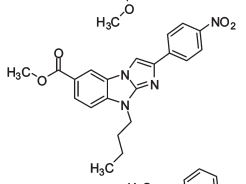
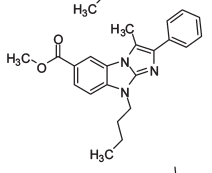
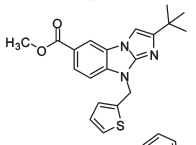
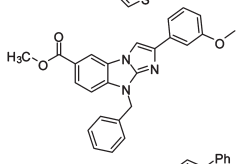
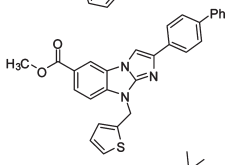
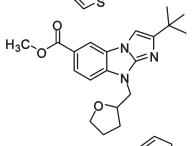
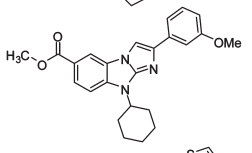
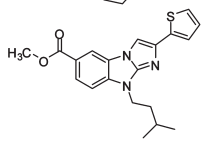
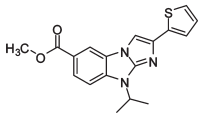
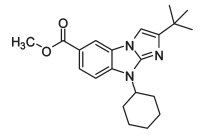
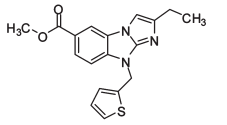
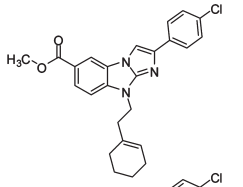
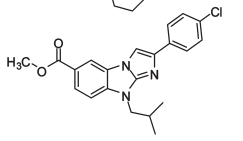
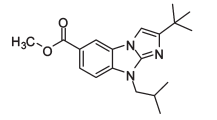
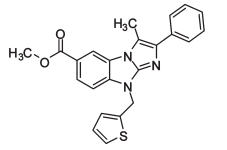
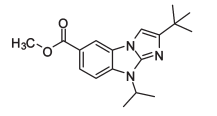
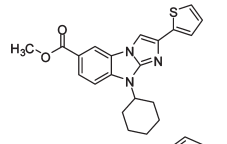
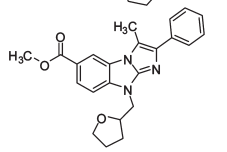
Table 1. Representative Imidazo[1,2-*a*]benzimidazole Derivatives

Entry	Compounds	Mass[a]	Yield(%)[b]	HPLC(%)[c]
7a		364	72	97
7b		384	80	93
7c		393	81	60
7d		362	77	89
7e		368	79	95
7f		412	82	84
7g		464	75	81
7h		356	88	99
7i		404	80	95
7j		404	65	95
7k		340	62	66
7l		354	87	70
7m		340	61	61
7n		434	79	68
7o		382	77	60
7p		328	84	90
7q		402	68	69
7r		314	88	69
7s		380	57	86
7t		390	79	95

[a] Mass recorded ESI as M + H. [b] Isolated yield after purification. [c] Crude HPLC purity after PEG cleavage.

The reaction progress was monitored by regular proton NMR spectroscopy (stepwise comparison of spectra of **5a**, **6a**, and **7a** are given in Supporting Information). The aromatic protons of PEG bound 2-amino-bezimidazole **5a** were shifted to its downfield region after condensation and appeared at 8.27, 8.14, and 7.45 ppm in the spectrum of PEG bound imidazo[1,2-*a*]benzimidazoles **6a**. These protons were subsequently shifted upfield in the ^{1}H NMR spectrum of compound 7a after removal of the polymer support. The characteristic peak for the newly formed imidazole ring proton (present at position 3 of imidazo-benzimidazole ring) appeared as a singlet at 7.63 ppm. Additional doublets integrating for two protons each in the aromatic region and one singlet for three protons at 2.38

