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Graphical Abstract

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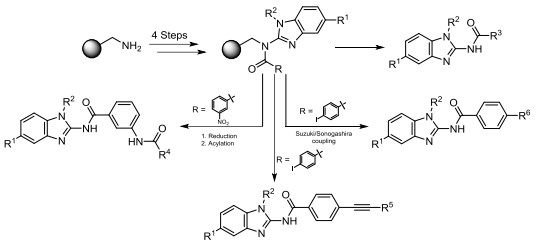

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Abstract: A 2-amido benzo[*d*]imidazole library has been constructed by solid-phase synthesis. The key step of this solid-phase synthesis involves the preparation of polymer-bound 2-amino benzo[*d*]imidazole resin through desulfurative cyclization of thiourea resin using DMC and DIPEA in DCM, and the resin is then functionalized by acylation at the 2-amine position to afford 2-amidobenzo[*d*]imidazole resin. In the case of 2-amidobenzo[*d*]imidazole resin having a *p*-I or *m*-NO_2, the resin was further functionalized by Suzuki/Sonogashira-coupling (*p*-I) and reduction to the primary amine (*m*-NO_2) followed by acylation. Finally, the functionalized 2-amido-benzo[*d*]imidazole resin was cleaved from the polymer support by treatment with cocktail of TFA and DCM. As a result, we obtained 2-amidobenzo[*d*]imidazole analogues in high yield and good purities.

KEYWORDS: Benzo[*d*]imidazole, Solid-phase, Desulfurative cyclization, Combinatorial synthesis

Introduction

Solid-phase organic synthesis (SPOS) is routinely used to prepare drug-like, small organic molecules in medicinal chemistry programs. This procedure enables the generation of massive numbers of small molecules.[1] Among these small molecules, heterocyclic compounds have played a vital role in the development of therapeutic agents.[2] Furthermore, to advance High Throughput Screening (HTS), the demand for construction of a large number of members of a heterocyclic compound library has increased. In this context, we have previously constructed a heterocyclic small molecule library on solid-phase using a carbon disulfide linker[3] and a Back-bonded Amide Linker (BAL).[4] As a continuation of our previous work, we now focus on the synthesis of 2-amidobenzo[*d*]imidazole, since benzo[*d*]imidazole is a well known biologically active structure in medicinal chemistry.[5]

