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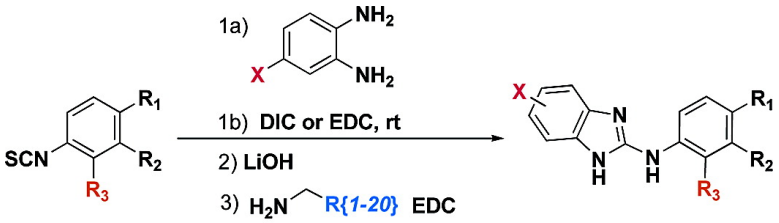

X = H, Br, C(O)NHCH$_2$R{*1-20*}
R_1 = H, (CH$_2$)$_n$C(O)NHCH$_2$R{*1-20*} (n = 0, 1, 2)
R_2 = H, C(O)NHCH$_2$R{*1-20*}
R_3 = H, CH$_3$

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Carbodiimide-Based Benzimidazole Library Method

Richard D. Carpenter,[†] Patrick B. DeBerdt,[†] Kit S. Lam,[‡] and Mark J. Kurth*,[†]

Department of Chemistry, University of California, Davis, One Shields Ave., Davis, California 95616, and Division of Hematology and Oncology, University of California Davis Cancer Center, University of California, Sacramento, California 95817

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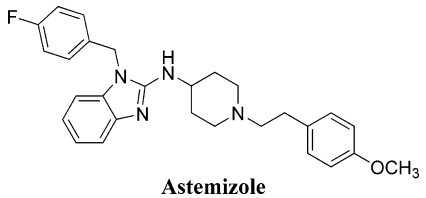
Using carbodiimide reagents [1,3-diisopropylcarbodiimide or *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC)], we have developed a mild, generalized, one-pot method that delivers *N*-2-arylaminobenzimidazole esters from commercially available aryl isothiocyanates and *o*-phenylenediamines. Following saponification and acidifying, the benzimidazole acids were isolated in overall yields ranging from 75 to 88% from the starting aryl isothiocyanates. Nine benzimidazole acids were converted into a library consisting of 180 benzimidazole amides following EDC coupling with commercially available amines. The National Institute of General Medical Science will dispense these benzimidazole amides to academia groups for pilot scale biomedical studies. Using these mild conditions and environmentally safe reagents, we demonstrated that these pharmaceutically ornate heterocycles can also be constructed on solid support.

Introduction

The benzimidazole ring system is a member of the class of heterocycles having heteroatoms at the 1- and 3-positions and comprise nearly one-quarter of the top-100-selling drugs.[1] Specifically, *N*-2-arylaminobenzimidazoles (**1**) have been an integral component in potent antihistamine drugs,[2] and they exhibit local anesthetic, adrenergic blocking, antispasmodic, sympathomimetic, analgesic, and antiserotonin activities.[2−4] Furthermore, this class of compounds has recently shown selective nanomolar activity against human prostanoid DP receptor antagonists, which are believed to be a key receptor target in the treatment of allergic rhinitis.[5−7] In a new antimalarial approach, in vivo studies have shown that the U.S. Food and Drug Administration-approved antihistamine astemizole inhibits the malaria parasite *Plasmodium falciparum*, possibly allowing a streamlined treatment for the most lethal disease worldwide.[8] This wide-ranging pharmaceutical activity is believed to derive from benzimidazole-mediated physicochemical properties; in particular, the relative acidity of *N*-aryl-2-aminobenzimidazoles facilitates favorable pharmacodynamics and pharmacokinetics, thereby making them ideal components of drug candidates.[7,9]



Astemizole

The chemistries employed to construct 2-aminobenzimidazoles have been reviewed,[7−10] with several methods existing to deliver these heterocycles from various precursors in fair to good yields. However, these methods suffer from the handling of highly toxic reagents,[10−21] uncommon synthetic precursors,[22−24] prolonged heating at elevated temperatures,[2,12−14,22,25−30] and/or insoluble transition metal salts.[9,12−14,18−21,31−34] These demands and drawbacks largely preclude the construction of this biologically diverse heterocycle on solid support for combinatorial libraries and high-throughput screening. Recently, Hioki reported the imine exchange of *o*-phenylenediamines and 2-aminothiophenols with azomethines on solid support which, upon cyclization and air oxidation, releases the benzimidazoles and benzothiazoles from the resin.[35] Herein, we report a mild, generalized, one-pot method that employs carbodiimide reagents [1,3-diisopropylcarbodiimide (DIC) or *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC)] to cyclodesulferize thiourea intermediates, delivering *N*-2-arylaminobenzimidazoles via either solution or solid-supported methods in 75−88% yield. We have also shown that this method can be utilized to construct *N*-2-arylaminobenzimidazoles on solid support and in good yields, with the benzimidazole moiety being retained on the resin. Using this approach, we have prepared nine benzimidazole esters that were then saponified and subsequently elaborated into a solution-phase library of 180 benzimidazole amide members.

As elaborated in Chart 1, these library members were chosen using Lipinski's rules of five—less than 5 H-bond donors, less than 10 H-bond acceptors, molecular weight less than 500, and a clog P (octanol/water) coefficient less than 5—as a guide to designing compounds with optimal oral availability, with over 90% of the benzimidazole amides reported here in accord with these rules.[36] The National Institute for General Medical Sciences (NIGMS) will distribute these benzimidazole amides, enabling this medicinally pertinent pharmacophore to partake in academia pilot-scale biomedical studies.

* To whom correspondence should be addressed. Phone: (530) 752-8192. Fax: (530) 752-8995. E-mail: mjkurth@ucdavis.edu.

[†] Department of Chemistry, University of California, Davis.

[‡] Division of Hematology and Oncology, University of California Davis Cancer Center.

