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Synthesis and Evaluation of a New Generation of Orally Efficacious Benzimidazole-Based Poly(ADP-ribose) Polymerase-1 (PARP-1) Inhibitors as Anticancer Agents

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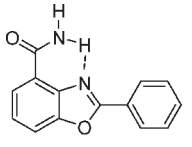
Small molecule inhibitors of PARP-1 have been pursued by various organizations as potential therapeutic agents either capable of sensitizing cytotoxic treatments or acting as stand-alone agents to combat cancer. As one of the strategies to expand our portfolio of PARP-1 inhibitors, we pursued unsaturated heterocycles to replace the saturated cyclic amine derivatives appended to the benzimidazole core. Not only did a variety of these new generation compounds maintain high enzymatic potency, many of them also displayed robust cellular activity. For example, the enzymatic IC_{50} and cellular EC_{50} values were as low as 1 nM or below. Compounds **24** (EC_{50} = 3.7 nM) and **44** (EC_{50} = 7.8 nM), featuring an oxadiazole and a pyridine moiety, respectively, demonstrated balanced potency and PK profiles. In addition, these two molecules exhibited potent oral in vivo efficacy in potentiating the cytotoxic agent temozolomide in a B16F10 murine melanoma model.

Introduction

Poly(ADP-ribose) polymerase-1 (PARP-1), also known as poly(ADP-ribose) synthetase or poly(ADP-ribose) transferase, is a nuclear enzyme that is part of a larger family of PARP[a] enzymes. DNA damage activates PARP-1, causing it to cleave its substrate nicotinamide adenine dinucleotide (NAD^+) and transfer ADP-ribose units to nuclear target proteins that can facilitate DNA repair. This mechanism allows cancer cells to escape apoptosis induced by DNA damaging treatments such as chemotherapy and radiation and enables cancer cells to repair the drug-induced DNA lesions.[1−3] The outcome represents one of the major components of acquired drug resistance. Overexpression of PARP-1 in cancer compared to normal cells thus makes the former more resistant to genotoxic stress.[4−6] Since DNA damaging agents (cytotoxic chemotherapy and radiation) remain a primary regimen to treat most cancer patients, maximizing their therapeutic benefit through inhibition of PARP-1 has become an attractive strategy. Experiments involving PARP-1 knockout have been shown to be effective in impairing DNA repair caused by genotoxic treatments.[7] More recently, several reports have suggested that PARP inhibition could have cytotoxic activities against BRCA1/2 deficient cells in the absence of any DNA damaging agent.[8,9] Meanwhile, small molecule inhibitors of PARP-1 have been pursued by various organizations as potential therapeutic agents either capable of sensitizing cytotoxic treatments or acting as stand-alone agents.[10−15] Some of them, including 4-(4-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-3-fluorobenzyl)phthalazin-1(2*H*)-one (AZD2281),[11] 8-fluoro-5-(4-((methylamino)methyl)phenyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-one (AG014699),[16] and (2-[(*R*)-2-methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide (**4**, ABT-888),[17] have demonstrated efficacy in various cancer xenograft models and are currently in human clinical trials.

More than a decade ago, scientists from the University of Newcastle identified a class of benzoxazole-4-carboxamide compounds as exemplified by **1** as weak PARP inhibitors.[18]



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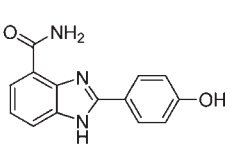

NU1085

They proposed that the nitrogen on benzoxazole formed an intramolecular hydrogen bond to the amide moiety, resulting in a desirable conformation for the latter to interact with the ribose nucleoside-binding domain of PARP. Later, they discovered structurally related benzimidazole-4-carboxamides as more potent PARP inhibitors.[19,20] The above-mentioned interaction in the nicotinamide binding site was confirmed by X-ray crystallography.[20] These compounds, as

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[a] Abbreviations: PARP, poly(ADP-ribose) polymerase; TMZ, temozolomide; PK, pharmacokinetic; TosMIC, toluenesulfonylmethyl isocyanide; CDI, 1,1′-carbonyldiimidazole; NBS, *N*-bromosuccinimide; BPO, benzoyl peroxide; TFA, trifluoroacetic acid; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; HOBT, 1-hydroxybenzotriazole; TFFH, tetramethylfluoroformamidinium hexafluorophosphate; TCDI, thiocarbonyldiimidazole; DBU, 1,8-diazabicyclo[5.4.0]-undec-7-ene; b.i.d., twice daily; q.d., every day; TGI, tumor growth inhibition; SEM, standard error of measurement; PBS, phosphate buffered saline; *F*, oral bioavailability; AUC, pharmacokinetic area under curve; C_{max}, pharmacokinetic maximum concentration; V_d, volume of distribution; CL, pharmacokinetic clearance; brd, broad.