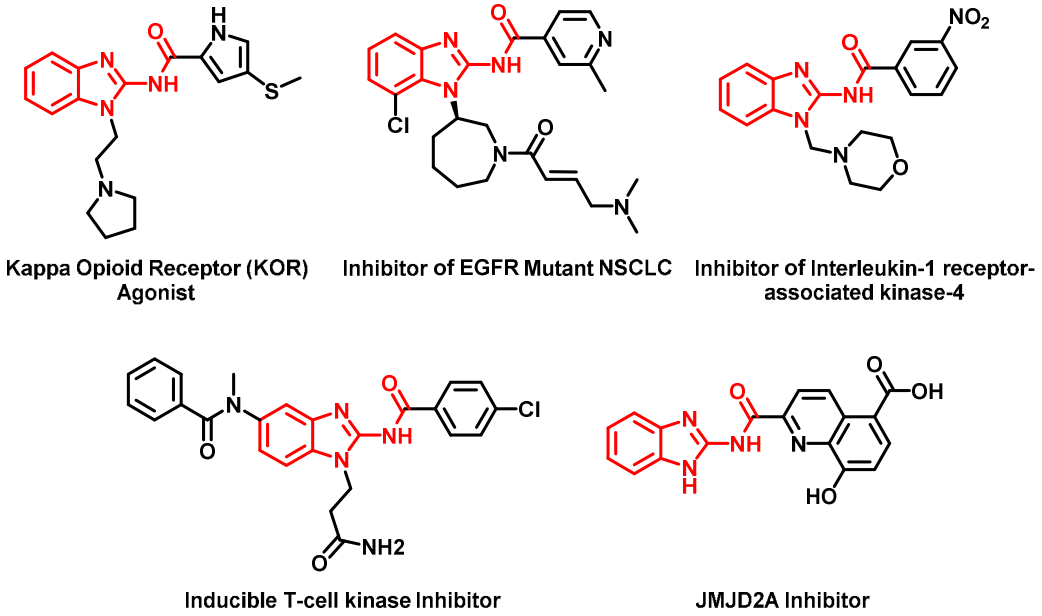


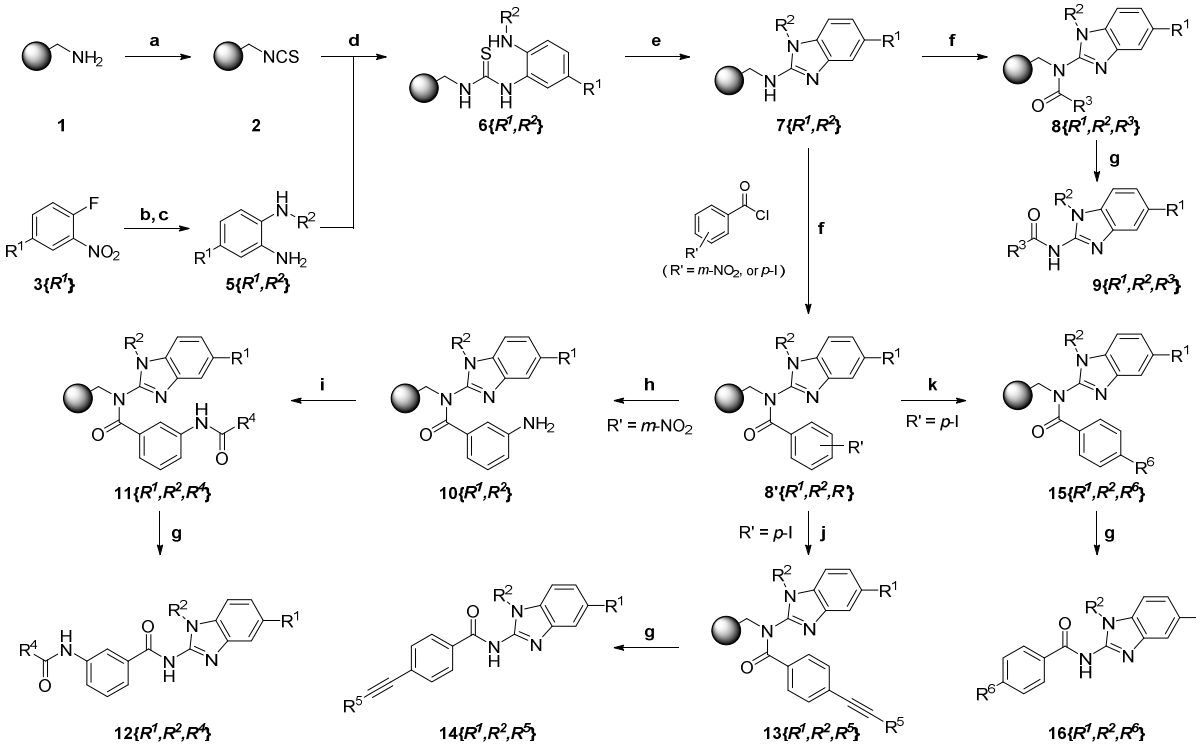
Figure 1. Representative biologically active compounds containing 2-amido-benzo[*d*]imidazole motif

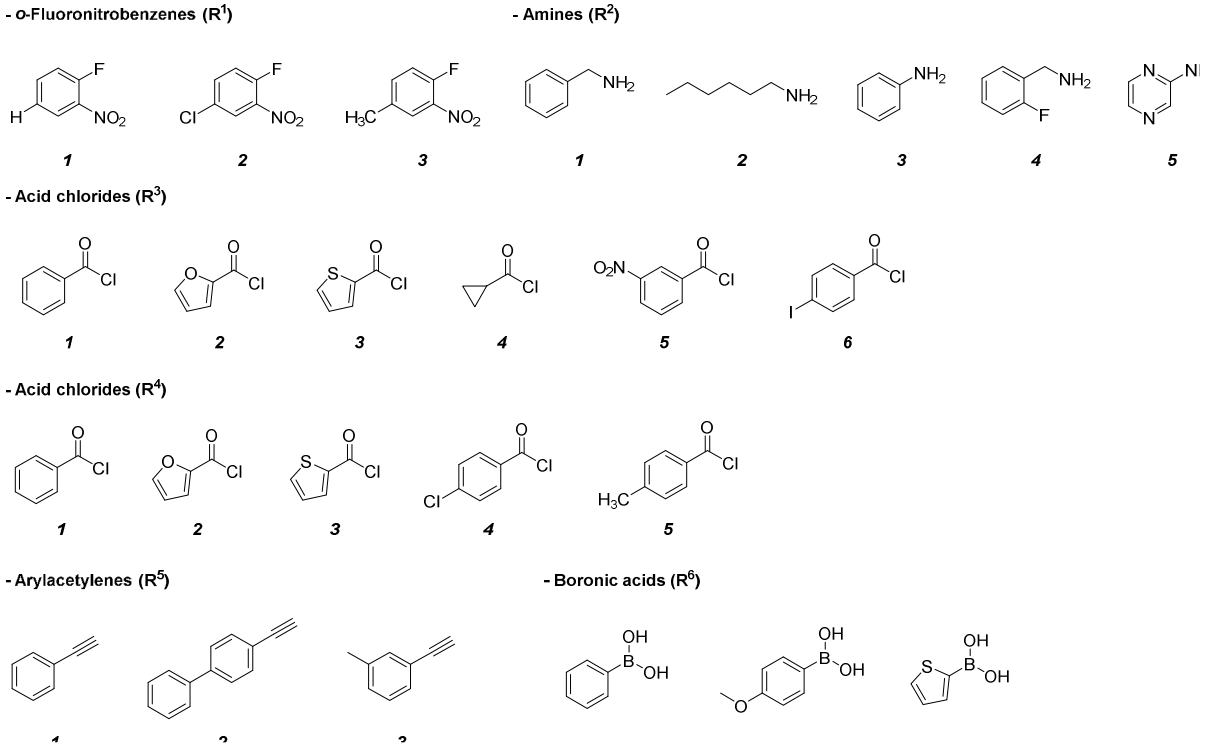
Figure 1 shows that in particular, 2-amidobenzo[*d*]imidazoles exhibit interesting biological activities, such as opioid type drug,[6] inhibitor of Epidermal Growth Factor Receptor (EGFR),[7] Interleukin-1 receptor associated kinase-4,[8] Inducible T-cell kinase (ITK),[9] and histone demethylase JMJD2A.[10] For this reason, benzo[*d*]imidazole core skeleton has been targeted for synthesis by many organic

and medicinal chemists.[11] However, although there are several synthetic methods in the literature to afford 2-amidobenzo[*d*]imidazole,[12] it is difficult to introduce diverse amide group at the 2-position of benzo[*d*]imidazole with the precedent methods, and the solid-phase synthesis of 2-amidobenzo[*d*]imidazole analogues is rare.[13] Thus, as a continuation of our ongoing project to construct small molecule libraries, we have tried to develop an expedient method to make a 2-amidobenzo[*d*]imidazole library on solid-phase in a combinatorial way. Herein, we report our recent progress on this project.