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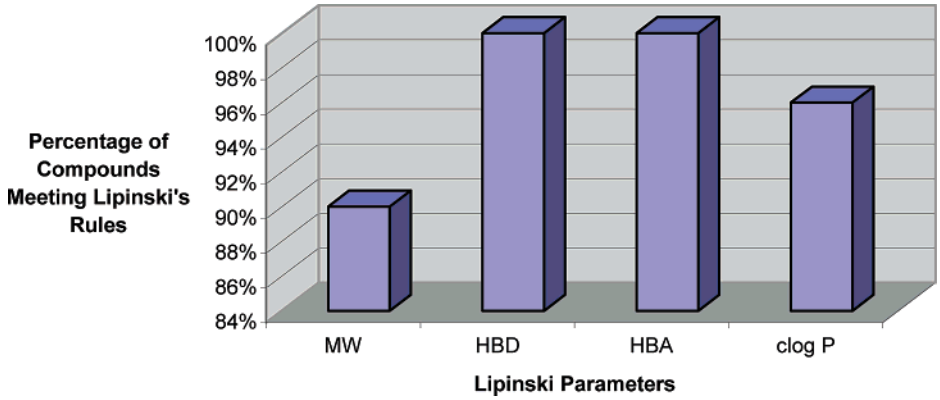
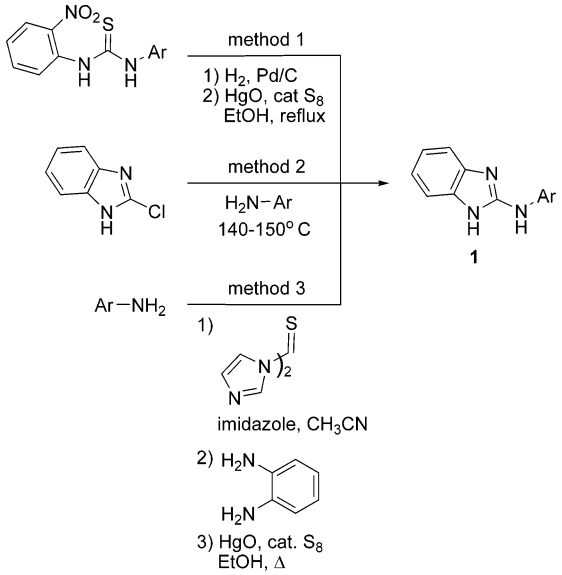
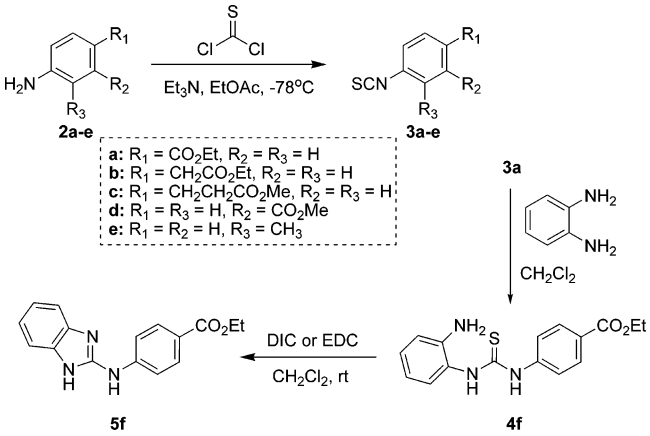
Chart 1. Benzimidazole Library Profile Chart for Lipinski's Rules of Five



Scheme 1. The Three Most Common Routes to 2-Aminobenzimidazoles



Scheme 2. Initial Approaches to Benzimidazoles



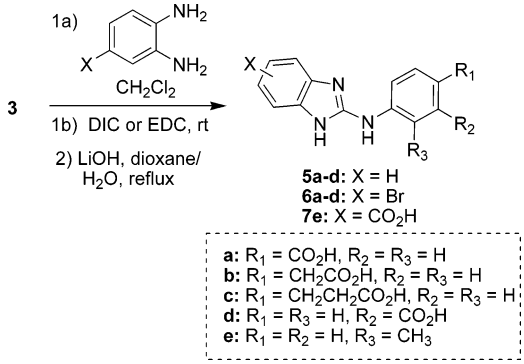
Results and Discussion

The most common synthetic approaches for 2-aminobenzimidazoles are shown in Scheme 1.[10] Method 1 suffers from overreduction of the thiourea,[10] and method 2 often yields self-arylation products.[2] In our hands, method 3,[10] which has been employed nearly exclusively since 1999, suffers from low yields (32−48%) and persistence impurities in the thiourea-generating step. Furthermore, the desulferizing cyclization step using mercury(II) oxide delivers the benzimidazole in less than optimal yields (48−70%), in addition to being hazardous to handle, as well as environmentally unfriendly with regard to the generation of highly toxic mercury salts.

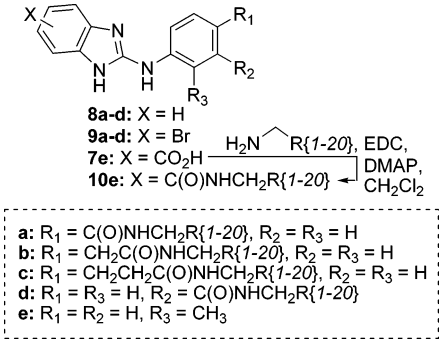
To circumvent these issues, we initially focused on using the more reactive aryl isothiocyanates for thiourea formation. Scheme 2 illustrates the treatment of aniline ester **2f** with thiophosgene in triethylamine to yield aryl isothiocyanate ester **3f** in 92% yield as a modification of Song's procedure.[37] The subsequent dropwise addition of **3f** to *o*-phenylenediamine gave the targeted bis-arylthiourea **4f** in 88% yield.[38] Following workup, crude LC/MS established the relative purity as >90%. With a relatively clean, high-yielding approach to the previously problematic thiourea in hand, we turned our attention to the heterocyclization reaction. Omar first reported the use of carbodiimide chemistry in the thiocondensation step by refluxing the thiourea together with DCC in benzene.[39] Apparently, purification and removal of *N*,*N*-dicyclohexylthiourea prevented the widespread application of this method. Recently, we treated an acyclic peptidomimetic thiourea with DIC under prolonged microwave irradiation to form a cyclic guanidine on solid support.[40] With this information in hand, we treated thiourea **3f** with 3 equiv of either DIC or EDC at room temperature and obtained the cyclized benzimidazole **5f** in 89−94% yields. In addition, *N*,*N*-diisopropylthiourea and the EDC-derived thiourea were isolated as the respective byproducts and characterized by LC/MS. We have found that the choice whether to employ DIC or EDC depends on the anticipated physical state of the targeted product. If a solid is expected, DIC should be employed, because after concentration, the product can easily be recrystallized from $CHCl_3$ and petroleum ether. If the product is an oil, then EDC should be employed, because the thiourea byproduct can be removed upon aqueous workup.

