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Multistep Parallel Synthesis of Substituted 5-Aminobenzimidazoles in Solution Phase

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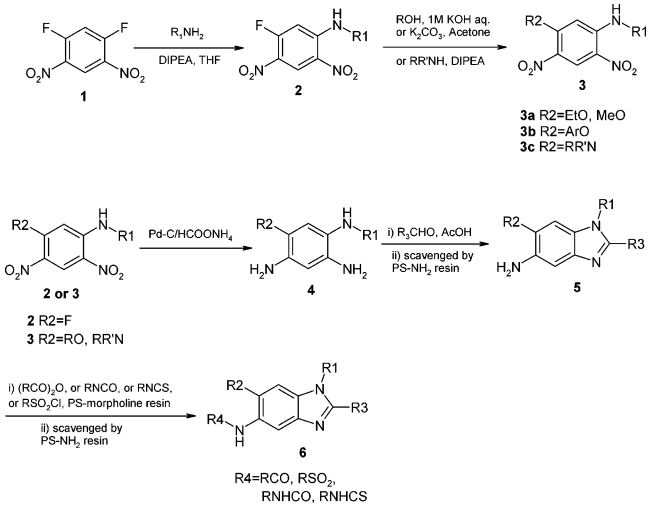
An efficient solution-phase parallel synthesis of multisubstituted 5-aminobenzimidazoles is described. The two fluorine atoms of 1,5-difluoro-2,4-dinitrobenzene (DFDNB) are sequentially and quantitatively replaced by nucleophiles. Simultaneous reduction of aromatic *m*-dinitro groups by Pd−C/$HCOONH_4$ results in 2,4,5-benzenetriamines, which are continuously condensed with aldehydes to successfully construct the benzimidazole ring without additional oxidants. The free aromatic amino group is further modified by anhydrides, isocyanates, isothiocyanates, and sulfonyl chlorides. All the reactions involved here are highly effective in giving the desired products at room temperature. Four diversity points are introduced in the final products.

Introduction

In recent years, combinatorial chemistry has been widely used by medicinal chemists in both drug lead discovery and optimization.[1] Although it derived from peptide synthesis on solid support, small molecular heterocycles have attracted more attention because they can offer a high degree of structural diversity and are more druglike.[2] Solid-phase synthesis has proved to be an effective way of synthesizing new compounds because of the easy purification by a simple filtration−washing step. However, several disadvantages restrict its wide application.[3] Solution-phase synthesis combined with scavenging techniques has become an effective approach for library construction because of its irreplaceable characteristics. These advantages include the facts that (1) many classical reactions and analytical techniques can be directly used, (2) the reaction scale is unlimited, and (3) an additional link-and-cleavage operation required for the resin is not needed.[4]

Benzimidazole has long been recognized as a "privileged substructure" for drug design. It is an important moiety incorporated into many drugs with various biological activities and therapeutic applications including antiviral,[5] antifungal,[6] antitumor,[7] antihistaminics,[8] etc. Among them, some 5-aminobenzimidazole derivatives were proved to be thrombin inhibitors or 5-HT_3 antagonists.[9] Efficient preparation of a benzimidazole library is, therefore, of considerable synthetic interest for both medicinal chemists and organic chemists. Many papers reported solid- or solution-phase synthetic methods for benzimidazoles, but few of them are related to the solution-phase parallel synthesis of a 5-aminobenzimidazole library.[10]

Scheme 1. Synthetic Route to 5-Aminobenzimidazole Derivatives



1,5-Difluoro-2,4-dinitrobenzene (DFDNB) is a protein cross-linker and also a versatile reagent for the efficient introduction of diverse library scaffolds.[11] We have launched a project to construct scaffold-directed heterocyclic libraries using DFDNB as the starting material.[12] Herein, we report our recent efforts on multistep parallel solution-phase synthesis of 5-aminobenzimidazole derivatives with four diversity points.

Results and Discussion

The synthetic route to the substituted 5-aminobenzimidazoles is depicted in Scheme 1. Previously, we used primary amines and amino acids as nucleophiles to quantitatively replace two fluorine atoms of DFDNB.[12] Herein, we further extend the nucleophiles to alcohols, phenols, and secondary amines in order to increase the diversity (R_2) of **3**. It was found that nucleophilic substitution with alcohols and phenols

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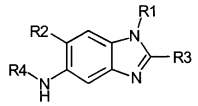
Table 1. MW and HPLC Purity for the Representative Substituted 5-Aminobenzimidazole Derivatives **5** and **6**



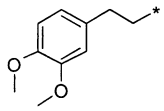
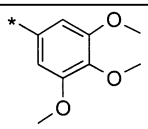
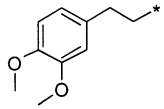
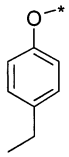
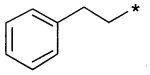
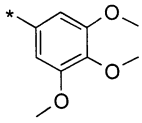
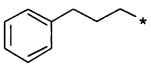
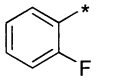
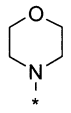
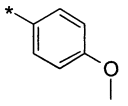
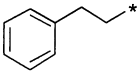
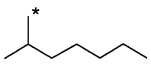
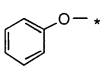
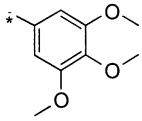
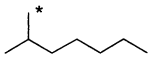
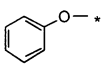
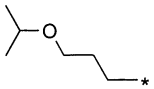
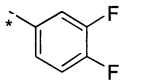
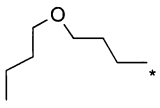
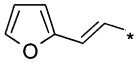
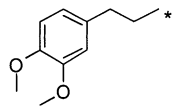
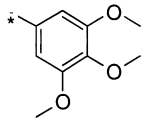
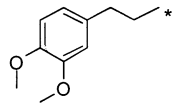
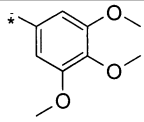
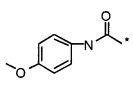
Entry	R1	R2	R3	R4	HPLC purity[a] (%)	MS (found)	MW (calcd.)
5a				H	100.0	482.2	481
5b				H	98.4	500.0	499
5c				H	100.0	422.2	421
5d				H	100.0	466.2	465
5e				H	100.0	367.3	366
5f				H	98.0	428.1	427
5g				H	98.6	490.2	489
5h				H	93.9	394.2	393
5i				H	95.4	364.2	363
5j				H	98.3	483.2	482
6a					100.0	524.2	523
6b					97.1	631.2	630

Table 1 (Continued)