Results and Discussion

Scheme 1[a]





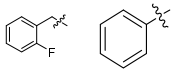
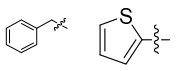
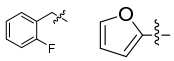
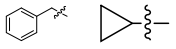
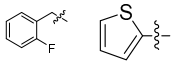
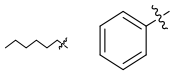
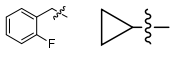
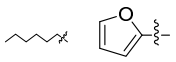
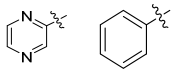
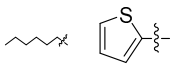
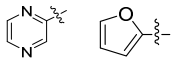
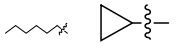
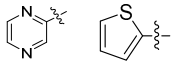
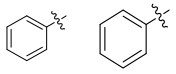
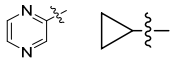
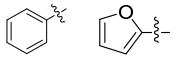
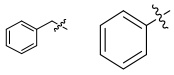
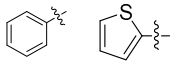
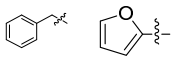
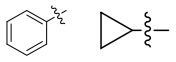
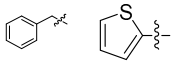
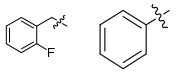
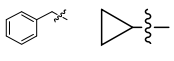
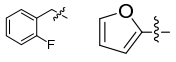
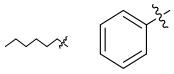
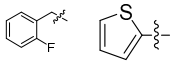
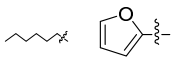
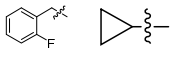
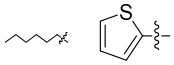
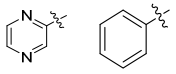
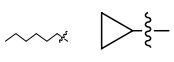
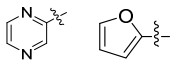
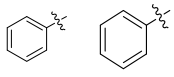
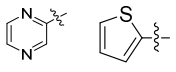
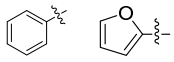
[a] Reaction condition: (a) CS_2, Triethylamine, *p*-TsCl, THF, rt, 19 h (b) In the case of alkylamine(R^2): K_2CO_3, DMF, 50 °C, 4 h; In the case of aniline(R^2) KF, K_2CO_3, 170 °C, 9 h; In the case of pyrazine-2-amine(R^2): KOH, DMSO, rt, 1.5 h (c) $SnCl_2$ and E.A, 80 °C, 2 h; In the case of the reduction of pyrazine-2-amine: NH_4Cl, Fe, THF/ D.W, 60 °C, 24 h; (d) Triethylamine, THF, 50 °C, 12 h; (e) DMC, DIPEA, MC, rt, 6 h; (f) acid chlorides, pyridine, 60 °C, 12 h; (g) TFA, MC, rt, 4 h; (h) $SnCl_2$, DMF, rt, 12 h; (i) acid chlorides, pyridine, 60 °C, 12 h; (j) In the case of R^2=benzyl: arylacetylenes, $Pd(PPh_3)_2Cl_2$, CuI, diethylamine, 60 °C, 12 h; In the case of R^2=phenyl: arylacetylenes, $Pd(PPh_3)_2Cl_2$, CuI, diethylamine, rt, 24 h; (k) boronic acids, $Ph_2(dba)_3$, Xphos, CS_2CO_3, 1,4-Dioxane/ D.W, 110 °C, 12 h.

On the basis of solid-phase parallel synthesis, Scheme 1 shows the synthetic route to afford 2-amidobenzo[*d*]imidazole analogues **9**, **12**, **14**, and **16**. To obtain thiourea resin **6**, we used 4-benzyloxy-2-methoxybenzylamine (BOMBA) resin **1** as the starting material. BOMBA resin **1** reacted with CS_2 and *p*-TsCl in the presence of Et_3N in THF at room temperature for 18 h. The formation of isothiocyanate terminated resin **2** was checked by its attenuated total reflection (ATR) single bead Fourier transform infrared (FTIR) spectrum, which showed the presence of a typical isothiocyanate peak at 2,071 cm^{-1} (Fig. S1). Resin **2** was reacted with 1,2-phenylenediamine-derived from *ortho*-fluoro nitro benzene via nucleophilic aromatic substitution and reduction-to afford thiourea resin **6** (yields for the nucleophilic aromatic substitution and the reduction reactions are summarized in Table S1 and Table S2). The formation of thiourea resin **6** was signaled by the disappearance of the isothiocyanate peak at 2,071 cm^{-1} (Fig. S1). To obtain benzo[*d*]imidazole resin **7**, we screened several solution-phase reaction conditions for desulfurative cyclization (Table S3-5).

As a result, we used 2-chloro-1,3-dimethylimidazolinium chloride (DMC) for desulfurative cyclization of the resin **6** and obtained benzo[*d*]imidazole resin **7** as signaled by an imine peak at 1,659 cm^{-1} (Fig. S1). With resin **7** in hand, we introduced various acid chlorides at the 2-amine position to afford 2-amidobenzo[*d*]imidazole resin **8**. The reaction proceeded in pyridine at 60 °C for 12 h and we monitored by an amide peak at 1,670 cm^{-1} (Fig. S1). To obtain our desired 2-amidobenzo[*d*]imidazole derivative **9**, resin **8** was treated with a cocktail of TFA and DCM (1:9, v/v) at room temperature for 4 h (Table 1).