With these efficient, clean, and mild routes to thioureas and the benzimidazoles in hand, we next attempted the one-pot conversion of aryl isothiocyantes + diamines → benzimidazoles as shown in Scheme 3. For this transformation, the aryl isothiocyanate ester (**3a**−**e** prepared from anilines + thiophosgene, as shown in Scheme 2) was added dropwise to a solution of the diamine (1.05 equiv) in CH_2Cl_2 with subsequent stirring overnight at room temperature. After 16 h, TLC analysis revealed that the starting material was consumed. DIC or EDC (3 equiv) was then added, and the

Scheme 3. One-Pot Benzimidazole Synthesis



Scheme 4. Solution-Phase Benzimidazole Amide Library



reaction continuted at room temperature with monitoring by TLC. The aryl isothiocyanate, diamine, and carbodiimide reagents were not added simultaneously because of Jochims report that alkyl isothiocyanates in the presence of carbodiimide reagents undergo a [2 + 2] cycloaddition.[41] It should be noted that 2,6-dimethylphenylisothiocyanate failed to react with *o*-phenylenediamines, presumably due to the methyl groups congesting the C═S, thereby impeding the proper Bürgi−Dunitz trajectory of the nucleophile and resulting in poor orbital overlap.[42] 4-Nitro-*o*-phenylenediamine also failed to react with aryl isothiocyanates, ostensibly due to the drastic electron-withdrawing effect of the nitro group both inductively and through resonance.

In most instances, the heterocyclization step was complete after 4−8 h; however, some of these reactions required 16 h. Upon reaction completion, the solvent was removed via rotary evaporation under reduced pressure, and if DIC was employed, the product was purified via recrystallization from $CHCl_3$/petroleum ether. The filtered precipitate was washed first with water and then with petroleum ether to remove the diisopropylthiourea byproduct. When EDC was employed, the concentrated residue was taken up in ethyl acetate and subjected to water and brine washes, followed by drying and concentration.

The resulting benzimidazole esters were readily saponified by the action of LiOH in refluxing dioxane/H_2O. The cooled reaction mixtures were concentrated under reduced pressure, and the residue was taken up in 2 M aq NaOH. At pH 10, the benzimidazole acids are dianions and, consequently, readily soluble in water. After washing the resulting basic aqueous layer twice with ether, the aqueous layer was acidified to pH 2 with conc HCl, causing the benzimidazole acid to precipitate. After filtration and washing sequentially with ether and 2 M HCl, benzimidazole acids **5a**−**d**, **6a**−**d**, and **7e** were obtained in 75−88% overall yield from the starting aryl isothiocyanates.

With this high-yield, high-purity route to these benzimidazole acids in hand, we turned to acid → amide diversification by coupling these 9 acids to 20 commercially available amines. Employing EDC in CH_2Cl_2 for activation/dehydration, we constructed a solution-phase library of 180 benzimidazole amide chemset members **8a**−**d**{*1*−*20*}, **9a**−**d**{*1*−*20*}, and **10e**{*1*−*20*}, as shown in Scheme 4, with the structures of R{*1*−*20*} shown in Figure 1. The relative acidity of the *N*-2-arylaminobenzimidazole moiety (pKa ∼ 6−7)[10] results in a delocalized anion that does not compete with branched primary amines in the coupling step. These coupling reactions were typically monitored by TLC, and at reaction completion, each individual reaction mixture was concentrated at reduced pressure. The residue was dissolved in ethyl acetate, washed sequentially with water and brine, dried ($MgSO_4$), filtered, and concentrated. Each chemset member was then subjected to LC/MS analysis, with 95% of them meeting the >80% purity criterion without purification. The chemset members not meeting this standard were purified via reversed-phase HPLC.

Finally, the utility of this mild DIC-based heterocyclization has been demonstrated on solid support. As outlined in Scheme 5, Rink amide resin was swollen in DMF followed by Fmoc deprotection with 20% piperidine in DMF. To this Rink-amine resin was coupled 3,4-dinitrobenzoic acid, and the resin-bound dinitro groups were reduced with $SnCl_2 \cdot 2H_2O$ in DMF. The resulting resin was divided into four flasks, and a different commercially available aryl isothiocyanate was added to each. DIC was added next, and the

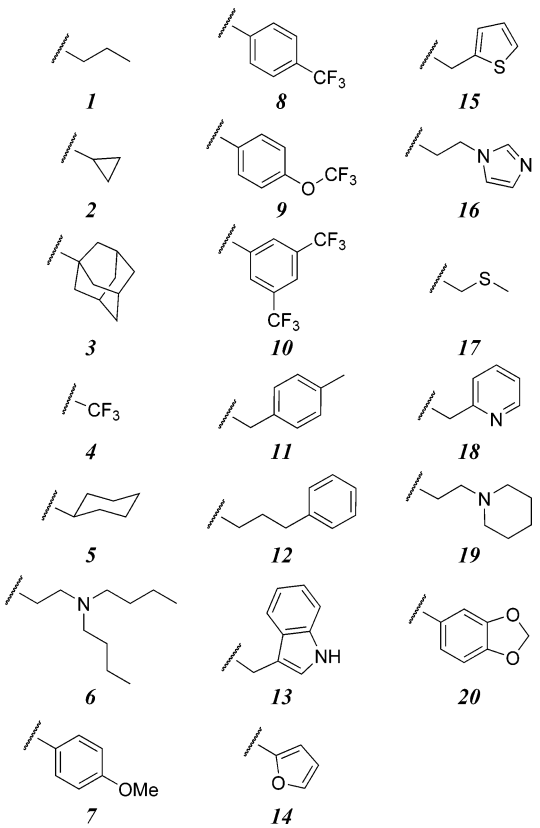
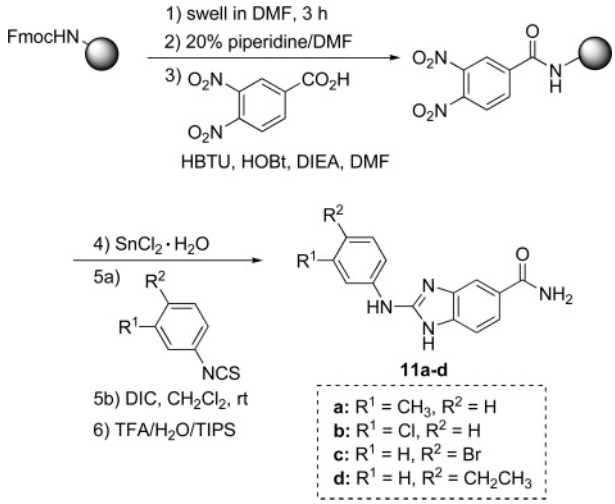