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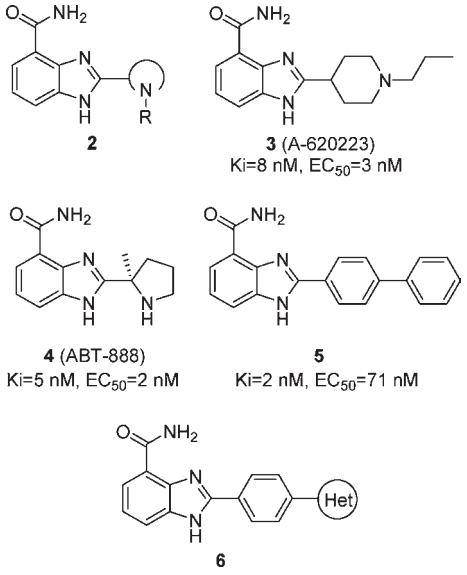
represented by 2-(4-hydroxyphenyl)benzimidazole-4-carboxamide (NU1085), showed weak to modest cellular activities.[20,21] We have recently reported a series of benzimidazole-based inhibitors for PARP-1 as anticancer agents.[22,23] Our earlier PARP-1 inhibitors (**2**) featured a piperidyl or pyrrolidinyl moiety,



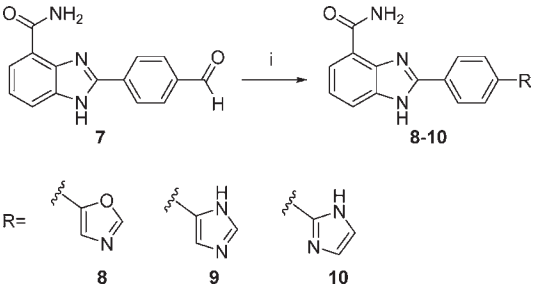
with or without a simple alkyl group (R) on the nitrogen, off the 2-position of a benzimidazole core. We have successfully developed preclinical and clinical candidates, A-620223 (**3**)[22] and **4**.[17,23,24] We also learned that R being a proton or an alkyl group on **2** was generally required for good cellular potency. In an attempt to diversify the benzimidazole-based PARP-1 inhibitors, we opted to develop a newer generation of this class of inhibitors by drastically changing the characteristics of the non-benzimidazole portion of the molecules. A more recent inhibitor (**5**) with a bis-phenyl moiety exhibited encouraging enzymatic inhibition (K_i = 2 nM) but suffered from relatively weak cellular activity (EC_{50} = 71 nM). In this paper, we disclose our development of a distinct class of inhibitors (**6**) possessing unsaturated heterocycles appended to the benzimidazole core. Not only did a number of these inhibitors demonstrate high potency in both enzymatic and cellular assays, some of them, such as **24** and **44**, also exhibited good pharmacokinetic (PK) properties and potent oral in vivo efficacy in potentiating the cytotoxic agent temozolomide (TMZ) in a mouse xenograft model.

Chemistry

Because of the vast variety of heterocycles in existence and the diverse chemistry associated with their syntheses, the plan for the structure−activity relationship studies discussed in this paper was to strike a balance between the analogue diversity and synthetic convergence and simplicity. As such, we generally chose to take advantage of the well-established chemistry previously reported by us[22,28] and others[19,21] to assemble key intermediates with proper functional groups attached for heterocycle formation.