Table 1. Yields and purities of the 2-amido-benzo[*d*]imidazole derivatives 9

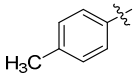
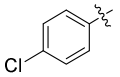
No	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]	No	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]
9{*1,1,1*}	H			29	100	**9{*2,3,3*}**	Cl			28	100
9{*1,1,2*}	H			41	100	**9{*2,3,4*}**	Cl			29	100
9{*1,1,3*}	H			27	100	**9{*2,4,1*}**	Cl			48	98.15
9{*1,1,4*}	H			22	100	**9{*2,4,2*}**	Cl			54	100
9{*1,2,1*}	H			22	100	**9{*2,4,3*}**	Cl			48	95.26
9{*1,2,2*}	H			29	100	**9{*2,4,4*}**	Cl			41	100
9{*1,2,3*}	H			48	100	**9{*2,5,1*}**	Cl			17	98.34
9{*1,2,4*}	H			8	97.33	**9{*2,5,2*}**	Cl			23	100
9{*1,3,1*}	H			34	100	**9{*2,5,3*}**	Cl			17	100
9{*1,3,2*}	H			42	100	**9{*2,5,4*}**	Cl			Trace	-
9{*1,3,3*}	H			28	100	**9{*3,1,1*}**	CH_3			30	100
9{*1,3,4*}	H			71	100	**9{*3,1,2*}**	CH_3			38	100

9{*1,4,1*}	H			47	100	**9{*3,1,3*}**	CH_3			31	100
9{*1,4,2*}	H			49	100	**9{*3,1,4*}**	CH_3			37	100
9{*1,4,3*}	H			33	98.96	**9{*3,2,1*}**	CH_3			11	100
9{*1,4,4*}	H			48	100	**9{*3,2,2*}**	CH_3			25	100
9{*1,5,1*}	H			34	100	**9{*3,2,3*}**	CH_3			14	100
9{*1,5,2*}	H			29	100	**9{*3,2,4*}**	CH_3			Trace	-
9{*1,5,3*}	H			40	94.24	**9{*3,3,1*}**	CH_3			37	92.98
9{*1,5,4*}	H			Trace	-	**9{*3,3,2*}**	CH_3			37	98.65
9{*2,1,1*}	Cl			30	100	**9{*3,3,3*}**	CH_3			29	94.43
9{*2,1,2*}	Cl			42	98.54	**9{*3,3,4*}**	CH_3			63	100
9{*2,1,3*}	Cl			51	94.19	**9{*3,4,1*}**	CH_3			50	100
9{*2,1,4*}	Cl			Trace	-	**9{*3,4,2*}**	CH_3			48	100
9{*2,2,1*}	Cl			24	98.28	**9{*3,4,3*}**	CH_3			49	100
9{*2,2,2*}	Cl			31	100	**9{*3,4,4*}**	CH_3			28	100
9{*2,2,3*}	Cl			21	100	**9{*3,5,1*}**	CH_3			12	94.03
9{*2,2,4*}	Cl			30	100	**9{*3,5,2*}**	CH_3			42	100
9{*2,3,1*}	Cl			20	100	**9{*3,5,3*}**	CH_3			26	97.33
9{*2,3,2*}	Cl			29	97.68	**9{*3,5,4*}**	CH_3			29	100

[a] is for five-step overall yields (loading capacity of the resin **1** is 1.02 mmol/g). [b] All of the purified products were checked by LC/MS.

As can be seen in Table 1, most of the 2-amidobenzo[*d*]imidazole derivatives **9** were obtained in good yields and high purities, 2-amidobenzo[*d*]imidazole derivatives **9{*1,5,4*}**, **9{*2,1,4*}**, **9{*2,5,4*}**, and **9{*3,2,4*}** having a cyclopropane group at R^3 were only obtained in a trace. Next, in the case of 2-amido-benzo[*d*]imidazole resin **8'** equipped with a *m*-nitro group, the nitro group was reduced using Tin(ll) chloride in DMF at room temperature for 12 h to generate 2-amidobenzo[*d*]imidazole **10** having a primary amine at the *meta* position. The reaction was monitored by the disappearance of nitro group peaks at 1,347 and 1,531 cm^{-1} and the appearance of a broad amine peak at 3,330 cm^{-1} (Fig. S1). Resin **10** was next reacted with various acid chlorides in pyridine (neat) at 60 °C. As a result, we obtained 2-amidobenzo[*d*]imidazole resin **11**, which was signaled by the disappearance of the broad amine peak at 3,330 cm^{-1} and the appearance of an amide peak at 1,680 cm^{-1} (Fig. S1). To afford the desired 2-amidobenzo[*d*]imidazole **12**, resin **11** was treated with a cocktail of TFA and DCM (1:9, v/v) at room temperature for 4 h. Table 2 summarizes the yields and purities of 2-amidobenzo[*d*]imidazole **12**.

Table 2. Yields and purities of the 2-amido benzo[*d*]imidazole derivatives 12

No	R^1	R^2	R^4	Yield (%)[a]	Purity (%)[b]
12{*1,3,1*}	H			24	100
12{*1,3,2*}	H			24	100
12{*1,3,3*}	H			37	100
12{*1,3,4*}	H			17	100
12{*1,3,5*}	H			11	100

[a] is for seven-step overall yields (loading capacity of the resin **1** is 1.02 mmol/g). [b] All of the purified products were checked by LC/MS.

Next, 2-amidobenzo[*d*]imidazole **8'** having a *p*-iodo group was diversified by a Suzuki-coupling or Sonogashira-coupling reactions. First, we used diverse arylacetylenes to yield Sonogashira-coupled 2-amidobenzo[*d*]imidazole resin **13** in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and diethylamine at 60 °C for 12 h followed by treatment with cocktail of TFA and DCM (1:9, v/v) at

room temperature for 4 h. As a result, we obtained Sonogashira-coupled 2-amidobenzo[*d*]imidazole **14** in high yields and purities (Table 3). Finally, for more diversity on the 2-amidobenzo[*d*]imidazole core, we conducted Suziki-coupling reaction with a 2-amidobenzo[*d*]imidazole **8'** having a *p*-iodo group. The Suziki-coupling reaction proceeded well with boronic acids, $Ph_2(dba)_3$, Xphos, and CS_2CO_3 in 1,4-Dioxane/ D.W (9:1, v/v) at 110 °C for 12 h. The Suzuki-coupled 2-amidobenzo[*d*]imidazole resin **15** was treated with a cocktail of TFA and DCM (1:9, v/v) at room temperature for 4 h to yield Suzuki-coupled 2-amidobenzo[*d*]imidazole analogues **16**. Table 3 summarizes the yields and purities.