Figure 1. Structures of R{*1*−*20*} for benzimidazole amide library.

Scheme 5. Solid-Phase Carbodiimide Heterocyclizations



mixtures were agitated overnight to effect each thiourea → benzimidazole heterocyclization. Product benzimidazoles were released from the resin by TFA treatment (95% TFA/2.5% H_2O/2.5% TIPS), followed by concentration, analysis, and purification by reversed-phase HPLC. The four heterocycles were analyzed by LC/MS, with each giving the correct mass and each having >80% crude purity. The overall yield for the five synthetic steps from Rink resin ranged from 70 to 80%.

Conclusions

Starting from commercially available materials (aryl isothiocyanates + *o*-phenylenediamines), we have demonstrated a mild, one-pot synthesis to *N*-2-arylaminobenzimidazoles in which carbodiimide reagents thiocondense intermediate thioureas in the cyclodesulferization step. To minimize purification, the choice of carbodiimide reagent (DIC or EDC) depends on the expected physical state of the targeted products, with solids employing DIC and oils utilizing EDC. On solid support, the choice of carbodiimide reagent becomes moot due to the ease of washing away DIC and the thiourea byproduct as the resin is filtered. This simple, generalized, one-pot aryl isothiocyanate → benzimidazole approach delivers the benzimidazole system in good yields from commercially available materials, and mild reaction conditions enable heterocycle construction in either solution or solid phases. Using this method on solid phase in conjunction with one bead/one compound combinatorial strategies and high-throughput screening will allow large libraries to be synthesized and rapidly screened, thereby increasing the probability of finding a hit and facilitating the drug discovery process. The benzimidazole amide library, with its members containing this diverse and medicinally relevant pharmacophore, will be available to academia, and they will be allocated by NIGMS as part of their Pilot Scale Library Project.

Experimental Section

General Procedures. All chemicals were purchased from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (silica gel 60, F254) and visualized with UV light. Flash chromatography was performed with silica gel 60 (230−400 mesh). NMR spectra (^1H at 300 MHz, 400 MHz, ^{13}C at 75 MHz, 100 MHz) were recorded in DMSO-d_6 and acetone-d_6 as solvents, and chemical shifts are expressed in parts per million related to internal TMS. The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 100−900 Da, 20-V cone voltage, and Xterra MS C_{18} column (2.1 mm × 50 mm × 3.5 μm). CC refers to column chromatography. The specifications on the preparative HPLC are as follows: 7 mL/min flow rate, Xterra Prep MS C_{18} OBD column (19 mm × 100 mm) and dual wavelength absorbance detector. Concentration refers to rotary evaporation under reduced pressure. Rink amide resin (0.5 mmol/g loading, 100−200 mesh) was purchased from Tianjin Nankai Hecheng Sci & Tech. Co., Ltd, (batch number GRM-0406-J). After each solid-phase step, the resin was washed by sequential treatment with the following solvents: DMF (2 × 5 mL), H_2O (2 × 5 mL), CH_3OH, (3 × 5 mL), and CH_2Cl_2 (5 × 5 mL).

General Procedure for Aryl Isothiocyanate Esters: Ethyl 4-Isothiocyanatobenzoate (3a). A solution of thiophosgene (30.0 mmol, 2.30 mL) in ethyl acetate (130 mL) was cooled to −78 °C, followed by the dropwise addition of a solution of triethylamine (60.1 mmol, 8.37 mL) in ethyl acetate (80 mL) over 30 min. After vigorous stirring for 10 min, a solution of appropriate aniline ester (4.5 g, 27.3 mmol) in ethyl acetate (80 mL) was added over 30 min, followed by the reaction proceeding to room temperature over 12 h. The workup consisted of diluting with ethyl acetate, followed by washing sequentially with water (200 mL × 2) and brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the crude product was purified via short-path CC (hexanes/ethyl acetate, 9:1) to give **3a** (5.03 g, 89% yield). The analytical data are in accord with literature values.[43]

Ethyl 2-(4-Isothiocyanatophenyl)acetate (3b). Yield 5.20 g, 93%. The analytical data are in accord with literature values.[44]

Methyl 3-(4-Isothiocyanatophenyl)propanoate (3c). To a solution of anhydrous methanol (125 mL) was added acetyl chloride (39.4 mmol, 2.8 mL), followed by stirring for 30 min under a nitrogen atmosphere. 3-(4-Aminophenyl)-propanoic acid (5.0 g, 30.3 mmol) was added, and the solution was refluxed for 8 h. After the reaction was completed as determined by TLC, the crude product was concentrated to a minimal volume before precipitation with ether gave the esterified product (5.04 g) that was subsequently used without further purification. The analytical data are in accord with literature values.[45] The aniline ester was then subjected to the general procedure for aryl isothiocyanate esters, which upon completion gave **3c** (5.41 g, 90% yield from the acid); IR (neat): 2073, 1723. ^1H NMR (300 MHz, acetone-d_6): δ 7.91 (d, 2H), 7.31 (d, 2H), 3.68 (s, 3H), 2.91 (t, 2H), 2.54 (t, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 173.1, 140.2, 137.0, 130.3, 128.7, 125.8, 52.0, 33.4, 30.2; ESI-MS *m*/*z* 163 $(M - NCS + H)^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 220 nm.