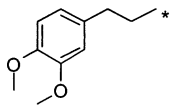
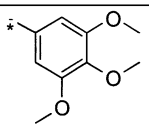
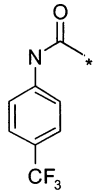
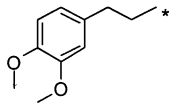
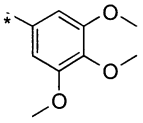
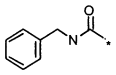
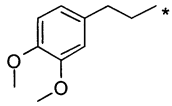
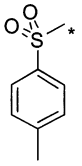
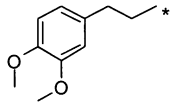
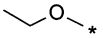
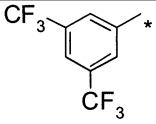
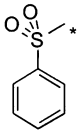
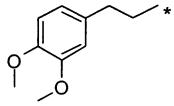
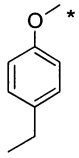
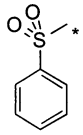
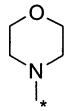
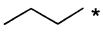
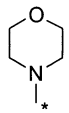
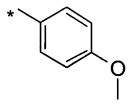
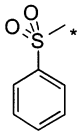
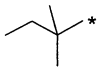
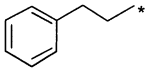
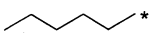
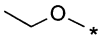
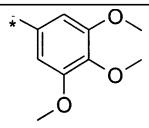
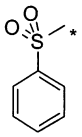
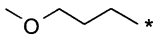
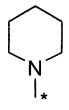
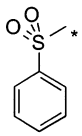
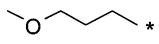
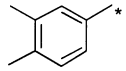
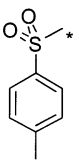
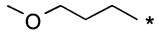
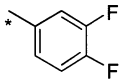
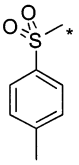
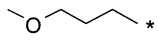
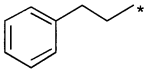
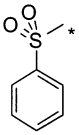
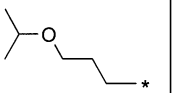
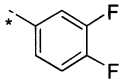
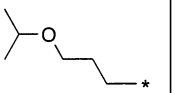
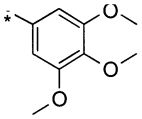
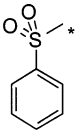
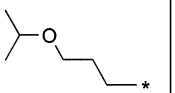
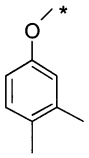
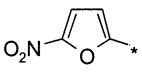
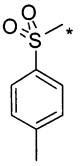
Entry	R1	R2	R3	R4	HPLC purity[a] (%)	MS (found)	MW (calcd.)
6c					94.2	669.2	668
6d					91.5	615.2	614
6e					100.0	552.2	551
6f					96.7	694.2	693
6g					96.6	635.2	634
6h					93.4	380.3	379
6i					100.0	507.2	506
6j					99.6	470.1	469
6k					100.0	554.2	553
6l					100.0	511.2	510
6m					99.2	591.2	590

Table 1 (Continued)

Entry	R1	R2	R3	R4	HPLC purity[a] (%)	MS (found)	MW (calcd.)
6n					98.3	584.2	583
6o					99.6	604.2	603
6p					98.9	570.3	569
6q					100.0	406.2	405
6r					100.0	558.3	557
6s					100.0	619.2	618

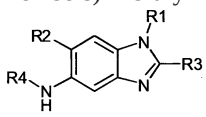
[a] Purity based on the integration area of the HPLC peaks (the detection wavelength was 254 nm).

in the presence of inorganic bases (K_2CO_3 or KOH) led to **3** in both high yield and purity at room temperature. Simultaneous reduction of the aromatic *m*-dinitro groups to generate **4** was still achieved by utilization of $HCOONH_4$ and Pd−C.[12a] Thus, some building blocks containing hydrogen-sensitive or potential catalyst poisoning groups had to be excluded from the library synthesis.[12a]

Although we had tried to isolate pure 2,4,5-benzenetriamines **4**, it was found to be a very easily oxidizable substance, and the reaction solution generally turned quickly from colorless to red and then to deep purple in air. HPLC−MS analysis indicated that the reduction product eventually degraded to a complex mixture during isolation in all our attempts. We, therefore, decided to adopt a continuous strategy without purifying **4**, in which the reaction solution was directly filtered into another reaction vessel containing the aldehyde (R_3CHO) to yield **5**.

Construction of the benzimidazole ring **5** is the key step of the route. Most popular synthetic methods can be divided into two groups according to the pathway. The first one involves the coupling of 1,2-phenylenediamines with carboxylic acids (or equivalents) through dehydrogenation catalyzed by a strong acid.[13] The second one involves forming Schiff's base intermediates of 1,2-phenylenediamines and aldehydes, then oxidative cyclization using various oxidants such as DDQ and oxone.[14] Although we followed the conditions using carboxylic acids or aldehydes and DDQ to construct the benzimidazole ring, the anticipated products **5** were not obtained. It was reasoned that the harsh conditions including heat and oxidation for cyclization might lead to the decomposition of **4** very quickly. Therefore, much milder reaction conditions were tested for the efficient preparation of **5**. Fortunately, **5** could be gained in high yield when **4** reacted continuously with excess aldehyde in a weakly acidic solution (6% HOAc) at room temperature without additional oxidants. Reaction of the equivalent aldehyde with **4** mostly gave a purity of **5** of less than 80% by HPLC analysis. Therefore, the excess aldehyde might account for the prevention of the oxidation of **4**. The remaining aldehyde was removed using an aminomethyl polystyrene scavenger resin. We performed the experiments on scales ranging from 0.05−2.0 mmol and successfully

Table 2. MW and HPLC Purity for a Small Size (24 Members) Library[a]