Table 3. Yields and purities of the 2-amido benzo[*d*]imidazole derivatives 14 and 16

No	R^1	R^2	R^6	Yield (%)[a]	Purity (%)[b]	No	R^1	R^2	R^6	Yield (%)[a]	Purity (%)[b]
14{*1,1,1*}	H			28	100	**16{*1,1,1*}**	H			21	100
14{*1,1,2*}	H			14	100	**16{*1,1,2*}**	H			21	98.99
14{*1,1,3*}	H			33	100	**16{*1,1,3*}**	H			8	98.96
14{*1,3,1*}	H			34	100	**16{*1,3,1*}**	H			30	98.06
14{*1,3,2*}	H			37	100	**16{*1,3,2*}**	H			33	100
14{*1,3,3*}	H			35	95.42	**16{*1,3,3*}**	H			21	98.87

[a] is for seven-step overall yields (loading capacity of resin **1** is 1.02 mmol/g). [b] All of the purified products were checked by LC/MS.

In the drug discovery process, the ultimate goal is often to develop orally available drugs. To achieve this, Lipinski's rule and related parameters are used to measure a drug's potential to be used as an orally available drug. In this context, we calculated the physicochemical properties of our 2-amidobenzo[*d*]imidazole derivatives **9, 12**, **14**, and **16**. Figure 2 shows that most of the key parameters are within the range of those predicted to afford orally availability

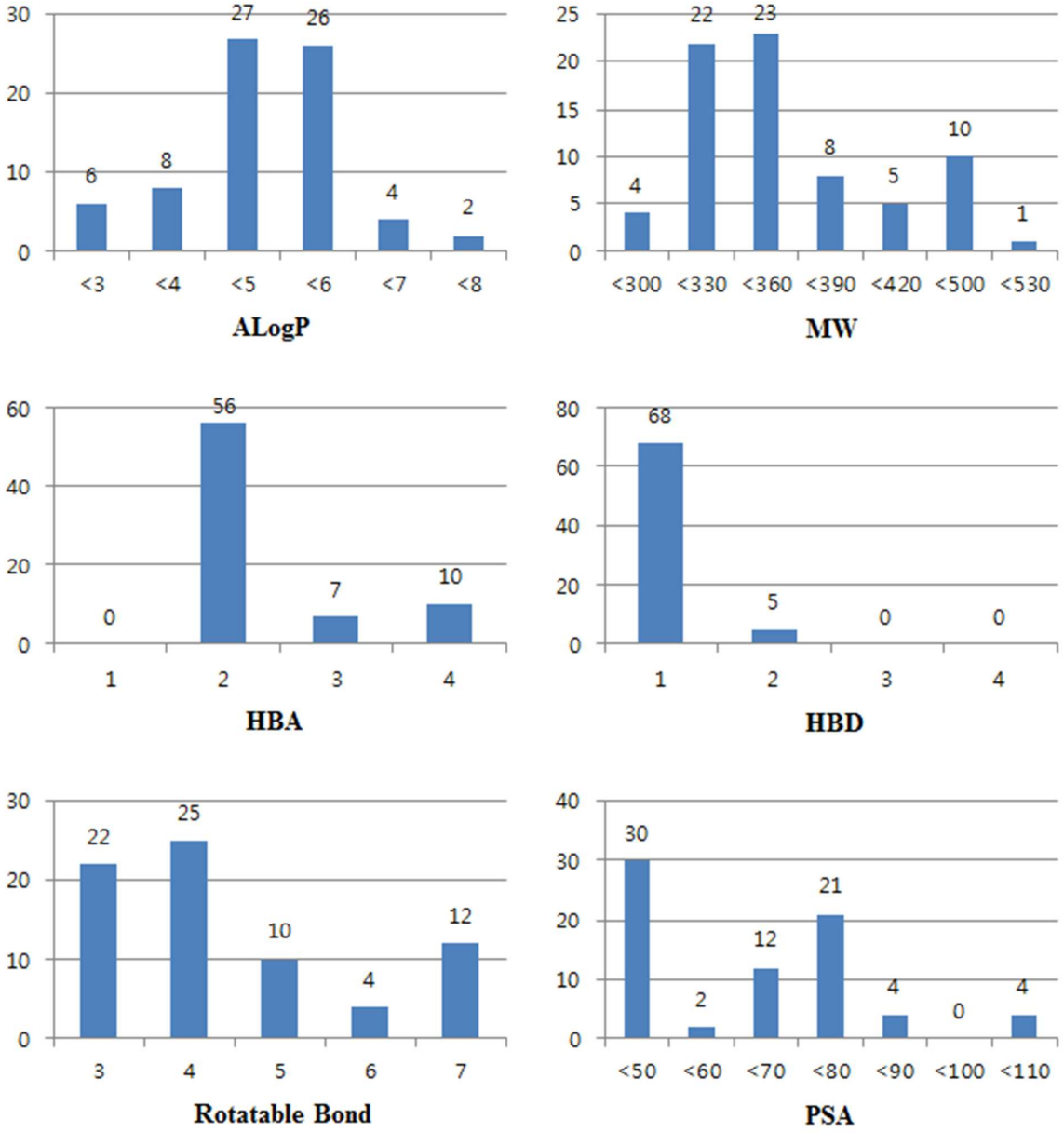


Figure 2. Physicochemical properties of 2-amidobenzo[*d*]imidazole analogues.