Methyl 3-Isothiocyanatobenzoate (3d). Yield 7.06 g, 92%. The analytical data are in accord with literature values.[46]

1-Isothiocyanato-2-methylbenzene (3e). Yield 12.67 g, 91%. The analytical data are in accord with literature values.[47]

General Procedure for Benzimidazole Acids: 4-(1*H*-Benzo[*d*]imidazol-2-ylamino)benzoic Acid (5a). To a solution of *o*-phenylenediamine (1.76 g, 16.3 mmol) in CH_2Cl_2 (75 mL) was added a solution of the aryl isothiocyanate ester (for **3a**, 3.0 g, 15.5 mmol) in CH_2Cl_2 (75 mL) dropwise over 30 min, followed by stirring for 16 h at room temperature. After TLC showed that the aryl isothiocyanate was consumed, the appropriate carbodiimide reagent (DIC or EDC) was added (for **5a**, DIC (46.5 mmol, 7.2 mL)), and the reaction proceeded at room temperature until TLC showed the intermediate thiourea was consumed. In most instances, this was between 4 and 8 h., but in some cases, this took as long as 16 h (**5a**, 6 h). If DIC was employed (**5a**), the concentrated crude product was recrystallized from hot $CHCl_3$ and petroleum ether to give the benzimidazole ester (3.67 g). If EDC was utilized, then the residue was taken up in ethyl acetate/H_2O, followed by washing (H_2O, brine), drying ($MgSO_4$), and concentration to give the benzimidazole ester (4.08 g), which was used without further purification. A solution of the benzimidazole ester (4.08 g, 15.3 mmol) in dioxane/H_2O (125 mL/80 mL) was treated with LiOH (1.83 g, 76.4 mmol), and the solution was refluxed for 16 h. The reaction mixture was concentrated, and the residue was taken up in aqueous 2 M NaOH. This basic water layer (pH ~10) was washed twice with ether before being acidified with concentrated HCl to pH ~2−3, at which point **5a** precipitated as a white solid (3.38 g, 86%). The analytical data are in accord with literature values.[27]

2-(4-(1*H*-Benzo[*d*]imidazol-2-ylamino)phenyl)acetic Acid (5b). Yield 4.82 g, 83%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.76 (s, 1H), 7.46−7.45 (m, 2H), 7.41 (d, 2H), 7.38 (d, 2H), 7.27−7.23 (m, 2H), 3.63 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.6, 147.6, 134.8, 132.9, 130.8, 129.81, 129.80, 123.5, 122.44, 122.42, 111.9, 40.2; ESI-MS *m*/*z* 268 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

3-(4-(1*H*-Benzo[*d*]imidazol-2-ylamino)phenyl)propanoic Acid (5c). Yield 1.51 g, 79%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.47 (s, 1H), 7.44−7.42 (m, 2H), 7.41 (d, 2H), 7.35 (d, 2H), 7.22−7.19 (m, 2H), 2.84 (t, 2H), 2.54 (t, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 174.4, 148.8, 138.7, 135.5, 131.52, 131.51, 123.6, 122.5, 112.6, 35.9, 30.5; ESI-MS *m*/*z* 282 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 220 nm.

3-(1*H*-Benzo[*d*]imidazol-2-ylamino)benzoic Acid (5d). Yield 2.32 g, 88%. The analytical data are in accord with literature values.[49]

4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)benzoic Acid (6a). Yield 2.17 g, 84%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.68 (s, 1H), 7.94 (d, 2H), 7.68 (d, 2H), 7.60 (s, 1H), 7.38 (d, 1H), 7.29 (d, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.5, 149.0, 142.7, 135.1, 132.7, 131.5, 126.1, 125.7, 119.7, 115.8, 114.8; ESI-MS *m*/*z* 332, 334 $(M + H)^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)phenyl)acetic Acid (6b). Yield 3.31 g, 79%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.0 (s, 1H), 7.61 (s, 1H), 7.46−7.35 (m, 6H), 3.62 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 173.2, 148.6, 135.3, 133.5, 132.2, 131.4, 130.1, 126.7, 123.0, 115.6, 115.2, 114.3, 41.0; ESI-MS *m*/*z* 346, 348 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

3-(4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)phenyl)propanoic Acid (6c). Yield 1.27 g, 78%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.77 (s, 1H), 7.56 (s, 1H), 7.38−7.32 (m, 6H), 2.83, (t, 2H), 2.55 (t, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 173.7, 148.3, 139.0, 134.0, 131.5, 129.7, 129.5, 126.0, 122.8, 114.9, 114.5, 113.6, 35.2, 29.9; ESI-MS *m*/*z* 360, 362 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 220 nm.

3-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)benzoic Acid (6d). Yield 3.30 g, 87%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.86 (s, 1H), 8.06 (s, 1H), 7.83 (d, 1H), 7.77, (d, 1H), 7.61, (s, 1H), 7.57 (t, 1H), 7.41−7.33 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ ESI-MS *m*/*z* 332, 334 $(M + H)^+$. Purity was determined to be 99% by HPLC analysis on the basis of absorption at 220 nm.

2-(*o*-Tolylamino)-1*H*-benzo[*d*]imidazole-5^6-carboxylic Acid (7e). Yield 2.15 g, 80%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.38 (s, 1H), 7.93 (s, 1H), 7.86 (d, 1H), 7.47 (apparent t, 2H), 7.40 (apparent t, 1H), 7.37−7.32 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.7, 142.0, 141.9, 141.6, 138.6, 131.3, 129.1, 126.4, 125.4, 124.9, 123.9, 123.7, 119.1, 115.2, 17.6; ESI-MS *m*/*z* 268 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