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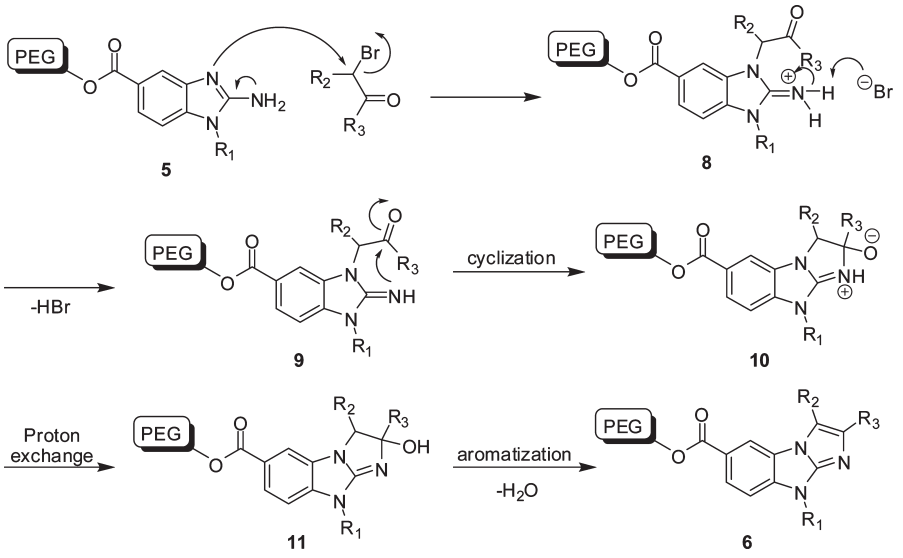

Figure 2. Possible mechanism for regioselective condensation reaction.

ppm from the 4-methyl phenyl group (substitution at 2-position) were evidence for the condensation of ketone with benzimidazole. The complete removal of PEG support was evidenced by the absences of a distinctive peak at 3.67 ppm which represented the polyethylene glycol absorbance in the proton NMR spectrum of compound **7a**.

On the basis of these optimized reaction conditions, a representative library of imidazo[1,2-*a*]benzimidazoles derivatives **7** was synthesized by the reaction of equimolar amounts of PEG bound 2-aminobenzimidazoles **5** and various α-bromoketones in a 1:3 mixture of methanol and acetone under microwave irradiation followed by the removal of the polymer support. The results are summarized in Table 1. The protocol was applied not only to aromatic ketones with electron-withdrawing groups or electron-donating groups, but also to aliphatic ketones which highlighted the versatility of the methodology. Reactions with aliphatic ketones provided the desired product in good yields (Table 1, entry e, h and p) while heteroaromatic ketones resulted in moderate yields (Table 1, entry j, k and s). In the case of aromatic ketones with electron-donating and electron-withdrawing groups, no reasonable differences were observed on the yields. Hence, the new protocol could be applied to a wide range of substrate including different types of primary and secondary α-bromoketones (Table 1, entries d, q, and t). Furthermore, the reaction procedure is fast and easy to operate and the soluble PEG support facilitates the workup procedure as it requires only simple precipitation and purification by ether wash. To demonstrate the advantages of microwave heating, a similar reaction of PEG bound 2-amino-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate **5a** and 2-bromo-1-*p*-tolylethanone in a mixture of acetone-methanol was investigated using conventional heating condition. It was observed that the condensation reaction via conventional heating required 20 h and afforded PEG bound imidazo[1,2-*a*]benzimidazoles **6a** in moderate yield (59%). However, the same reaction under microwave irradiation took only 15 min and afforded **6a** in 97% yield. This demonstrates that microwave-promoted reaction not only reduces the reaction time but also improves the yields significantly.

The plausible steps involved in the regioselective condensation of benzimidazole with α-haloketones to provide the imidazole fused benzimidazoles are depicted in Figure 2. Based on the observed outcome of the reaction, we proposed that the reaction proceeded via a sequence of nucleophilic bromo-substitution, intramolecular cyclization, followed by aromatization. Initially the bromo-group was selectively substituted by secondary amine through the electronic resonance of the 2-amino group of **5** leading to the *N*-alkylated adduct **8** which further liberation of protons afford intermediate **9**. The regioselectivity is due to the character of internal secondary amines as a soft nucleophile which preferentially reacts with soft halide electrophile. Subsequently, the intramolecular cyclization through condensation of amine with carbonyl functionality of ketone affords intermediate **10**, which on proton exchange leads to cyclic adduct **11**. Aromatization with elimination of a water molecule from adduct **11** affords imidazole fused benzimidazole **6**.

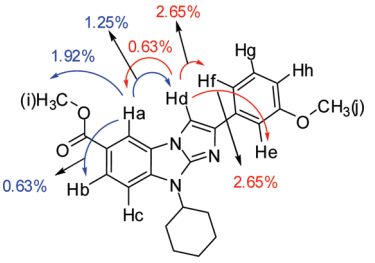

Figure 3. Important NOE interactions in compound **7i**.