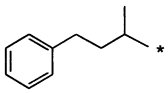
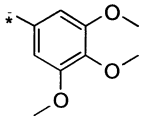
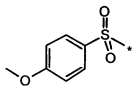
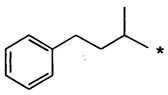
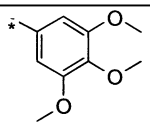
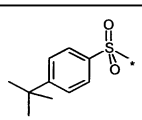
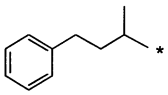
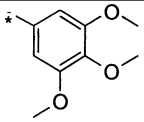
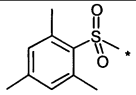
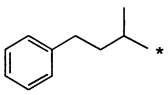
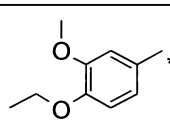
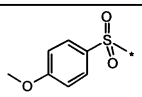
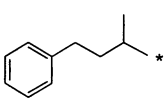
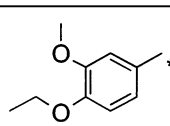
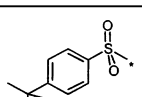
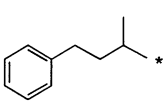
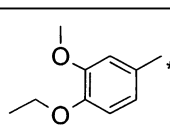
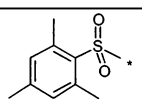
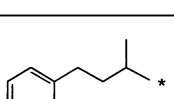
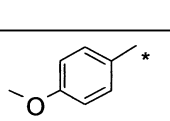
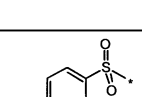
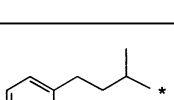
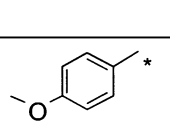
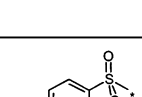
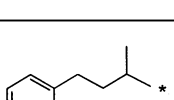
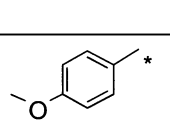
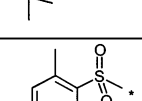
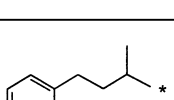
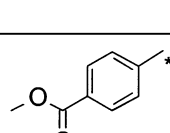
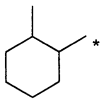
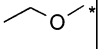
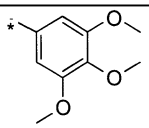
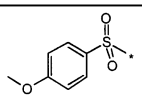
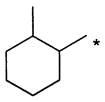
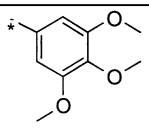
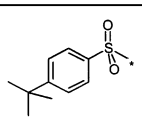
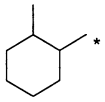
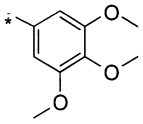
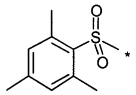
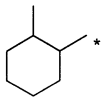
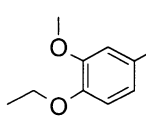
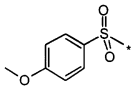
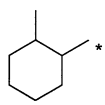
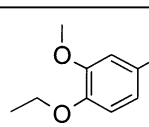
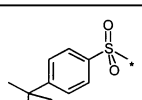
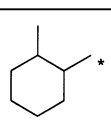
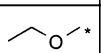
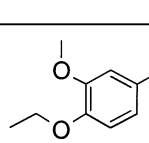
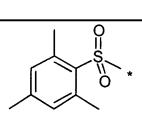
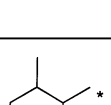
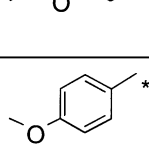
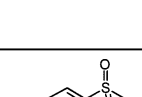
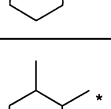
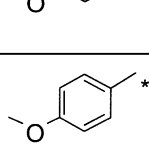
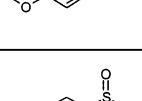
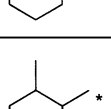
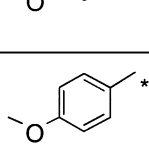
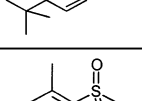
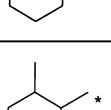
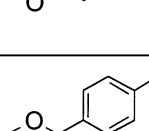
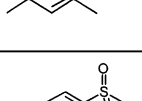
Entry	R1	R2	R3	R4	HPLC purity[b] (%)	MS (found)	MW (calcd.)
1					81.2	632.2	631
2					92.2	658.2	657
3					95.4	644.2	643
4					88.6	616.2	615
5					93.4	642.2	641
6					97.3	628.2	627
7					84.9	572.2	571
8					93.9	598.2	597
9					94.7	584.2	583
10					74.9	600.1	599
11					86.5	626.2	625
12					89.0	612.2	611

Table 2 (Continued)

Entry	R1	R2	R3	R4	HPLC purity[b] (%)	MS (found)	MW (calcd.)
13[c]					98.6	610.2	609
14[c]					99.6	636.2	635
15[c]					100.0	622.2	621
16[c]					97.0	594.2	593
17[c]					98.0	620.2	619
18[c]					100.0	606.2	605
19[c]					94.3	550.1	549
20[c]					99.0	576.2	575
21[c]					99.1	562.2	561
22[c]					87.4	578.1	577
23[c]					77.5	604.1	603
24[c]					90.1	590.2	589

[a] The HPLC and MS data of these compounds are available in the Supporting Information. [b] Purity based on the integration area of the HPLC peaks (the detection wavelength was 254 nm). [c] Mixture of cis and trans isomers.

obtained **5** each time in approximately 80% yield. Typical compounds were characterized by HPLC−MS and NMR after purification by silica gel chromatography (Table 1). This method can employ aromatic aldehydes with both electron-donating (entries **5a**, **5c**, **5e**, and **5g**) and electron-withdrawing groups (entries **5d** and **5i**). In addition, aliphatic (entries **5f**, **5h**, and **5j**) and heterocyclic (entry **5b**) aldehydes can also be used to construct the benzimidazole ring.

The reason for the spontaneous oxidation is still not clear. It was previously reported that the initially formed imines could act as both reducing and oxidizing agents and produced benzimidazoles along with reductive alkylation side products.[15] We did detect the reductive alkylation products by HPLC−MS analysis when using only ethanol as the solvent. But this could be avoided by selecting an appropriate combination of solvents, such as DMF/EtOH, THF/EtOH, or dioxane/EtOH. Another obstacle, however, appeared when DMF/EtOH was employed as a combined solvent. The Schiff's base between **5** and the remaining DMF was often found when performing acylation by sulfonyl chloride in the presence of an organic base, such as morpholine resin. This usually gave a major peak in the HPLC−MS analysis corresponding to the $[M + 56]^+$ ion in the ESI mass spectrum. Thus, THF/EtOH or dioxane/EtOH was finally selected. Because of the observed instability of **4**, the continuous synthesis of **5** was initially carried out under an argon atmosphere, but later this was found to be unnecessary. This also implies that aldehyde might protect **4** from oxidation or oxygen might not participate directly in the process of dehydrogenation. We suspect that the HCO group of DMF or a trace amount of superoxide in the THF and 1,4-dioxane might play a role in the oxidation process.

The free aromatic amino group of **5** may be modified in different ways. Acylation is an easy, effective one and can produce many biologically active compounds.[16,17] Here, we selected anhydride, sulfonyl chloride, isocyanate, and isothiocyanate to introduce the forth diversity point (R_4). It should be emphasized that it was necessary to thoroughly wash the intermediate **5** with saturated sodium dicarbonate solution before acylation. Otherwise, remaining acetic acid or formic acid could also acylate the amino group to decrease the purity of **6**. Acylation by the anhydride could be quickly completed in 30 min as monitored by HPLC−MS analysis. Acylation by isocyanate was also completed at room temperature overnight. Acylation by isothiocyanate often needed heating to 40 °C or prolonging the reaction time to drive the reaction to completion. Acylation by sulfonyl chloride encountered many difficulties. Although pyridine was a good solvent for sulfonylation and the reaction could finish in 30 min, it was not suitable for library synthesis because of its unpleasant odor and difficulty of removal. Finally, we found that the reaction could take place smoothly in dry dichloromethane (DCM) with morpholine polystyrene resin as the organic base. After the acylation, all excess acylating reagents were scavenged by commercially available aminomethyl polystyrene resin to give the desired products **6**, which were further purified by silica gel column chromatography and characterized by HPLC−MS and NMR. The representatively synthesized 5-aminobenzimidazole derivatives **6** are also listed in Table 1.

Generally, at the optimization stage of the reaction conditions, four kinds of side products were found in the final products according to the HPLC−MS analysis. These impurities include condensation products of **4** with acetic acid, reductive alkylation or dialkylation products of **4** with aldehydes, and acetylated and formylated products of **5**. The amounts of the first two side products could be minimized as low as possible by controlling the amount of acetic acid and selecting suitable mixed solvents as mentioned above. The last two side products appeared only after the addition of basic resin. Therefore, it was essential that the reaction reagents/solvents were completely removed and that **5** was thoroughly washed with saturated sodium dicarbonate solution prior to the next reaction. A small size (24 members) library was prepared in a parallel manner, producing **6** in 59% to ∼90% overall yield for three continuous reaction steps. Each crude product was analyzed by HPLC−MS and gave 75% to ∼100% purity at 254 nm (Table 2). Among them, the purity of two compounds was lower than 80% with major impurities being unreacted intermediates or undesired acylation products as characterized by HPLC−MS analysis.