In conclusion, we developed a robust solid-phase synthetic route to construct the 2-amido-benzo[*d*]imidazole libraries. Unlike the precedent methods,[12] we first synthesized 2-aminobenzo[*d*]imidazole core skeleton of resin **7**, and then introduced numerous acid chlorides at the 2-amine position to afford 2-amidobenzo[*d*]imidazole resin **8**. Resin **8** was treated with a cocktail of TFA and DCM (1:9, v/v) to cleave our desired 2-amidobenzo[*d*]imidazole analogues **9** in high yields

and purities. In the case of *m*-nitro or *p*-iodo substituted 2-amidobenzo[*d*]imidazole resin **8'**, we carried out further diversifications, such as amide formation or Suzuki and Sonogashira-couplings, followed by cleavage by treatment with a cocktail of TFA and DCM (1:9, v/v), to yield numerous 2-amidobenzo[*d*]imidazole derivatives **12**, **14**, and **16**. Finally, to measure the potential of our constructed libraries to afford orally available compounds, we calculated physicochemical parameters such as ALogP, molecular weight, hydrogen bonding acceptor, and donor, rotatable bond, and polar surface area. Indeed, most of the key parameters fall within the acceptable range for an oral drug.

Experimental section

General Procedure for Synthesis

All the chemicals were of reagent grade, and were used as purchased. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin layer plates (for solution-phase synthesis), and by ATR-FTIR spectrometry (for solid-phase synthesis). The crude product mixtures were purified by flash chromatography using CombiFlash® Rf+ (Teledyne ISCO). Flash column chromatography was carried out on Merck silica gel 60 (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded in δ units relative to deuterated solvent as an internal reference using 500 MHz NMR spectrometry (Bruker). For liquid chromatography tandem mass spectrometry (ESI, PDA detection), a 6460 Triple Quad LC/MS (Agilent) was used. High-resolution mass spectrometry was performed using a 6550 iFunnel Q-TOF LC/MS system (Agilent).

Representative Procedure for the Preparation of 2-nitroanilines (4{*1,1*}−4{*3,5*})

In the case of alkyl amine : 1-fluoro-2-nitrobenzene (1.47 ml, 14 mmol) was added to a stirred solution of benzylamine (1.68 ml, 15.4 mmol) and K_2CO_3 (1.94 g, 14 mmol) in DMF (5 ml) at room temperature. The reaction mixture was heated to 40 °C, and was stirred for 4 h. After 4 h, the

reaction mixture was cooled to room temperature and extracted with ethyl acetate and distilled water. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/E.A), to afford 3.297 g (94 %, orange solid) of the desired N-benzyl-2-nitroaniline **4{*1,1*}**. ^{1}H NMR (500 MHz, DMSO) δ 8.67 (t, *J* = 5.7 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.35 (dt, *J* = 15.2, 7.8 Hz, 4H), 7.25 (t, *J* = 7.0 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.67 (dd, *J* = 8.4, 7.1 Hz, 1H), 4.63 (d, *J* = 6.1 Hz, 2H). LC-MS (ESI): m/z = 229.1 $[M+H]^+$.

In the case of aniline: aniline (2.05 ml, 22.5 mmol) was stirred with 1-fluoro-2-nitrobenzene (1.58 ml, 15 mmol), K_2CO_3 (3.11 g, 22.5 mmol), and KF (0.8715 g, 15 mmol) at 170 °C for 9 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate and distilled water. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/E.A) to afford 2.919 g (91 %, red-orange solid) of the desired 2-nitro-*N*-phenylaniline **4{*1,3*}**. ^{1}H NMR (500 MHz, DMSO) δ 9.37 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 1H). LC-MS (ESI): m/z = 215.1 $[M+H]^+$.

In the case of 2-aminopyrazine: 1-fluoro-2-nitrobenzene (1.58 ml, 15 mmol) was added to a stirred solution of 2-aminopyrazine (2.1 ml, 22.5 mmol) and KOH (4.951 g, 75 mmol) in DMSO (18 ml) at room temperature. The reaction mixture was stirred for 1.5 h and extracted with ethyl acetate and cold distilled water, after which the aqueous layer was removed. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/E.A), to afford 2.3583 g (73 %, orange solid) of the desired N-(2-nitrophenyl)pyrazin-2-amine **4{*1,5*}**. ^{1}H

NMR (500 MHz, DMSO) δ 9.91 (s, 1H), 8.43 (s, 1H), 8.09 (d, *J* = 13.6 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H). LC-MS (ESI): m/z = 217.1 $[M+H]^+$.

Representative Procedure for the Preparation of 1,2-diamines (5{*1,1*}−5{*3,5*})

In the case of alkyl amine and aniline: $SnCl_2$ (11.2815 g, 50 mmol) was added to a stirred solution of N-benzyl-2-nitroaniline **4{*1,1*}** (2.4 g, 10 mmol) in ethyl acetate. (20 ml). The reaction mixture was stirred at 80 °C for 2 h, and the mixture was neutralized with saturated aqueous $NaHCO_3$ solution, undissolved material was removed by filtration with celite. The filtrate was extracted with ethyl acetate and distilled water, after which the aqueous layer was removed. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/E.A), to afford 1.919 g (90 %, dark red oil) of the desired N^1-benzylbenzene-1,2-diamine **5{*1,1*}**. ^{1}H NMR (500 MHz, DMSO) δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 7.3 Hz, 1H), 6.57 – 6.51 (m, 1H), 6.41 – 6.36 (m, 2H), 6.35 – 6.30 (m, 1H), 5.09 (t, *J* = 5.3 Hz, 1H), 4.55 (s, 2H), 4.28 (d, *J* = 5.4 Hz, 2H). LC-MS (ESI): m/z = 199.1 $[M+H]^+$.