To confirm the results obtained along with the regioselectivity of the condensation reaction, we carried the 1D NOE analysis of compound **7i**. The characteristic NOE interaction is shown in Figure 3. The irradiation of the Ha proton leading to enhancement of the Hb and Hd proton signals by 0.63% and 1.25%, respectively, which also enhanced the Hi proton signal by 1.92%. Additionally, irradiating the Hd proton enhances the Ha proton peak by 0.63% and He/Hf proton signals by 2.65%. Moreover, in the NOESY spectrum of compound **7i**, Hd proton shows interaction with Ha, He and Hf protons. Since there is no correlation of Ha with He and Hf protons, this clearly confirms the structure of compound **7i** and demonstrates the regioselective outcome of the condensation reaction (Figure 3).

To further confirm the structure for the regioselectivity and to support the NOE study, we further undertook the

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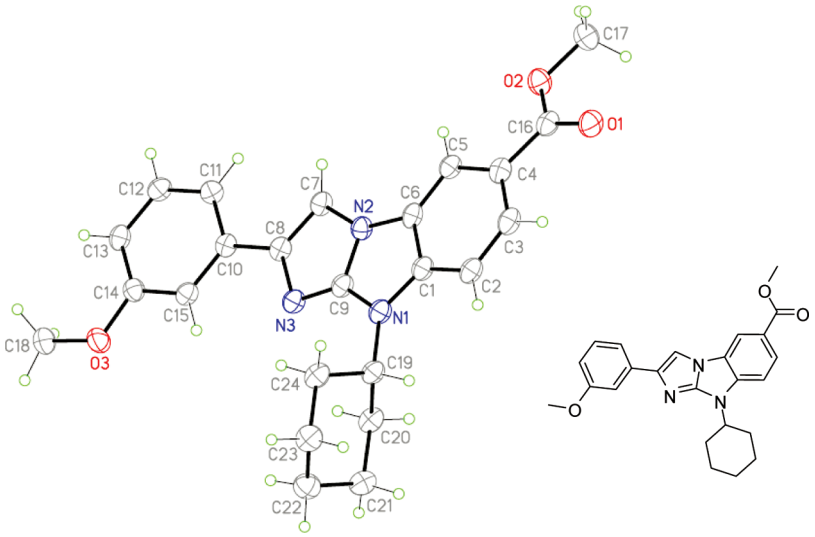

Figure 4. ORTEP diagram of compound **7i**.

X-ray crystallographic study of compound **7i**. The Figure 4 depicts the ORTEP diagram of compound **7i** (X-ray crystallographic data were specified in Supporting Information). The X-ray crystal structure of compound **7i** indicates that the 3-methoxy benzyl group was present at C8 carbon and the C7 carbon bears hydrogen atom which unambiguously confirms its structure.

CONCLUSION

In conclusion, we have developed a liquid phase method for the construction of guanidine embedded heterocyclic library. The simple and rapid synthesis of various imidazole-fused benzimidazole derivatives was achieved on soluble polymer support using focused microwave irradiations. The key steps in this synthesis includes the alkylation of PEG linked amino-benzimidazole with α-bromoketones, followed by intramolecular cyclization to furnish imidazo[1,2-*a*]benzimidazole derivatives in one pot. The excellent regioselectivity was observed during the one pot condensation reaction which was further supported by its NOE and X-ray crystallographic studies. The microwave heating dramatically shortens the time required for the reaction, while PEG support facilitates the workup procedures by simple precipitation. This novel protocol provides the rapid pathway to access the biologically interesting small heterocyclic molecules using microwave conditions in conjunction with soluble polymer support.

EXPERIMENTAL PROCEDURES

General Methods. Methanol and acetone were distilled before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230−400 mesh). All the microwave experiments were performed in a Biotage initiator under optimized reaction conditions of power and pressure. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Normal phase HPLC was performed on a Shimadzu LC-10AT series machine with a Hypersil (250 × 4.6 mm) analytical column. PEG was purchased from SHOWA.