Conclusion

We have developed an efficient method for the parallel solution-phase synthesis of 5-aminobenzimidazole derivatives from DFDNB. This procedure includes primary (the first diversity point) and secondary (the second diversity point) nucleophilic substitution of DFDNB, reduction of aromatic *m*-dinitro groups, condensation with aldehydes (the third diversity point) to construct the benzimidazole ring, and acylation by anhydrides, isocyanates, isothiocyanates, or sulfonyl chlorides (the forth diversity point). All the reactions involved here are highly effective at room temperature in giving the desired product. The procedure can be operated in a continuous approach, and four diversity points have been introduced in the final product **6**. It is likely that this approach can be used to generate a high-quality larger library for biological evaluation.

Experimental Section

All chemical reagents were purchased from Acros Organics (Geel, Belgium) and used without further purification. Dry DCM was redistilled from phosphorus pentoxide. Aminomethyl polystyrene resin (loading 1.3 mmol/g, 1% DVB cross-linked, 100−200 mesh) and Merrifield resin (loading 4.19 mmol/g, 1% DVB cross-linked, 100−200 mesh) were purchased from Tianjin Hecheng Corporation (Tianjin, China). Morpholine polystyrene resin (loading 4.04 mmol/g, 1% DVB cross-linked, 100−200 mesh) was prepared from Merrifield resin according to the literature method.[18] HPLC analysis was performed on a Shimadzu HPLC system equipped with an SPD-10A VP detector, an LC-10AT VP pump, and a DGU-12A degasser. The column employed was a Kromasil C18 column (4.6 μm, 4.6 mm × 50 mm) from DIKMA. The eluent was a mixture of acetonitrile and water containing 0.05% TFA, with a linear gradient from 5:95 v/v acetonitrile−H_2O to 95:5 v/v acetonitrile−H_2O over 5 min at a 1 mL/min flow rate. The UV detection was done at 254 nm. Auto HPLC−MS analysis was performed on a ThermoFinnigan LCQ-Advantage mass

spectrometer equipped with a Gilson 322 pump, Gilson UV−vis-152 detector, Gilson 215 liquid handler, and a fluent splitter. The elution gradient, flow rate, and detection wavelength were the same as above. Five percent of the eluent was split into the MS system. Mass spectra were recorded in either positive or negative ion mode using electrospray ionization. All NMR experiments were carried out on a Varian Mercury 300 or 500 MHz NMR spectrometer equipped with an autosampler using $CDCl_3$ as the solvent. Parallel synthesis was carried out on an H + P Labortechnik GmbH parallel synthesizer. Parallel evaporation of the solvents was carried out on an HT-4 series Genevac evaporator. Parallel filtration was performed on a parallel-filtering apparatus designed by ourselves.[19] Phase separators were purchased from Argonaut Inc. (Mid Glamorgan, U.K.).

General Procedure for the Synthesis of Intermediate 2.[12] To a magnetically stirred solution of 1.0 equiv (typically 5.0 mmol) of 1,5-difluoro-2,4-dinitrobenzene and 1.1 equiv of diisopropylethylamine (DIPEA) in 50 mL of THF was added dropwise a solution of 1.0 equiv of primary amine in 50 mL of THF. The reaction mixture was continuously stirred for an additional 1 h at room temperature. The solvent was evaporated, and water was added to precipitate **2**. The desired intermediate **2** was then collected by filtration and washed thoroughly with water. For a typical compound, [2-(3,4-dimethoxy-phenyl)-ethyl]-(5-fluoro-2,4-dinitro-phenyl)-amine, 1.808 g of yellow powder was obtained in 99% yield, with an HPLC purity >99%. ESI-MS: *m*/*z* 364.0 $(M - H)^-$.

General Procedure for the Synthesis of Intermediate 3. 1. Method 1. To a magnetically stirred solution of intermediate **2** (typically 4.0 mmol) in 20 mL of THF and 30 mL of alcohols (EtOH or MeOH), 1 M KOH aqueous solution was added dropwise until a yellow precipitate appeared. The reaction mixture was shaken manually for 2 min, and enough water (100 mL) was added. Then **3a** was collected by filtration and washed thoroughly with water. For a typical compound, [2-(3,4-dimethoxy-phenyl)-ethyl]-(5-ethoxy-2,4-dinitro-phenyl)-amine, 1.461 g of yellow powder was obtained in 93% yield, with an HPLC purity >99%. ESI-MS: *m*/*z* 390.0 $(M - H)^-$.

2. Method 2. To a magnetically stirred solution of 1.0 equiv of intermediate **2** (typically 4.0 mmol) in 20 mL of acetone, 1.2 equiv of phenols and 2.0 equiv of anhydrous K_2CO_3 were added. The reaction mixture was shaken mechanically at room temperature for at least 5 h until the total disappearance of **2** as detected by HPLC analysis was confirmed. Enough water (100 mL) was added to give **3b** as a yellow precipitate. Then **3b** was collected by filtration and washed thoroughly with water. For a typical compound, [2-(3,4-dimethoxy-phenyl)-ethyl]-[5-(4-ethyl-phenoxy)-2,4-dinitro-phenyl]-amine, 1.465 g of yellow powder was obtained in 78% yield, with an HPLC purity >99%. ESI-MS: *m*/*z* 466.0 $(M - H)^-$.

3. Method 3. To a magnetically stirred solution of 1.0 equiv of intermediate **2** (typically 4.0 mmol) in 20 mL of THF, 1.1 equiv of DIPEA and 1.1 equiv of secondary amines were added. The reaction mixture was shaken mechanically at room temperature overnight and evaporated to dryness to give a yellow solid or oil. Enough water (100 mL) was added to give **3c** as a yellow precipitate. Then **3c** was collected by filtration and washed thoroughly with water. For a typical compound, [2-(3,4-dimethoxy-phenyl)-ethyl]-(5-morpholin-4-yl-2,4-dinitro-phenyl)-amine, 1.499 g of yellow powder was obtained in 87% yield, with an HPLC purity >99%. ESI-MS: *m*/*z* 431.0 $(M - H)^-$.