In the case of 2-aminopyrazine: A solution of N-(2-nitrophenyl)pyrazin-2-amine **4{*1,5*}** (1.081 g, 5 mmol) in THF (26.25 ml) was followed by the addition of a solution of NH_4Cl (1.3373 g, 25 mmol) in H_2O (8.75 ml). To the above was added Fe (1.3963 g, 25 mmol) in several batches, while warming to a temperature of 60 °C, followed by shaking for 24 h. The reaction mixture was cooled to room temperature and undissolved material was removed by filtration. The filtrate was dried over $MgSO_4$ and evaporated to afford the crude product, which was purified by column chromatography on silica gel (hexane/THF), to afford 405.1 mg (44 %, orange solid) of the desired N^1-(pyrazin-2-yl)benzene-1,2-diamine **5{*1,5*}**. ^{1}H NMR (500 MHz, DMSO) δ 8.32 (s, 1H), 8.00 (d, *J* = 1.4 Hz, 1H), 7.98 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.80 (d, *J* = 2.7 Hz, 1H), 7.27 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.90 (td, *J* = 7.9, 1.4 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.56 (td, *J* = 7.6, 1.4 Hz, 1H), 5.76 (s, 1H), 4.88 (s,

2H). LC-MS (ESI): m/z = 187.2 $[M+H]^+$.

Representative Procedure for the Preparation of the Isothiocyanate Terminated Resin 2

To a mixture of BOMBA resin 1 (8 g, 8.24 mmol) in THF (65 mL), Et_3N (11.48 ml, 82.4 mmol) and CS_2 (2.98 ml, 49.44 mmol) were added at 0 °C, resulting in a suspension. After shaking the suspension for 3 h at room temperature, *p*-TsCl (9.43 g, 49.44 mmol) was added slowly at 0 °C, and the suspension was shaken for 12 h at room temperature. Isothiocyanate terminated resin 2 was filtered, washed successively with THF (60 mL), MeOH (100 mL), H_2O (100 mL), MeOH (×2) (150 mL), and DCM (×2) (150 mL), and dried under high vacuum.

Representative Procedure for the Preparation of the Thiourea Resin 6 (6{*1,1*}-6{*3,5*})

To a mixture of isothiocyanate terminated resin 2 (1.55 g, 1.52 mmol) in THF (10 ml), Et_3N (0.646 ml, 4.64 mmol) and N^1-benzylbenzene-1,2-diamine **5{*1,1*}** (0.92 g, 4.64 mmol) were added at room temperature. The mixture was heated at 50 °C, followed by shaking for 12 h, filtered, washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the Preparation of the cyclized Resin 7

Preparation of 1-(2-(benzylamino)phenyl)thiourea Resin **6{*1,1*}**. To a suspension of thiourea resin **6{*1,1*}** (1.55 g, 1.52 mmol) in DCM (10 ml), DIPEA (0.809 ml, 4.64 mmol) and 2-chloro-1 3-dimethylimidazolium chloride (0.786 g, 4.64 mmol) were added, successively. The reaction mixture was shaken for 6 h at room temperature. 1-Benzyl-1*H*-benzo[*d*]imidazol-2-amine resin **7{*1,1*}** was filtered, washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the Acylation Reaction (8{*1,1,1*}-8{*3,5,4*})

In the case of benzoyl chloride: Preparation of 1-benzyl-1*H*-benzo[*d*]imidazol-2-amine Resin **7{*1,1*}**. To a suspension of cyclized resin **7{*1,1*}** (0.23 g, 0.204 mmol) in pyridine (2 ml), benzoyl chloride

(0.119 ml, 1.02 mmol) and DMAP (cat. amount, 2-3 particles) were added successively. The reaction mixture was shaken for 12 h at 60 °C. *N*-(1-Benzyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide resin **8{*1,1,1*}** was filtered, washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the Reduction Reaction

Preparation of 3-nitro-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide Resin **8'{*1,3,5*}**. To a suspension of acylated resin **8'{*1,3,5*}** (1.0 g, 1.02 mmol) in DMF (5 ml), $SnCl_2$ (1.15 g, 5.1 mmol) was added successively. The reaction mixture was shaken for 12 h at room temperature. 3-Amino-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide resin **10{*1,3*}** was filtered, washed successively with DCM, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the amide bond Reaction (11{*1,3,1*}-11{*1,3,5*})

Preparation of 3-amino-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide Resin **10{*1,3*}**. To a suspension of reduced resin **10{*1,3*}** (0.23 g, 0.204 mmol) in pyridine (2 ml), benzoyl chloride (0.119 ml, 1.02 mmol) and DMAP (cat. amount, 2-3 particles) were added successively. The reaction mixture was shaken for 12 h at 60 °C. 3-Benzamido-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide resin **11{*1,3,1*}** was filtered, washed successively with DCM, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the Sonogashira Coupling Reaction (13{*1,1,1*}-13{*1,3,3*})

In the case of R^2 = benzyl: Preparation of *N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)-4-iodobenzamide resin **8'{*1,1,6*}**. To a suspension of *N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)-4-iodobenzamide resin **8'{*1,1,6*}** (0.25 g, 0.204 mmol) in DMF (1 ml), $Pd(PPh_3)_2Cl_2$ (28.6 mg, 0.0408 mmol), CuI (7.8 mg, 0.0408 mmol), phenylacetylene (0.0672 ml, 0.612 mmol), and diethylamine (0.1266 ml, 1.224 mmol) were added. The reaction mixture was shaken for 12 h at 60 °C. The resin was filtered, washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried

under high vacuum.

In the case of R^2 = phenyl: Preparation of 4-iodo-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide resin **8'{*1,3,6*}**. To a suspension of 4-iodo-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide resin **8'{*1,3,6*}** (0.25 g, 0.204 mmol) in DMF (1 ml), $Pd(PPh_3)_2Cl_2$ (28.6 mg, 0.0408 mmol), CuI (7.8 mg, 0.0408 mmol), phenylacetylene (0.0672 ml, 0.612 mmol), and diethylamine (0.1266 ml, 1.224 mmol) were added. The reaction mixture was shaken for 24 h at room temperature. The resin was filtered, washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the Suzuki Coupling Reaction (15{*1,1,1*}–15{*1,3,3*})

Preparation of *N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)-4-iodobenzamide resin **8'{*1,1,6*}**. To a suspension of *N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)-4-iodobenzamide resin **8'{*1,1,6*}** (0.25 g, 0.204 mmol) in 1,4-dioxane (1.8 ml), $Pd_2(dba)_3$ (37.4 mg, 0.0408 mmol), XPhos (39 mg, 0.0816 mmol), phenylboronic acid (74.6 mg, 0.612 mmol), and Cs_2CO_3 (332.2 mg, 1.02 mmol) dissolved in H_2O (0.2 ml) were added. The reaction mixture was shaken for 12 h at 110 °C, and cooled to room temperature. The resin was filtered, washed successively with DCM, MeOH, H_2O, MeOH (×2), and DCM (×2), and dried under high vacuum.