General Procedure for Solution-Phase Benzimidazole Amides: 4-(1*H*-Benzo[*d*]imidazol-2-ylamino)-*N*-(cyclopropylmethyl)benzamide (8a{*2*}). To a solution of benzimidazole acid **8a** (30 mg, 0.118 mmol) in CH_2Cl_2 (8 mL) was added (aminomethyl)cyclopropane (0.354 mmol, 30.4 μL) and *N*,*N*′-dimethylaminopyridine (1.4 mg, 0.011 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 15 min, EDC (67.9 mg, 0.354 mmol) was added, and the solution was warmed to room temperature over 10 h. After TLC showed reaction completion, the crude product was concentrated and taken up in ethyl acetate and H_2O. The organic layer was separated and washed additionally with water and brine, followed by drying ($MgSO_4$) and concentration to afford compound **8a**{*2*} (31 mg, 88%). ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.93−7.81 (m, 4H), 7.35 (dd, 2H), 7.18 (dt, 2H), 3.28−3.25 (m, 2H), 1.13−1.04 (m, 1H), 0.46 (dd, 2H), 0.26 (dd, 2H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 167.0, 150.9, 144.4, 129.0, 128.1, 121.4, 117.2, 44.8, 11.8, 3.8; ESI-MS *m*/*z* 307 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

4-(1*H*-Benzo[*d*]imidazol-2-ylamino)-*N*-(2-(piperidin-1-yl)ethyl)benzamide (8a{*19*}). Yield 32 mg, 75%. ^{1}H NMR (acetone-d_6, 400 MHz): δ 10.04 (s, 1H), 7.99 (d, 2H), 7.57 (d, 2H), 7.50 (dd, 2H), 7.32 (d, 2H), 3.75−3.70 (m, 2H),

3.08 (t, 2H), 2.42 (dd, 4H); 2.01−1.93 (m, 1H), 1.61−1.19 (m, 4H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 168.0, 141.9, 139.4, 132.3, 129.2, 127.1, 126.7, 125.4, 123.9, 121.3, 115.8, 113.8, 52.9, 51.6, 40.8, 22.2, 21.7; ESI-MS *m*/*z* 364 (M + H)$^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 220 nm.

4-(1*H*-Benzo[*d*]imidazol-2-ylamino)-*N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)benzamide (8a{*20*}). Yield 33 mg, 71%. ^{1}H NMR (acetone-d_6, 400 MHz): δ 8.16 (bs, 1H), 7.92 (d, 2H), 7.35 (s, 1H), 7.03 (d, 1H), 6.91 (d, 2H), 6.84 (d, 2H), 6.78 (d, 2H), 5.94 (s, 2H), 4.51 (d, 2H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 167.1, 150.9, 148.6, 147.4, 144.6, 134.8, 129.1, 127.8, 121.6, 121.5, 117.3, 109.0, 108.7, 101.8, 43.8; ESI-MS *m*/*z* 387 (M + H)$^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-(1*H*-Benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(3,5-bis(trifluoromethyl)benzyl)acetamide (8b{*10*}). Yield 45 mg, 81%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.62 (bs, 1H), 8.57 (d, 1H), 7.77 (d, 2H), 7.48 (dd, 2H), 7.37 (d, 2H), 7.31 (dd, 2H), 7.26 (d, 2H), 3.71 (d, 2H), 3.41 (s, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 171.3, 145.0, 143.0, 135.49, 135.45, 131.4, 130.7, 128.1, 125.2, 124.5, 123.6, 119.7, 115.8, 112.5, 43.1, 39.0; ESI-MS *m*/*z* 493 (M + H)$^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-(1*H*-Benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(4-methylphenethyl)acetamide (8b{*11*}). Yield 33 mg, 77%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.82 (d, 2H), 7.48−7.42 (m, 6H), 7.32−7.27 (m, 4H), 3.52 (d, 2H), 3.41−3.16 (m, 2H), 2.89 (apparent t, 2H), 2.07 (s, 3H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 171.4, 151.0, 135.2, 134.6, 130.8, 129.7, 123.8, 122.3, 119.4, 117.8, 117.6, 117.5, 115.3, 111.9, 109.5, 42.3, 35.9, 23.1; ESI-MS *m*/*z* 385 (M + H)$^+$. Purity was determined to be 94% by HPLC analysis on the basis of absorption at 220 nm.

3-(4-(1*H*-Benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(2,2,2-trifluoroethyl)propanamide (8c{*4*}). Yield 26 mg, 68%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.80−7.70 (m, 2H), 7.34−7.29 (m, 2H), 7.23−7.15 (m, 2H), 7.02−6.98 (m, 2H), 3.97 (t, 2H), 3.61 (apparent s, 2H), 2.60 (t, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 173.0, 151.8, 143.0, 140.0, 134.6, 132.8, 130.4, 129.5, 122.9, 122.7, 122.4, 121.0, 119.1, 118.4, 113.3, 45.1, 38.3; ESI-MS *m*/*z* 363 (M + H)$^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 220 nm.

3-(4-(1*H*-Benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(2-(thiophen-2-yl)ethyl)propanamide (8c{*15*}). Yield 35 mg, 84%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 9.09 (bs, 1H), 8.73 (bs, 1H), 7.74 (dd, 2H), 7.50−7.28 (m, 1H), 7.32−7.27 (m, 4H), 7.24−7.19 (m, 2H), 7.13 (d, 2H), 7.00 (dd, 2H), 4.41 (t, 2H), 2.89−2.87 (m, 2H), 2.53 (t, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 172.8, 152.0, 150.2, 148.65, 148.63, 148.3, 141.7, 140.0, 134.8, 130.1, 129.8, 129.6, 121.7, 119.7, 118.6, 54.6, 42.7, 38.7, 31.7; ESI-MS *m*/*z* 391 (M + H)$^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

3-(1*H*-Benzo[*d*]imidazol-2-ylamino)-*N*-(3-(1*H*-imidazol-1-yl)propyl)benzamide (8d{*16*}). Yield 30 mg, 70%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.20 (bs, 1H), 7.94 (apparent s, 2H), 7.78 (d, 2H), 7.38−7.23 (m, 2H), 7.18 (s, 1H), 7.00 (t, 1H), 6.89 (dd, 2H), 4.68 (d, 2H), 4.48 (d, 2H), 2.94−2.82 (m, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 168.1, 151.3, 146.1, 144.4, 142.2, 136.2, 132.2, 131.7, 129.8, 129.1, 122.7, 119.1, 117.2, 54.3, 45.4, 43.4; ESI-MS *m*/*z* 361 (M + H)$^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 220 nm.