(The general procedure applied to the synthesis of **7a** was applied to the synthesis of all the other final compounds of general formula 7)

*Methyl 9-(2-Methoxyethyl)-2-(4-methylphenyl)-9H-imidazo-[1,2-a]benzoimidazole-6-carboxylate (**7a**).* PEG-bound 2-amino-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate **5a** was prepared as described in Supporting Information. 2-Bromo-1-*p*-tolylethanone (0.426 g, 2.0 mmol) was added to a solution of PEG bound 2-amino-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate **5a** (2.234 g, 1.0 mmol) in methanol−acetone (1:3, 20 mL). The reaction mixture was irradiated under microwave at 150 °C (15 bar) for 15 min. The reaction is monitored by thin layer chromatography and ^{1}H NMR spectroscopy. When the reaction had completed, the reaction mixture was concentrated under reduced pressure and precipitated with cold ether (35 mL). The precipitate was filtered, washed by cold ether and dried well to furnish the PEG-bound 9-(2-methoxyethyl)-2-(4-methylphenyl)-9*H*-imidazo-[1,2-*a*]benzoimidazole-6-carboxylate **6a**. The solution of this PEG-bound imidazo[1,2-*a*]benzoimidazole **6a** in methanol (20 mL) was added to a solution of potassium cyanide (0.130 g, 2.0 mmol.) in 5 mL of methanol. The mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the mixture was precipitated by cold ether solution. The PEG was removed by filtration and was washed by cold ether (25 mL × 3). The combined filtrate was collected and dried well to afford title compounds **7a**, which was directly submitted to crude HPLC purity. After column chromatography purification over silica gel using ethyl-acetate/n-hexane (1:3) as eluent, methyl 9-(2-methoxyethyl)-2-(4-methylphenyl)-9*H*-imidazo[1,2-*a*]benzoimidazole-6-carboxylate **7a** was obtained in overall 72% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, J = 1.4 Hz, 1H), 8.01 (dd, J = 8.5, 1.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.63 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 4.42 (t, J = 5.2 Hz, 2H), 3.96 (s, 3H), 3.89 (t, J = 5.2 Hz, 2H), 3.34 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 150.3, 145.4, 139.8, 137.1, 132.1, 129.6, 125.5, 125.4, 124.5, 122.2, 122.5, 110.1, 102.2, 71.0, 59.3, 52.5, 44.0, 21.6. MS (ESI^{+}) m/z: 364 $(M + H)^{+}$. HRMS Calcd for $C_{21}H_{22}N_3O_3$: m/z 364.1661; Found

364.1664 $(M + 1)^+$. IR (cm^{-1}, neat): 2929, 1712, 1600, 889. HPLC Purity: 97%.

*Methyl 2-(4-Chlorophenyl)-9-(2-methoxyethyl)-9H-imidazo[1,2-a]-benzoimidazole-6-carboxylate (**7b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 1.3 Hz, 1H), 8.06 (dd, J = 8.5, 1.3 Hz, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.67 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 8.6 Hz, 2H), 4.43 (t, J = 5.2 Hz, 2H), 3.97 (s, 3H), 3.90 (t, J = 5.2 Hz, 2H), 3.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 150.4, 144.2, 139.9, 133.5, 133.0, 129.1, 126.8, 125.7, 124.4, 122.5, 112.7, 110.3, 102.8, 70.9, 59.4, 52.6, 44.1. MS (ESI^+) m/z: 384 $(M + H)^+$. HRMS Calcd for $C_{20}H_{19}ClN_3O_3$: m/z 384.1115; Found 384.1117 $(M + 1)^+$. IR (cm^{-1}, neat): 3060, 1706, 1625, 831. HPLC Purity: 93%

*Methyl 9-Butyl-2-(4-nitrophenyl)-9H-imidazo[1,2-a]benzo-imidazole-6-carboxylate (**7c**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.05 (dd, J = 8.5, 1.4 Hz, 1H), 7.96 (d, J = 8.8 Hz, 2H), 7.80 (s, 1H), 7.29 (d, J = 8.5 Hz, 1H), 4.24 (t, J = 7.4 Hz, 2H), 3.97 (s, 3H), 1.97 (quint, J = 7.4 Hz, 2H), 1.45 (sextet, J = 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 150.9, 146.7, 143.1, 141.1, 139.4, 126.2, 125.6, 124.5, 124.1, 122.5, 113.2, 109.5, 104.9, 52.7, 43.8, 30.8, 20.5, 14.0. MS (ESI^+) m/z: 393 $(M + H)^+$. HRMS Calcd for $C_{21}H_{21}N_4O_4$: m/z 393.1563; Found 393.1565. IR (cm^{-1}, neat): 2950, 1714, 1606, 1500, 759. HPLC Purity: 60%