General Procedure for the Synthesis of Intermediate 5. To a solution of 1.0 mmol of substituted dinitro compound **2** or **3** in 15 mL of 1,4-dioxane and 15 mL of ethanol under stirring was added 1.5 g of $HCOONH_4$ and 200 mg of 10% Pd−C. The reaction mixture turned from yellow to red and then to colorless in 30 min at room temperature. The catalyst and undissolved excess $HCOONH_4$ were filtered, and the filtrate was added directly into a solution of 1.2 mmol of aldehydes and 3 mL of glacial acetic acid in 15 mL of 1,4-dioxane. After stirring at room temperature overnight, excess aldehyde was scavenged by 600 mg (3.9 equiv to excess aldehyde) of aminomethyl polystyrene resin as monitored by HPLC analysis. After the aldehyde was completely removed, the resin was filtered and washed with EtOH. The combined filtrate was evaporated in vacuo to dryness. The residue was dissolved in a mixture of saturated sodium bicarbonate solution and DCM. The organic layer was separated by a phase separator and then evaporated in vacuo to give **5**. The representative compounds **5a**−**5j** were further purified by silica gel column chromatography eluting with EtOAc/petroleum ether (1:1). For a typical compound **5a**, 1-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-fluoro-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-ylamine, 405 mg of light brown solid was obtained in 84.1% yield, and it was fully characterized. ^{1}H NMR (300 MHz): δ 2.94 (t, 2H, J = 6.6 Hz), 3.61 (s, 3H), 3.79 (s, 3H), 3.83 (s, 6H), 3.87 (s, 3H), 4.41 (t, 2H, J = 6.6 Hz), 6.03 (d, 1H, J = 1.8 Hz), 6.30 (dd, 1H, J = 8.1 Hz, J = 1.8 Hz), 6.51 (s, 2H), 6.58 (d, 1H, J = 8.1 Hz), 7.09 (d, 1H, J = 10.2 Hz), 7.19 (d, 1H, J = 8.1 Hz). ^{13}C NMR (125 MHz): δ 34.7, 46.4, 55.6, 55.7, 56.2, 60.9, 97.0, 97.2, 105.9, 106.5, 111.1, 111.5, 120.5, 125.3, 127.7, 129.4, 131.3, 139.1, 147.8, 148.8, 149.3, 151.2, 153.1, 154.0.

The others (**5b**−**5j**) were characterized by ^{1}H NMR as described below:

1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-(4-ethyl-phenoxy)-2-thiophen-2-yl-1*H*-benzoimidazol-5-ylamine (5b). ^{1}H NMR (300 MHz): δ 1.23 (t, 3H, J = 7.8 Hz), 2.63 (m, 2H, J = 7.8 Hz), 2.98 (t, 2H, J = 7.2 Hz), 3.67 (s, 3H), 3.80 (s, 3H), 4.42 (t, 2H, J = 7.2 Hz), 6.32 (d, 1H, J = 1.8 Hz), 6.50 (dd, 1H, J = 8.1 Hz, J = 1.8 Hz), 6.68 (d, 1H, J = 8.1 Hz), 6.82 (s, 1H), 6.88 (d, 2H, J = 8.4 Hz), 7.09 (dd, 1H, J = 3.6 Hz, J = 4.8 Hz), 7.15 (d, 2H, J = 8.4 Hz), 7.29 (d, 1H, J = 3.6 Hz), 7.43 (d, 1H, J = 4.8 Hz).

6-Fluoro-1-phenethyl-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-ylamine (5c). ^{1}H NMR (300 MHz): δ 3.03 (t, 2H, J = 7.2 Hz), 3.84 (s, 6H), 3.89 (s, 3H), 4.41 (t, 2H, J = 7.2 Hz), 6.61 (s, 2H), 6.62 (d, 1H, J = 4.2 Hz), 6.86 (m, 2H), 7.05 (d, 1H, J = 10.2 Hz), 7.17−7.20 (m, 3H).

6-(3,5-Dimethyl-phenoxy)-2-(2-fluoro-phenyl)-1-(3-phenyl-propyl)-1*H*-benzoimidazol-5-ylamine (5d). ^{1}H NMR (300 MHz): δ1.99 (m, 2H), 2.28 (s, 6H), 2.43 (t, 2H, J = 7.5

Hz), 3.99 (t, 2H, J = 7.5 Hz), 6.63 (s, 2H), 6.73 (s, 1H), 6.92 (s, 1H), 6.94−7.30 (m, 8H), 7.48 (m, 1H), 7.62 (m, 1H).

2-(4-Methoxy-phenyl)-6-morpholin-4-yl-1-propyl-1*H*-benzoimidazol-5-ylamine (5e). ^{1}H NMR (300 MHz): δ 0.88 (t, 3H, J = 7.5 Hz), 1.78 (m, 2H), 2.99 (t, 4H, J = 4.2 Hz), 3.87 (s, 3H), 3.91 (t, 4H, J = 4.2 Hz), 4.10 (t, 2H, J = 7.5 Hz), 6.96 (s, 1H), 7.01 (d, 2H, J = 9.0 Hz), 7.15 (s, 1H), 7.60 (d, 2H, J = 9.0 Hz).

6-(3,5-Dimethyl-phenoxy)-1-(1,1-dimethyl-propyl)-2-phenethyl-1*H*-benzoimidazol-5-ylamine (5f). ^{1}H NMR (300 MHz): δ 0.69 (t, 3H, J = 7.2 Hz), 1.75 (s, 6H), 2.02 (m, 2H), 2.26 (s, 6H), 3.30 (m, 4H), 6.56 (s, 2H), 6.68 (s, 1H), 7.16 (s, 1H), 7.26 (s, 1H), 7.30−7.33 (m, 5H).

1-(1-Methyl-hexyl)-6-phenoxy-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-ylamine (5g). ^{1}H NMR (300 MHz): δ 0.73 (t, 3H, J = 7.2 Hz), 0.92−1.16 (m, 6H), 1.56 (d, 3H, J = 6.9 Hz), 2.02 (m, 2H), 3.88 (s, 6H), 3.90 (s, 3H), 4.52 (m, 1H), 6.80 (s, 2H), 6.96 (d, 2H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.15 (s, 1H), 7.23 (s, 1H), 7.30 (t, 2H, J = 7.5 Hz).

2-(1-Ethyl-propyl)-1-(1-methyl-heptyl)-6-phenoxy-1*H*-benzoimidazol-5-ylamine (5h). ^{1}H NMR (300 MHz): δ 0.87 (t, 3H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.2 Hz), 0.97 (t, 3H, J = 7.2 Hz), 1.26 (m, 6H), 1.56 (d, 3H, J = 6.9 Hz), 1.87 (m, 4H), 2.05 (m, 2H), 2.81 (m, 1H), 4.48 (m, 1H), 7.03 (d, 2H, J = 7.8 Hz), 7.09 (t, 1H, J = 7.8 Hz), 7.15 (s, 1H), 7.26 (s, 1H), 7.36 (t, 2H, J = 7.8 Hz).

2-(3,4-Difluoro-phenyl)-6-fluoro-1-(3-isopropoxy-propyl)-1*H*-benzoimidazol-5-ylamine (5i). ^{1}H NMR (300 MHz): δ 1.09 (d, 6H, J = 6.3 Hz), 2.00 (m, 2H), 3.31 (t, 2H, J = 5.4 Hz), 3.43 (m, 1H), 4.28 (t, 2H, J = 6.9 Hz), 7.13 (d, 1H, J = 9.9 Hz), 7.16 (d, 1H, J = 7.8 Hz), 7.30 (t, 1H, J = 9.0 Hz), 7.48 (m, 1H), 7.62 (t, 1H, J = 9.0 Hz).