3-(1*H*-Benzo[*d*]imidazol-2-ylamino)-*N*-(2-(pyridin-2-yl)-ethyl)benzamide (8d{*18*}). Yield 27 mg, 63%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.26 (s, 1H), 8.12−7.99 (m, 2H), 7.30−717 (m, 7H), 6.99 (dd, 2H), 3.43 (dd, 2H), 2.12 (dd, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 166.0, 151.6, 150.3, 143.6, 142.1, 137.1, 129.1, 129.0, 126.5, 121.1, 120.9, 120.2, 116.9, 51.6, 36.2; ESI-MS *m*/*z* 358 (M + H)$^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)-*N*-(4-(trifluoromethyl)benzyl)benzamide (9a{*7*}). Yield 28 mg, 65%. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.98 (d, 2H), 7.68 (s, 1H), 7.59, (d, 2H), 7.46 (apparent s, 3H), 7.27 (dd, 1H), 6.96−6.92 (m, 2H), 3.67 (d, 2H), 3.17 (d 2H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 166.9, 150.5, 140.8, 134.1, 132.0, 131.4, 130.8, 130.1, 128.1, 127.3, 121.9, 121.1, 116.5, 115.9, 115.8, 114.5, 114.4, 41.6; ESI-MS *m*/*z* 489, 491 (M + H)$^+$. Purity was determined to be 94% by HPLC analysis on the basis of absorption at 220 nm.

4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)-*N*-(furan-2-ylmethyl)benzamide (9a{*14*}). Yield 27 mg, 72%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.39 (bs, 1H), 8.07 (dd, 2H), 7.65 (dd, 2H), 7.68−7.63 (m, 3H), 7.46 (apparent s, 2H), 3.89 (s, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 166.3, 150.1, 145.7, 144.5, 140.2, 131.4, 129.5, 128.8, 126.6, 125.9, 121.3, 120.2, 115.2, 113.7, 40.6; ESI-MS *m*/*z* 411, 413 (M + H)$^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 220 nm.

4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)-*N*-(2-(methylthio)ethyl)benzamide (9a{*17*}). Yield 31 mg, 86%. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.93 (d, 2H), 7.68 (s, 1H), 7.55 (d, 1H), 7.46 (d, 1H), 7.12 (dd, 2H), 3.63 (t, 2H), 2.88 (t, 2H), 2.28 (s, 3H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 166.7, 150.6, 140.0, 137.4, 136.3, 133.0, 129.9, 127.4, 122.0, 116.5, 115.7, 114.3, 42.3, 36.0, 21.0; ESI-MS *m*/*z* 405, 407 (M + H)$^+$. Purity was determined to be 94% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(3-(dibutylamino)propyl)acetamide (9b{*6*}). Yield 29 mg, 66%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.19 (d, 2H), 7.79 (dd, 2H), 7.51 (s, 1H), 7.34−7.28 (m, 3H), 7.17 (d, 1H), 3.49 (s, 2H), 3.27 (d, 2H), 3.05 (apparent s, 4H), 2.86−2.73 (m, 2H), 1.68−1.49 (m, 4H), 1.31−1.26 (m, 2H), 1.01 (t, 6H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 171.4, 155.2, 152.7, 150.2, 140.1, 130.4, 123.6, 120.2, 119.2, 118.6, 113.2, 107.4, 56.9, 52.5, 45.5, 43.4, 39.0, 35.3, 28.8, 24.4, 19.1; ESI-MS *m*/*z* 514, 516 (M + H)$^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(4-(trifluoromethoxy)benzyl)acet-amide (9b{*9*}). Yield 31 mg, 69%. ^{1}H NMR (acetone-d_6, 400 MHz): δ 8.13 (d,

2H), 7.71 (d, 2H), 7.45 (s, 1H), 7.29−7.21 (m, 4H), 7.12 (dd, 2H), 3.45 (s, 2H), 3.0 (s, 2H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 171.6, 152.8, 140.1, 132.8, 131.6, 130.5, 130.0, 128.2, 123.7, 122.2, 122.1, 121.9, 121.8, 121.6, 118.7, 112.9, 107.8, 42.9, 39.0; ESI-MS *m*/*z* 519, 521 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 220 nm.

3-[4-(5^6-Bromo-1*H*-benzoimidazol-2-ylamino)-phenyl]-*N*-cyclohexylmethylpropionamide (9c{*5*}). Yield 30 mg, 79%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.12 (bs, 1H), 7.73 (d, 2H), 7.43 (s, 1H), 7.21−7.07 (m, 5H), 2.98 (apparent s, 2H), 2.87 (t, 2H), 2.77 (apparent s, 2H), 1.93−1.88 (m, 5H), 1.74−1.51 (m, 5H), 1.41 (apparent s, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 172.8, 157.1, 153.2, 150.2, 139.7, 134.9, 129.5, 123.3, 119.2, 118.5, 116.5, 114.2, 113.0, 41.6, 39.0, 38.0, 37.8, 37.6, 37.4, 35.3; ESI-MS *m*/*z* 455, 457 $(M + H)^+$. Purity was determined to be 94% by HPLC analysis on the basis of absorption at 220 nm.

3-(4-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)phenyl)-*N*-(4-phenylbutyl)propanamide (9c{*12*}). Yield 34 mg, 82%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.11, (d, 1H), 7.71 (dd, 2H), 7.47 (s, 1H), 7.32−7.22 (m, 5H), 7.10−7.05 (m, 1H), 6.86 (d, 2H), 3.92 (dd, 2H), 3.15 (t, 2H), 2.88 (t, 2H), 2.45 (t 2H), 1.88 (t, 2H), 1.39−1.18 (m, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 172.6, 150.3, 139.6, 138.2, 135.9, 135.3, 129.7, 129.6, 129.4, 123.6, 120.1, 119.3, 119.0, 118.6, 113.2, 107.4, 39.0, 38.6, 36.7, 36.6, 32.0, 31.7; ESI-MS *m*/*z* 491, 493 $(M + H)^+$. Purity was determined to be 93% by HPLC analysis on the basis of absorption at 220 nm.