*Methyl 9-Butyl-3-methyl-2-phenyl-9H-imidazo[1,2-a]benzo-imidazole-6-carboxylate (**7d**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 1.3 Hz, 1H), 8.04 (dd, J = 8.5, 1.3 Hz, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 4.25 (t, J = 7.4 Hz, 2H), 3.98 (s, 3H), 2.85 (s, 3H), 1.96 (quint, J = 7.4 Hz, 2H), 1.43 (sextet, J = 7.4 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 148.7, 140.3, 139.5, 135.7, 128.8, 128.1, 126.9, 125.4, 125.1, 121.8, 114.8, 112.4, 108.9, 52.6, 43.6, 30.9, 20.5, 14.1, 11.5. MS (ESI^+) m/z: 362 $(M + H)^+$. HRMS Calcd for $C_{22}H_{24}N_3O_4$: m/z 362.1868; Found 362.1870. IR (cm^{-1}, neat): 2950, 1716, 1602, 761. HPLC Purity: 89%

*Methyl 2-(tert-Butyl)-9-(2-thienylmethyl)-9H-imidazo[1,2-a]-benzoimidazole-6-carboxylate (**7e**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 1.3 Hz, 1H), 7.93 (dd, J = 8.5, 1.3 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H), 7.13 (dd, J = 3.5, 1.0 Hz, 1H), 7.12 (s, 1H), 6.92 (dd, J = 5.0, 3.5 Hz, 1H), 5.55 (s, 2H), 3.93 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 156.6, 149.6, 138.4, 138.0, 127.5, 127.4, 126.0, 125.1, 125.0, 122.3, 112.3, 109.6, 100.9, 52.5, 42.2, 33.2, 30.4. MS (ESI^+) m/z: 368 $(M + H)^+$. HRMS Calcd for $C_{20}H_{22}N_3O_2S$: m/z 368.1433; Found 368.1436. IR (cm^{-1}, neat): 2925, 1716, 1623, 707. HPLC Purity: 97%

*Methyl 9-Benzyl-2-(3-methoxyphenyl)-9H-imidazo[1,2-a]benzo-imidazole-6-carboxylate (**7f**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J = 1.3 Hz, 1H), 7.95 (dd, J = 8.5, 1.3 Hz, 1H), 7.71 (s, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.41 (dd, J = 8.0, 1.6 Hz, 1H), 7.37−7.27 (m, 6H), 7.15 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 8.0, 1.6 Hz, 1H), 5.47 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 160.3, 150.7, 145.3, 139.0, 136.3, 135.7, 130.0, 129.3, 128.5, 127.8, 125.7, 124.8, 122.6, 118.1, 113.5, 112.9, 110.9, 110.0, 103.0, 55.7, 52.6, 47.6. MS (ESI^+) m/z: 412 $(M + H)^+$. HRMS Calcd for $C_{25}H_{22}N_3O_3$: m/z 412.1661; Found 412.1664. IR (cm^{-1}, neat): 2954, 1714, 1604, 761. HPLC Purity: 84%

*Methyl 2-(4-Phenylphenyl)-9-(2-thienylmethyl)-9H-imida-zo[1,2-a]benzoimidazole-6-carboxylate (**7g**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 1.2 Hz, 1H), 8.00 (dd, J = 8.6, 1.2 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 7.2 Hz, 2H), 7.68 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 5.0 Hz, 1H), 7.22 (d, J = 3.5 Hz, 1H), 6.97 (dd, J = 5.0, 3.5 Hz, 1H), 5.62 (s, 2H), 3.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 150.2, 145.1, 141.2, 140.2, 138.6, 137.7, 134.0, 129.1, 127.7, 127.6, 127.5, 127.5, 127.3, 126.2, 126.0, 125.7, 124.9, 122.8, 112.9, 109.8, 102.9, 52.6, 42.3. MS (ESI^+) m/z: 464 $(M + H)^+$. HRMS Calcd for $C_{28}H_{22}N_3O_2S$: m/z 464.1433; Found 464.1435. IR (cm^{-1}, neat): 2942, 1698, 1592, 842, 701. HPLC Purity: 81%