1-(3-Butoxy-propyl)-2-(2-furan-2-yl-vinyl)-6-(quinolin-8-yloxy)-1*H*-benzoimidazol-5-ylamine (5j). ^{1}H NMR (300 MHz): δ 0.75 (t, 3H, J = 7.5 Hz), 1.22 (m, 2H), 1.46 (m, 2H), 2.00 (m, 2H), 3.27 (t, 4H, J = 6.6 Hz), 4.25 (t, 2H, J = 6.6 Hz), 6.46 (dd, 1H, J = 3.6 Hz, J = 1.8 Hz), 6.50 (d, 1H, J = 3.6 Hz), 6.93 (dd, 1H, J = 7.8 Hz, J = 1.8 Hz,), 6.99 (d, 1H, J = 15.9 Hz), 7.11 (s, 1H), 7.20 (s, 1H), 7.36 (t, 1H, J = 7.8 Hz), 7.44 (d, 1H, J = 1.8 Hz), 7.48 (t, 1H, J = 1.8 Hz), 7.51 (d, 1H, J = 3.6 Hz,), 7.69 (d, 1H, J = 15.9 Hz), 8.20 (dd, 1H, J = 7.8 Hz, J = 1.8 Hz), 9.03 (dd, 1H, J = 4.2 Hz, J = 1.8 Hz).

General Procedure for the Synthesis of 6. 1. Method 1. To a solution of 0.10 mmol of **5** in 1.5 mL of dry DCM, 0.30 mmol of different acylating reagents (anhydride, isocyanate, or isothiocyanate) was added. The reaction mixture was shaken mechanically at room temperature for at least 24 h. To the reaction mixture, 500 mg (3.2 equiv to excess acylating reagent) of aminomethyl polystyrene resin was added to remove excess acylating reagent. Then the resin was filtered and washed with dry DCM. The combined filtrate was evaporated in vacuo to give products **6**. For a typical compound **6q**, 39.3 mg of white powder was obtained in 97% yield.

2. Method 2. To a solution of 0.10 mmol of **5** in 1.5 mL of dry DCM, 200 mg (8.0 equiv to **5**) of morpholine resin and 0.30 mmol of sulfonyl chloride were added. After the reaction mixture was shaken at room temperature for at least 24 h, the resin was filtered and washed with dry DCM. To the filtrate, 500 mg (3.2 equiv to excess sulfonyl chloride) of aminomethyl polystyrene resin was added to remove excess sulfonyl chloride. Then the resin was filtered and washed with dry DCM. The combined filtrate was evaporated in vacuo to give product **6**. For a typical compound **6i**, 42.3 mg of white powder was obtained in 83% yield.

The representative compounds **6a**−**6s** were further purified by silica gel column chromatography eluting with EtOAc/petroleum ether (1:1). For a typical compound **6h**, *N*-(6-morpholin-4-yl-1-propyl-2-pyridin-3-yl-1*H*-benzoimidazol-5-yl)-acetamide, 30.3 mg of light yellow solid was obtained in 88% yield, and it was fully characterized. ^{1}H NMR (300 MHz): δ 0.86 (t, 3H, J = 7.2 Hz), 1.81 (m, 2H), 2.21 (s, 3H), 2.94 (m, 4H), 3.90 (m, 4H), 4.16 (t, 2H, J = 7.2 Hz), 7.16 (s, 1H), 7.45 (m, 1H), 8.07 (d, 1H, J = 8.1 Hz), 8.57 (s, 1H, exchangeable with D_2O), 8.71 (s, 1H), 8.81 (s, 1H), 8.91 (s, 1H). ^{13}C NMR (125 MHz): δ 11.2, 23.3, 24.9, 46.4, 53.3, 67.7, 102.1, 111.0, 123.7, 127.0, 129.6, 131.8, 137.1, 138.6, 140.5, 149.3, 150.4, 150.9, 167.8.

The others (**6a**−**6s**) were characterized by ^{1}H NMR as described below:

***N*-[1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-fluoro-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-yl]-acetamide (6a).** ^{1}H NMR (300 MHz): δ 2.25 (s, 3H), 2.93 (t, 2H, J = 6.6 Hz), 3.60 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.88 (s, 3H), 4.46 (t, 2H, J = 6.6 Hz), 6.04 (s, 1H), 6.28 (d, 1H, J = 8.7 Hz), 6.56 (s, 2H), 6.58 (d, 1H, J = 8.7 Hz), 7.13 (d, 1H, J = 10.5 Hz), 7.46 (br, 1H), 8.61 (d, 1H, J = 7.8 Hz).

1-[1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-fluoro-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-yl]-3-(4-methoxy-phenyl)-urea (6b). ^{1}H NMR (300 MHz): δ 2.90 (t, 2H, J = 6.6 Hz), 3.60 (s, 3H), 3.76 (s, 6H), 3.81 (s, 6H), 3.86 (s, 3H), 4.41 (t, 2H, J = 6.6 Hz), 6.06 (s, 1H), 6.27 (d, 1H, J = 7.8 Hz), 6.54 (s, 2H), 6.57 (d, 1H, J = 7.8 Hz), 6.84 (d, 2H, J = 8.4 Hz), 7.03 (br, 1H, exchangeable with D_2O), 7.08 (d, 1H, J = 10.5 Hz), 7.26 (d, 2H, J = 8.4 Hz), 8.32 (d, 1H, J = 7.5 Hz).

1-[1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-fluoro-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-yl]-3-(4-trifluoromethyl-phenyl)-urea (6c). ^{1}H NMR (300 MHz): δ 2.89 (t, 2H, J = 6.6 Hz), 3.59 (s, 3H), 3.74 (s, 3H), 3.77 (s, 6H), 3.83 (s, 3H), 4.40 (t, 2H, J = 6.6 Hz), 6.10 (s, 1H), 6.26 (d, 1H, J = 7.8 Hz), 6.54 (s, 2H), 6.55 (d, 1H, J = 7.8 Hz), 7.06 (d, 1H, J = 10.2 Hz), 7.39 (s, 4H), 7.61 (br, 1H), 8.30 (d, 1H, J = 6.6 Hz).

1-Benzyl-3-[1-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-fluoro-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-yl]-urea (6d). ^{1}H NMR (300 MHz): δ 2.91 (t, 2H, J = 6.6 Hz), 3.58 (s, 3H), 3.77 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 4.43 (t, 2H, J = 6.6 Hz), 4.47 (d, 2H, J = 4.8 Hz), 5.29 (br, 1H), 6.05 (s, 1H), 6.28 (d, 1H, J = 7.5 Hz), 6.55 (s, 2H), 6.58 (d, 1H, J = 7.5 Hz), 7.12 (d, 1H, J = 9.3 Hz), 7.24∼7.32 (m, 5H), 8.13 (d, 1H, J = 7.5 Hz).

***N*-{1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-fluoro-2-thiophen-2-yl-1*H*-benzoimidazol-5-yl}-4-methyl-benzenesulfonamide (6e).** ^{1}H NMR (300 MHz): δ 2.36 (s, 3H), 3.02 (t, 2H, J = 7.2 Hz), 3.67 (s, 3H), 3.82 (s, 3H), 4.48 (t, 2H, J = 7.2 Hz), 6.33 (d, 1H, J = 1.8 Hz), 6.51 (dd, 1H, J = 1.8

Hz, $J = 8.4$ Hz), 6.64 (d, 1H, $J = 2.4$ Hz), 6.70 (d, 1H, $J = 8.4$ Hz), 6.85 (d, 1H, $J = 9.6$ Hz), 7.13 (t, 1H, $J = 4.5$ Hz), 7.21 (d, 2H, $J = 7.8$ Hz), 7.35 (br, 1H), 7.50 (d, 1H, $J = 4.5$ Hz), 7.68 (d, 2H, $J = 7.8$ Hz), 7.85 (d, 1H, $J = 6.9$ Hz).