3-(5^6-Bromo-1*H*-benzo[*d*]imidazol-2-ylamino)-*N*-butyl-benzamide (9d{*1*}). Yield 27 mg, 77%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.20 (d, 1H), 8.13 (d, 1H), 7.50−7.24 (m, 4H), 6.56 (d, 1H), 3.39 (t, 2H), 1.59 (p, 2H), 1.39 (sext, 2H), 0.92 (t, 3H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 167.5, 150.2, 144.3, 142.0, 141.6, 137.1, 132.0, 129.6, 123.8, 121.5, 121.2, 121.1, 120.3, 117.3, 115.3, 113.4, 107.4, 40.1, 32.5, 20.8, 14.1; ESI-MS *m*/*z* 387, 389 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

***N*-Adamantan-1-ylmethyl-3-(5^6-bromo-1*H*-benzoimidazol-2-ylamino)benzamide (9d{*3*}).** Yield 35 mg, 80%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.27 (d, 1H), 8.13 (s, 1H), 7.98 (d, 1H), 7.48−7.31 (m, 3H), 7.27 (d, 1H), 7.12 (dd, 1H), 2.98 (s, 2H), 1.83−1.69 (m, 3H), 1.42−1.20 (m, 10H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 167.6, 155.2, 152.5, 150.2, 141.7, 137.0, 129.5, 123.7, 120.7, 120.4, 119.1, 117.1, 113.3, 107.5, 39.0, 29.1, 21.3; ESI-MS *m*/*z* 479, 481 $(M + H)^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 220 nm.

***N*-(4-Methoxybenzyl)-2-(*o*-tolylamino)-1*H*-benzo[*d*]imidazole-5^6-carboxamide (10e{*8*}).** Yield 31 mg, 76%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.69 (bs, 1H), 7.46−7.42 (m, 5H), 7.28 (dd, 2H), 7.21 (d, 2H), 6.85 (d, 2H), 4.32 (d, 2H), 3.75 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 170.9, 159.8, 150.7, 141.6, 138.1, 135.8, 135.5, 132.3, 131.7, 130.9, 129.7, 124.4, 123.4, 114.6, 112.5, 55.5, 43.1, 19.8; ESI-MS *m*/*z* 367 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

***N*-(2-(1*H*-Indol-2-yl)ethyl)-2-(*o*-tolylamino)-1*H*-benzo-[*d*]imidazole-5^6-carboxamide (10e{*13*}).** Yield 32 mg, 70%. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.33 (bs 1H), 7.97 (d, 1H), 7.90 (dd, 2H), 7.59 (d, 1H), 7.48−7.46 (m, 2H), 7.46−7.28 (m, 5H), 6.33 (dd, 1H), 4.60 (d, 2H), 2.40 (apparent s, 2H), 2.07 (s, 3H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 169.4, 153.4, 152.5, 142.8, 135.2, 133.1, 132.4, 131.1, 128.8, 128.3, 126.2, 124.0, 112.0, 111.5, 111.2, 107.8, 92.4, 37.2, 30.1, 18.2; ESI-MS *m*/*z* 410 $(M + H)^+$. Purity was determined to be 97% by HPLC analysis on the basis of absorption at 220 nm.

General Procedure for Solid-Phase Benzimidazole Amides: 2-(*m*-Tolylamino)-1*H*-benzo[*d*]imidazole-5^6-carboxamide (11a). Rink amide resin (750 mg, 0.38 mmol) was swollen in DMF (10 mL) for 3 h, followed by treatment with 20% piperidine in DMF (10 mL) for 20 min. After washing and a positive Kaiser test,[50] 3,4-dintrobenzoic acid (239 mg, 1.13 mmol) was coupled using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (427 mg, 1.13 mmol), *N*-hydroxybenzotriazole hydrate (152 mg, 1.13 mmol), and diisopropylethylamine (1.13 mmol, 196 μL) in DMF (10 mL). After shaking for 10 h, the resin was washed, followed by a negative Kaiser test. Treatment with $SnCl_2 \cdot 2H_2O$ (5.92 g, 26.3 mmol) in DMF (10 mL) for 5 h, followed by washing, gave a positive chloranil test.[51] The resin was split into four flasks (~188 mg each) with each flask receiving an aryl isothiocyanate (0.12 mmol, 9.04 μL of *m*-tolylisothiocyanate for **11a**) in CH_2Cl_2 (3 mL). After 16 h of shaking, DIC (0.281 mmol, 43.5 μL) was added, and the reactions continued for 10 h. The resin was then washed, vacuum-dried, and cleaved with 5 mL of TFA/triisopropylsilane/H_2O (95%/2.5%/2.5%) for 2 h. After this crude reaction product was drained and collected, the cleavage was repeated for an additional 2 h with fresh cleavage reagents. The combined crude cleavages were concentrated to a minimal volume, affording crude **11a**, which had a purity of 82% as determined by HPLC at 220 nm. Preparative HPLC at 220 and 250 nm gave **11a** as a light yellow oil (17.5 mg, 70% overall yield from Rink resin); ESI-MS *m*/*z* 267 $(M + H)^+$. Purity was determined to be 98% by HPLC analysis on the basis of absorption at 220 nm.

2-(3-Bromophenylamino)-1*H*-benzo[*d*]imidazole-5^6-carboxamide (11b). Overall yield 17 mg, 78%; ESI-MS *m*/*z* 331, 333 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-Chlorophenylamino)-1*H*-benzo[*d*]imidazole-5^6-carboxamide (11c). Overall yield 22 mg, 80%; ESI-MS *m*/*z* 287, 289 $(M + H)^+$. Purity was determined to be 96% by HPLC analysis on the basis of absorption at 220 nm.

2-(4-Ethylphenylamino)-1*H*-benzo[*d*]imidazole-5^6-carboxamide (11d). Overall yield 19 mg, 72%; ESI-MS *m*/*z* 281 $(M + H)^+$. Purity was determined to be 95% by HPLC analysis on the basis of absorption at 220 nm.

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Supporting Information Available. The analytical spectral data (^{1}H and ^{13}C NMR, LC/MS) of benzimidazole amides are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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