*Methyl 2-(tert-Butyl)-9-(tetrahydro-2-furanylmethyl)-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7h**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 1.5 Hz, 1H), 7.97 (dd, J = 8.6, 1.5 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.10 (s, 1H), 4.43 (m, 1H), 4.36 (dd, J = 14.5, 3.6 Hz, 1H), 4.22 (dd, J = 14.5, 6.3 Hz, 1H), 3.94 (s, 3H), 3.86−3.65 (m, 2H), 2.16−1.73 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 156.4, 150.2, 139.7, 125.0, 124.7, 122.0, 112.1, 110.3, 100.6, 78.0, 68.7, 52.5, 48.0, 33.1, 30.4(3C), 29.2, 26.2. MS (ESI^+) m/z: 356 $(M + H)^+$. HRMS Calcd for $C_{20}H_{26}N_3O_3$: m/z 356.1974; Found 356.1976 $(M + 1)^+$. IR (cm^{-1}, neat): 2956, 1716, 1596. HPLC Purity: 99%

*Methyl 9-Cyclohexyl-2-(2-methoxyphenyl)-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7i**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 1.5 Hz, 1H), 8.00 (dd, J = 8.6, 1.5 Hz, 1H), 7.67 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 6.82 (dd, J = 8.0, 2.3 Hz, 1H), 4.38 (m, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.43 (q, J = 12.2 Hz, 2H), 2.07−1.79 (m, 4H), 1.51 (quint, J = 12.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 160.3, 149.9, 145.1, 138.5, 136.5, 129.9, 125.3, 124.9, 121.7, 118.2, 113.1, 112.8, 111.1, 110.0, 102.3, 56.0, 55.7, 52.5, 30.9, 26.2, 25.5. MS (ESI^+) m/z: 404 $(M + H)^+$. HRMS Calcd for $C_{24}H_{26}N_3O_3$: m/z 404.1974; Found 404.1976 $(M + 1)^+$. IR (cm^{-1}, neat): 2931, 1708, 1610, 742. HPLC Purity: 95%

*Methyl 9-Isopentyl-2-(2-thienyl)-9H-imidazo[1,2-a]benzo-imidazole-6-carboxylate (**7j**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 1.4 Hz, 1H), 8.04 (dd, J = 8.5, 1.4 Hz, 1H), 7.60 (s, 1H), 7.40 (dd, J = 3.5, 1.1 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.24 (dd, J = 5.0, 1.1 Hz, 1H), 7.07 (dd, J = 5.0, 3.5 Hz, 1H), 4.25 (t, J = 7.6 Hz, 2H), 3.97 (s, 3H), 1.86 (q, J = 7.0 Hz, 2H), 1.71 (sextet, J = 6.7 Hz, 1H), 1.03 (d, J = 6.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 150.3, 140.2, 139.1, 138., 128.0, 125.6, 124.4, 124.1, 123.1, 122.3, 112.9, 109.3, 102.1, 52.6, 42.4, 37.4, 26.2, 22.8. MS (ESI^+) m/z: 368 $(M + H)^+$. HRMS Calcd for $C_{20}H_{22}N_3O_2S$: m/z 368.1433; Found 368.1435. IR (cm^{-1}, neat): 2954, 1716, 1623, 701. HPLC Purity: 95%

*Methyl 9-Isopropyl-2-(2-thienyl)-9H-imidazo[1,2-a]benzo-imidazole-6-carboxylate (**7k**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 1.5 Hz, 1H), 8.02 (dd, J = 8.6, 1.5 Hz, 1H), 7.61 (s, 1H), 7.41 (dd, J = 3.6, 1.1 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 5.1, 1.1 Hz, 1H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 4.87 (septet, J = 6.9 Hz, 1H), 3.97 (s, 3H), 1.74 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 149.6, 140.2, 138.7, 138.2, 127.9, 125.4, 124.5, 124.1, 123.0, 122.0, 112.8, 110.1, 101.7, 52.6, 48.4, 21.0. MS (ESI^+) m/z: 340 $(M + H)^+$. HRMS Calcd for $C_{18}H_{18}N_3O_2S$: m/z 340.1120; Found 340.1122. IR (cm^{-1}, neat): 2979, 1714, 1592, 705. HPLC Purity: 66%

*Methyl 2-(tert-Butyl)-9-cyclohexyl-9H-imidazo[1,2-a]benzo-imidazole-6-carboxylate (**7l**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 1.5 Hz, 1H), 7.94 (dd, J = 8.6, 1.5 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.11 (s, 1H), 4.37 (m, 1H), 3.93 (s, 3H), 2.33 (q,