***N*-{2-(3,5-Bis-trifluoromethyl-phenyl)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-ethoxy-1*H*-benzoimidazol-5-yl}-benzenesulfonamide (6f).** ^{1}H NMR (300 MHz): δ 1.43 (t, 3H, $J = 6.6$ Hz), 2.92 (t, 2H, $J = 6.0$ Hz), 3.47 (s, 3H), 3.78 (s, 3H), 4.00 (m, 2H), 4.47 (t, 2H, $J = 6.0$ Hz), 5.90 (s, 1H), 6.04 (d, 1H, $J = 7.8$ Hz), 6.54 (d, 1H, $J = 7.8$ Hz), 6.77 (s, 1H), 7.18 (s, 1H), 7.48 (t, 2H, $J = 7.8$ Hz), 7.52 (t, 1H, $J = 7.8$ Hz), 7.76 (s, 2H), 7.84 (d, 2H, $J = 7.8$ Hz), 7.89 (br, 1H), 7.93 (s, 1H).

***N*-[1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6-(4-ethyl-phenoxy)-2-pyridin-3-yl-1*H*-benzoimidazol-5-yl]-4-methyl-benzenesulfonamide (6 g).** ^{1}H NMR (300 MHz): δ 1.26 (t, 3H, $J = 7.5$ Hz), 2.36 (s, 3H), 2.65 (m, 2H, $J = 7.5$ Hz), 2.76 (t, 2H, $J = 6.0$ Hz), 3.53 (s, 3H), 3.81 (s, 3H), 4.31 (t, 2H, $J = 6.0$ Hz), 5.91 (s, 1H), 6.08 (d, 1H, $J = 8.4$ Hz), 6.53 (d, 1H, $J = 8.4$ Hz), 6.60 (d, 2H, $J = 7.8$ Hz), 6.76 (s, 1H), 7.11 (d, 2H, $J = 7.8$ Hz), 7.12 (s, 1H), 7.14 (d, 2H, $J = 7.8$ Hz), 7.29 (m, 1H), 7.56 (d, 1H, $J = 8.1$ Hz), 7.66 (d, 2H, $J = 7.8$ Hz), 8.10 (s, 1H), 8.61 (s, 1H), 8.64 (s, 1H).

***N*-[2-(4-Methoxy-phenyl)-6-morpholin-4-yl-1-propyl-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6i).** ^{1}H NMR (300 MHz): δ 0.86 (t, 3H, $J = 7.2$ Hz), 1.78 (m, 2H), 2.59 (m, 4H), 3.80 (m, 4H), 3.88 (s, 3H), 4.10 (t, 2H, $J = 7.2$ Hz), 7.02 (d, 2H, $J = 8.1$ Hz), 7.09 (s, 1H), 7.39 (t, 2H, $J = 7.8$ Hz), 7.48 (t, 1H, $J = 7.8$ Hz), 7.61 (d, 2H, $J = 8.1$ Hz), 7.86 (d, 2H, $J = 7.8$ Hz), 7.97 (s, 1H), 8.03 (s, 1H, exchangeable with D_2O).

***N*-[6-(3,5-Dimethyl-phenoxy)-1-(1,1-dimethyl-propyl)-2-phenethyl-1*H*-benzoimidazol-5-yl]-acetamide (6j).** ^{1}H NMR (300 MHz): δ 0.65 (t, 3H, $J = 7.8$ Hz), 1.72 (s, 6H), 1.96 (m, 2H, $J = 7.8$ Hz), 2.11 (s, 3H), 2.26 (s, 6H), 3.31 (m, 4H), 6.58 (s, 2H), 6.72 (s, 1H), 7.21−7.31 (m, 6H), 7.52 (s, 1H, exchangeable with D_2O), 8.75 (s, 1H).

***N*-[6-Ethoxy-1-pentyl-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6k).** ^{1}H NMR (500 MHz): δ 0.82 (t, 3H, $J = 7.0$ Hz), 1.23 (m, 6H), 1.34 (t, 3H, $J = 7.0$ Hz), 1.75 (m, 2H), 3.90 (s, 9H), 4.16 (m, 2H), 6.65 (s, 1H), 6.90 (s, 2H), 7.02 (s, 1H), 7.38 (t, 2H, $J = 7.5$ Hz), 7.48 (t, 1H, $J = 7.5$ Hz), 7.79 (d, 2H, $J = 7.5$ Hz), 7.92 (s, 1H).

***N*-[1-(3-Methoxy-propyl)-6-piperidin-1-yl-2-thiophen-2-yl-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6l).** ^{1}H NMR (300 MHz): δ 1.56 (m, 2H), 1.67 (m, 4H), 2.06 (m, 2H), 2.50 (m, 4H), 3.26 (s, 3H), 3.30 (t, 2H, $J = 5.4$ Hz), 4.41 (t, 2H, $J = 7.2$ Hz), 7.10 (s, 1H), 7.16 (t, 1H, $J = 4.2$ Hz), 7.36 (t, 2H, $J = 7.2$ Hz), 7.45 (t, 1H, $J = 7.2$ Hz), 7.49 (d, 1H, $J = 4.2$ Hz), 7.57 (d, 1H, $J = 3.6$ Hz), 7.85 (d, 2H, $J = 7.2$ Hz), 7.99 (s, 1H), 8.19 (br, 1H).

***N*-[2-(4-Butoxy-phenyl)-1-(3-methoxy-propyl)-6-piperidin-1-yl-1*H*-benzoimidazol-5-yl]-4-methyl-benzenesulfonamide (6m).** ^{1}H NMR (300 MHz): δ 0.99 (t, 3H, $J = 7.5$ Hz), 1.52 (m, 4H), 1.68 (m, 4H), 1.80 (m, 2H), 1.93 (m, 2H), 2.31 (s, 3H), 2.54 (m, 4H), 3.18 (s, 3H), 3.20 (t, 2H, $J = 6.0$ Hz), 4.02 (t, 2H, $J = 6.0$ Hz), 4.26 (t, 2H, $J = 6.6$ Hz), 6.99 (d, 2H, $J = 7.8$ Hz), 7.11 (s,1H), 7.15 (d, 2H, $J = 7.8$ Hz), 7.62 (d, 2H, $J = 7.8$ Hz), 7.74 (d, 2H, $J = 7.8$ Hz), 7.95 (s, 1H), 8.18 (br, 1H).

***N*-[6-(3,5-Dimethyl-phenoxy)-2-(2,5-dimethyl-phenyl)-1-(3-methoxy-propyl)-1*H*-benzoimidazol-5-yl]-4-methyl-benzenesulfonamide (6n).** ^{1}H NMR (300 MHz): δ 1.68 (m, 2H), 2.17 (s, 3H), 2.24 (s, 6H), 2.34 (s, 3H), 2.36 (s, 3H), 3.00 (s, 3H), 3.05 (t, 2H, $J = 5.7$ Hz), 3.93 (t, 2H, $J = 6.9$ Hz), 6.30 (s, 2H), 6.74 (s, 1H), 6.80 (s, 1H), 6.97 (s, 1H), 7.15−7.20 (t, 5H), 7.67 (d, 2H, $J = 8.4$ Hz), 8.03 (s, 1H).