Representative Procedure for the Cleavage Reaction

In the case of acylated resins : Acylated resin **8{*1,1,1*}** (0.25 g, 0.204 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL), and shaken for 4 h at room temperature. The resin was filtered, washed with DCM and MeOH (×2), and the organic filtrate was collected and evaporated to remove TFA. The residue was dissolved in DCM, purified by column chromatography on silica gel, and triturated with hexane and ethyl acetate (9:1, v/v) to afford the desired product *N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide **9{*1,1,1*}** (29 %, five-steps overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.48 (s, 1H), 8.38 (d, *J* = 7.2 Hz, 2H), 7.52 – 7.40 (m, 5H), 7.38 – 7.26 (m, 4H), 7.18 (dd, *J* = 14.0, 6.7 Hz, 3H), 5.48 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.74, 154.24, 137.95, 135.81,

131.31, 129.43, 129.30, 128.90, 128.37, 128.03, 127.96, 127.74, 123.15, 123.12, 111.18, 109.82, 45.76. LC-MS (ESI): m/z = 328.3 $[M+H]^+$. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{17}N_3O$ 328.1444; found 328.1463.

In the case of acylated resins : Acylated resin **11{*1,3,1*}** (0.25 g, 0.204 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL), and shaken for 4 h at room temperature. The resin was filtered, washed with DCM and MeOH (×2), and organic filtrate was collected and evaporated to remove TFA. The residue was dissolved in DCM, purified by column chromatography on silica gel, and triturated with hexane and ethyl acetate (9:1, v/v), to afford the desired product (3-benzamido-*N*-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide) **12{*1,3,1*}** (24 %, seven-steps overall yield). ^{1}H NMR (500 MHz, DMSO) δ 13.02 (s, 1H), 10.38 (s, 1H), 8.46 (s, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 6.3 Hz, 1H), 7.74 (d, *J* = 18.5 Hz, 3H), 7.67 (dd, *J* = 17.5, 7.8 Hz, 3H), 7.64 – 7.57 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 3H), 7.36 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.27 – 7.17 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.87, 167.66, 143.50, 137.58, 132.98, 132.84, 132.16, 131.30, 130.85, 130.34, 129.96, 129.90, 128.98, 127.68, 127.40, 127.26, 127.18, 127.05, 126.91, 125.60, 121.31, 114.00, 111.90. LC-MS (ESI): m/z = 433.3 $[M+H]^+$. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{20}N_4O_2$ 433.1659; found 433.1676.

In the case of Sonogashira coupled resins : Sonogashira coupled resin **13{*1,1,1*}** (0.25 g, 0.204 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL), and shaken for 4 h at room temperature. The resin was filtered, washed with DCM and MeOH (×2), and organic filtrate was collected and evaporated to remove TFA. The residue was dissolved in DCM, purified by column chromatography on silica gel, and triturated with hexane and ethyl acetate (9:1, v/v), to afford the desired product *N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)-4-(phenylethynyl)benzamide **14{*1,1,1*}** (28 %, six-steps overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.46 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.56 (dd, *J* = 7.3, 2.0 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.27 (m, 7H), 7.24 – 7.15 (m, 3H), 5.49 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.01, 154.16, 137.58, 135.73,

131.69, 131.24, 129.42, 129.24, 128.93, 128.44, 128.38, 128.30, 128.08, 127.71, 126.08, 123.26, 123.23, 123.12, 111.22, 109.90, 91.25, 89.50, 45.81. LC-MS (ESI): m/z = 428.3 $[M+H]^+$. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{21}N_3O$ 428.1757; found 428.1776.

In the case of Suzuki coupled resins : Suzuki coupled resin **15{*1,1,1*}** (0.25 g, 0.204 mmol) was treated with a mixture of TFA and DCM (1:9, v/v, 2 mL), and shaken for 4 h at room temperature. The resin was filtered, washed with DCM and MeOH (×2), and organic filtrate was collected and evaporated to remove TFA. The residue was dissolved in DCM, purified by column chromatography on silica gel, and triturated with hexane and ethyl acetate (9:1, v/v) to afford the desired product (*N*-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)-[1,1'-biphenyl]-4-carboxamide) **16{*1,1,1*}** (21 %, six-steps overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.48 (s, 1H), 8.44 (d, *J* = 8.3 Hz, 2H), 7.67 (t, *J* = 8.2 Hz, 4H), 7.50 – 7.42 (m, 4H), 7.34 (ddd, *J* = 25.2, 16.6, 8.4 Hz, 5H), 7.23 – 7.15 (m, 3H), 5.50 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.53, 154.21, 143.96, 140.73, 136.86, 135.82, 129.82, 129.45, 128.92, 128.81, 128.36, 128.05, 127.76, 127.66, 127.27, 126.72, 123.17, 123.14, 111.17, 109.83, 45.79. LC-MS (ESI): m/z = 404.3 $[M+H]^+$. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{21}N_3O$ 404.1757; found 404.1778.

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Supporting Information Available: Full analytical data of compounds, along with copies of the ^{1}H NMR, ^{13}C NMR, LC/MS, and HRMS spectra of all synthesized compounds, are available in the Supporting Information.

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