J = 12.4 Hz, 2H), 2.01−1.65 (m, 4H), 1.51−1.41 (quint, J = 12.4, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 156.6, 149.5, 138.2, 124.8, 124.5, 121.2, 112.2, 109.9, 99.9, 55.6, 52.4, 33.1, 30.8, 30.5(3C), 26.1, 25.5. MS (ESI^+) m/z: 354 $(M + H)^+$. HRMS Calcd for $C_{21}H_{28}N_3O_2$: m/z 354.2181; Found 354.2179 $(M + 1)^+$. IR (cm^{-1}, neat): 2948, 1714, 1623, 1577; HPLC Purity: 70%

*Methyl 2-Ethyl-9-(2-thienylmethyl)-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7m**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 1.4 Hz, 1H), 7.97 (dd, J = 8.5, 1.4 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 3.5, 1.3 Hz, 1H), 7.14 (dd, J = 5.0, 1.3 Hz, 1H), 7.14 (s, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 5.56 (s, 2H), 3.96 (s, 3H), 2.78 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 149.6, 148.7, 138.4, 138.0, 127.4, 127.4, 126.1, 125.2, 125.0, 116.6, 112.5, 109.7, 102.7, 50.6, 42.2, 23.3, 13.8. MS (ESI^+) m/z: 340 $(M + H)^+$. HRMS Calcd for $C_{18}H_{18}N_3O_2S$: m/z 340.1120; Found 340.1122. IR (cm^{-1}, neat): 1712, 1621, 1594, 703. HPLC Purity: 61%

*Methyl 2-(4-Chlorophenyl)-9-[2-(1-cyclohexenyl)ethyl]-9H-imidazo[1,2-a] benzoimidazole-6-carboxylate (**7n**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J = 1.3 Hz, 1H), 8.02 (dd, J = 8.5, 1.3 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.62 (s, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 1H), 5.27 (br.s, 1H), 4.29 (t, J = 7.1 Hz, 2H), 3.96 (s, 3H), 2.53 (t, J = 7.1 Hz, 2H), 2.06−2.02 (m, 2H), 1.82−1.76 (m, 2H), 1.57 (m, 2H), 1.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 150.5, 144.2, 139.2, 133.9, 133.6, 132.9, 129.1, 126.8, 125.5, 125.3, 124.8, 122.2, 112.2, 109.4, 102.5, 52.6, 42.6, 36.7, 28.6, 25.5, 23.1, 22.4; MS (ESI^+) m/z: 434 $(M + H)^+$. HRMS Calcd for $C_{25}H_{25}ClN_3O_2$: m/z 434.1635; Found 434.1633$(M + 1)^+$. IR (cm^{-1}, neat): 2927, 1716, 1594, 835. HPLC Purity: 68%

*Methyl 2-(4-Chlorophenyl)-9-isobutyl-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7o**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, J = 1.5 Hz, 1H), 8.04 (dd, J = 8.5, 1.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.66 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 1H), 4.04 (d, J = 7.5 Hz, 2H), 3.97 (s, 3H), 2.51 (sextet, J = 6.8 Hz, 1H), 1.03 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 150.9, 144.3, 139.7, 133.6, 133.0, 129.1, 126.9, 125.6, 124.3, 122.2, 112.9, 109.5, 102.6, 52.6, 51.3, 28.6, 20.6. MS (ESI^+) m/z: 382 $(M + H)^+$. HRMS Calcd for $C_{21}H_{21}ClN_3O_2$: m/z 382.1322; Found 382.1320. IR (cm^{-1}, neat): 2956, 1708, 1594, 831. HPLC Purity: 60%

*Methyl 2-(tert-Butyl)-9-isobutyl-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7p**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 1.4 Hz, 1H), 7.96 (dd, J = 8.4, 1.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 4.00 (d, J = 7.5 Hz, 2H), 3.94 (s, 3H), 2.41 (sextet, J = 6.8 Hz, 1H), 1.37 (s, 9H), 0.98 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 156.6, 150.3, 139.4, 124.9, 124.6, 121.6, 112.3, 109.1, 100.3, 52.5, 51.0, 33.1, 30.4, 28.6, 20.5. MS (ESI^+) m/z: 328 $(M + H)^+$. HRMS Calcd for $C_{19}H_{26}N_3O_2$: m/z 328.2025; Found 328.2028. IR (cm^{-1}, neat): 2958, 1716, 1623. HPLC Purity: 90%