***N*-[2-(3,4-Difluoro-phenyl)-1-(3-methoxy-propyl)-6-(5,6,7,8-tetrahydro-naphthalen-1-yloxy)-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6o).** ^{1}H NMR (300 MHz): δ 1.77 (m, 6H), 2.40 (t, 2H, $J = 5.4$ Hz), 2.80 (t, 2H, $J = 5.4$ Hz), 3.04 (s, 3H), 3.10 (t, 2H, $J = 5.4$ Hz), 4.15 (t, 2H, $J = 6.9$ Hz), 6.23 (d, 1H, $J = 8.1$ Hz), 6.60 (s, 1H), 6.92 (t, 1H, $J = 6.9$ Hz), 6.98 (d, 1H, $J = 6.9$ Hz), 7.10 (s, 1H), 7.31 (s, 1H), 7.39 (t, 2H, $J = 7.8$ Hz), 7.52 (m, 1H), 7.59 (t, 1H, $J = 7.8$ Hz), 7.76 (d, 1H, $J = 6.6$ Hz), 7.82 (d, 2H, $J = 7.8$ Hz), 8.11 (s, 1H).

***N*-[6-(3,5-Dimethyl-phenoxy)-1-(3-methoxy-propyl)-2-phenethyl-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6p).** ^{1}H NMR (300 MHz): δ 1.77 (m, 2H), 2.20 (s, 6H), 3.11 (m, 4H), 3.12 (s, 3H), 3.24 (t, 2H, $J = 7.2$ Hz), 3.94 (t, 2H, $J = 7.2$ Hz), 6.21 (s, 2H), 6.70 (s, 1H), 6.71 (s, 1H), 6.98 (s, 1H), 7.24 (m, 5H), 7.33 (t, 2H, $J = 7.8$ Hz), 7.48 (t, 1H, $J = 7.8$ Hz), 7.74 (d, 2H, $J = 7.8$ Hz), 8.05 (s, 1H).

***N*-[2-(3,4-Difluoro-phenyl)-6-fluoro-1-(3-isopropoxy-propyl)-1*H*-benzoimidazol-5-yl]-acetamide (6q).** ^{1}H NMR (300 MHz): δ 1.10 (d, 6H, $J = 7.5$ Hz), 2.01 (m, 2H), 2.25 (s, 3H), 3.31 (t, 2H, $J = 5.4$ Hz), 3.44 (m, 1H), 4.33 (t, 2H, $J = 7.2$ Hz), 7.23 (d, 1H, $J = 10.2$ Hz), 7.33 (t, 1H, $J = 9.0$ Hz), 7.38 (s, 1H, exchangeable with D_2O), 7.53 (m, 1H), 7.64 (m, 1H), 8.61 (d, 1H, $J = 6.9$ Hz).

***N*-[6-Fluoro-1-(3-isopropoxy-propyl)-2-(3,4,5-trimethoxy-phenyl)-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6r).** ^{1}H NMR (500 MHz): δ 1.05 (d, 6H, $J = 6.0$ Hz), 1.97 (m, 2H), 3.30 (t, 2H, $J = 5.5$ Hz), 3.38 (m, 1H), 3.91 (s, 9H), 4.29 (t, 2H, $J = 7.5$ Hz), 6.91 (s, 2H), 7.10 (d, 1H, $J = 9.5$ Hz), 7.41 (t, 2H, $J = 8.0$ Hz), 7.51 (t, 1H, $J = 8.0$ Hz), 7.79 (d, 2H, $J = 8.0$ Hz), 7.88 (d, 1H, $J = 7.5$ Hz).

***N*-[6-(3,5-Dimethyl-phenoxy)-1-(3-isopropoxy-propyl)-2-(5-nitro-furan-2-yl)-1*H*-benzoimidazol-5-yl]-benzenesulfonamide (6s).** ^{1}H NMR (300 MHz): δ 0.95 (d, 6H, $J = 6.6$ Hz), 2.03 (m, 2H), 2.19 (s, 3H), 2.24 (s, 3H), 2.37 (s, 3H), 3.33 (t, 2H, $J = 6.0$ Hz), 3.42 (m, 1H), 4.43 (t, 2H, $J = 7.2$ Hz), 6.42 (d, 1H, $J = 8.4$ Hz), 6.47 (s, 1H), 6.77 (s, 1H), 7.01 (d, 1H, $J = 8.4$ Hz), 7.11 (s, 1H), 7.16 (d, 2H, $J = 8.1$ Hz), 7.40 (d, 1H, $J = 3.6$ Hz), 7.48 (d, 1H, $J = 3.6$ Hz), 7.66 (d, 2H, $J = 8.1$ Hz), 8.07 (s, 1H).

General Procedure for Library Synthesis. To each solution of eight intermediates **2** or **3** (0.15 mmol/compound) in 1 mL of 1,4-dioxane and 0.5 mL of ethanol was added 150 mg of $HCOONH_4$ and 20 mg of 10% Pd−C under magnetic stirring. When all reaction mixtures turned colorless, the solutions were simultaneously filtered into eight additional reaction vessels using a parallel-filtering apparatus with or without argon protection. Each reaction vessel contained a solution of 0.30 mmol of aldehyde and 150 μL of glacial acetic acid in 0.5 mL of 1,4-dioxane. All reaction

vessels were then put into the H + P Labortechnik GmbH parallel synthesizer and simultaneously stirred at room temperature overnight. The excess aldehyde in each reaction vessel was scavenged by 500 mg (4.3 equiv to excess aldehydes) of aminomethyl polystyrene resin. When all aldehydes were removed completely as monitored by HPLC−MS analysis, the resin was filtered and washed with EtOH. The combined filtrate of each reaction vessel was evaporated in vacuo to complete dryness using an HT-4 series Genevac evaporator. Each residue was subsequently dissolved in a mixture of 2 mL of saturated sodium bicarbonate solution and 2 mL of DCM, and the organic layer was separated using 15 mL of phase separators. All the individual collections were evaporated to complete dryness again to give intermediates **5**. Each **5** was then dissolved in 1.5 mL of dry DCM and was further divided equally into three additional reaction vessels for acylation by 0.15 mmol of three different sulfonyl chlorides in the presence of 100 mg (8.0 equiv to **5**) of morpholine resin or anhydrides, isocyanates, or isothiocyanates alone. The reaction mixtures were simultaneously stirred at room temperature for at least 24 h. To each reaction vessel was added 250 mg (3.2 equiv to excess acylating reagents) of aminomethyl polystyrene resin to remove excess acylating reagents after stirring at room temperature for 24 h. Then the resin was filtered and washed with dry DCM and the combined filtrate was evaporated to dryness to give a 24-member library of **6**. All the compounds were analyzed by an automated HPLC−MS system.

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Supporting Information Available. HPLC and MS data of the 24-member library. This material is available free of charge via the Internet at http://pubs.acs.org.

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