*Methyl 3-Methyl-2-phenyl-9-(2-thienylmethyl)-9H-imidazo-[1,2-a]benzoimidazole-6-carboxylate (**7q**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 1.4 Hz, 1H), 7.99 (dd, J = 8.5, 1.4 Hz, 1H), 7.76 (dd, J = 7.8, 1.2 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.32 (dt, J = 7.8, 1.2 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.21 (dd, J = 5.0, 1.1 Hz, 1H), 7.18 (dd, J = 3.5, 1.1 Hz, 1H), 6.95 (dd, J = 5.0, 3.5 Hz, 1H), 5.58 (s, 2H), 3.96 (s, 3H), 2.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 148.3, 140.3, 138.8, 137.8, 135.6, 128.8, 128.0, 127.5, 127.4, 127.0, 126.2, 125.4, 125.3, 122.5, 115.2, 112.4, 109.5, 52.6, 42.1, 11.5. MS (ESI^+) m/z: 402 $(M + H)^+$. HRMS Calcd for $C_{23}H_{20}N_3O_2S$: m/z 402.1276; Found 402.1278. IR (cm^{-1}, neat): 2937, 1706, 1629, 763. HPLC Purity: 69%

*Methyl 2-(tert-Butyl)-9-isopropyl-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7r**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.6, 1.5 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.11 (s, 1H), 4.84 (septet, J = 6.9 Hz, 1H), 3.94 (s, 3H), 1.68 (d, J = 6.9 Hz, 6H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 156.6, 149.4, 138.0, 124.8, 124.7, 121.3, 112.3, 109.8, 100.0, 52.4, 48.0, 33.1, 30.4(3C), 20.9. MS (ESI^+) m/z: 314 $(M + H)^+$. IR (cm^{-1}, neat): 2956, 1716, 1581. HPLC Purity: 69%

*Methyl 9-Cyclohexyl-2-(2-thienyl)-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7s**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 1.5 Hz, 1H), 8.02 (dd, J = 8.6, 1.5 Hz, 1H), 7.60 (s, 1H), 7.41 (dd, J = 3.5, 1.1 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.23 (dd, J = 5.1, 1.1 Hz, 1H), 7.07 (dd, J = 5.1, 3.5 Hz, 1H), 4.40 (m, 1H), 3.97 (s, 3H), 2.43 (q, J = 12.4 Hz, 2H), 2.08−1.98 (m, 4H), 1.53 (quint, J = 12.4 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 149.8, 140.1, 138.7, 138.4, 127.9, 125.3, 124.4, 124.1, 123.1, 121.9, 112.8, 110.2, 101.7, 56.0, 52.6, 30.9, 26.2, 25.5. MS (ESI^+) m/z: 380 $(M + H)^+$. HRMS Calcd for $C_{21}H_{22}N_3O_2S$: m/z 380.1433; Found 380.1430 $(M + 1)^+$. IR (cm^{-1}, neat): 3060, 1697, 1592, 701. HPLC Purity: 86%

*Methyl 3-Methyl-2-phenyl-9-(tetrahydro-2-furanylmethyl)-9H-imidazo[1,2-a]benzoimidazole-6-carboxylate (**7t**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 1.4 Hz, 1H), 8.02 (dd, J = 8.6, 1.4 Hz, 1H), 7.72 (d, J = 7.4 Hz, 2H), 7.47 (d, J = 8.6 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 4.50 (m, 1H), 4.36 (dd, J = 14.7, 3.6 Hz, 1H), 4.23 (dd, J = 14.7, 6.5 Hz, 1H), 3.96 (s, 3H), 3.85−3.70 (m, 2H), 2.83 (s, 3H), 2.13 (m, 1H), 1.93−1.77 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 148.9, 140.1, 135.6, 128.8, 128.0, 126.9, 125.4, 125.0, 122.1, 114.9, 112.2, 110.3, 77.9, 68.7, 52.5, 48.0, 31.3, 29.3, 26.2, 11.4. MS (ESI^+) m/z: 390 $(M + H)^+$. HRMS Calcd for $C_{23}H_{24}N_3O_3$: m/z 390.1818; Found 390.1814; IR (cm^{-1}, neat): 2948, 1712, 1604, 1241, 700. HPLC Purity: 95%

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures, ^{1}H NMR, ^{13}C NMR, LRMS, HRMS, and FT-IR spectral data of compounds **7a**−**t**, and the NOESY spectrum and X-ray crystallographic data of compound **7i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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