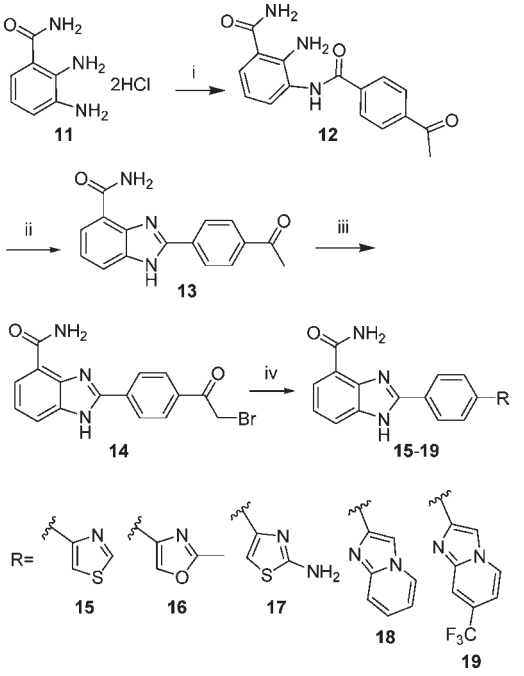
As illustrated in Scheme 1, the known 2-(4-formylphenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide **7**[21] was allowed to react with TosMIC and NaOMe to give oxazole **8**.[25] Reaction of **7** with TosMIC and NaCN followed by heating with NH_3/MeOH in a sealed tube at 110 °C afforded imidazole **9**.[26]

Scheme 1[a]



[a] Reagents and conditions; (i) for **8**, NaOMe, TosMIC, MeOH; (i) for **9**, (a) TosMIC, NaCN, (b) NH_3; (i) for **10**, glyoxal, NH_4OH.

Scheme 2[a]

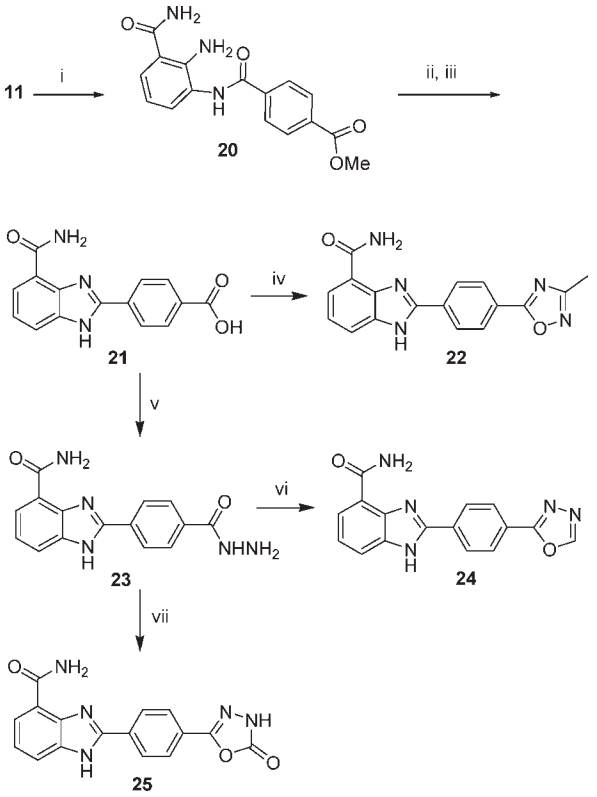


[a] Reagents and conditions: (i) 4-acetylbenzoic acid, CDI, pyridine, DMF; (ii) AcOH; (iii) NBS, BPO, TFA; (iv) for **15**, formamide, P_2S_5, $MgCO_3$; (iv) for **16**, urea, AcOH; (iv) for **17**, thiourea; (iv) for **18**, 2-aminopyridine; (iv) for **19**, 4-(trifluoromethyl)pyridin-2-amine.

The isomeric imidazole analogue **10** was obtained by treating **7** with glyoxal and ammonium hydroxide.[27]

The synthesis of compounds **15**−**19** is outlined in Scheme 2. Acylation of 2,3-diaminobenzamide (**11**)[28] in the presence of CDI and pyridine in DMF led to **12**, which was in turn cyclized under acidic (AcOH) conditions at 90 °C to furnish **13**. This ring closure strategy was shown in the early work by Griffin et al.[19] and later modified by White et al.[20] and Barkalow et al.[28] Subsequent bromination using NBS and catalytic BPO in TFA gave the versatile α-bromo ketone intermediate **14**, setting the stage for a number of different transformations. In situ formation of thioformamide with P_2S_5 and formamide followed by the addition of $MgCO_3$ converted **14** to thiazole **15**.[29] The 2-methyloxazole derivative **16** was prepared when **14** was heated in urea and acetic acid. Reacting **14** with thiourea in ethanol and water at 80 °C afforded 2-aminothiazole **17**. The α-bromo ketone moiety of **14** underwent cyclization in the presence of 2-aminopyridine to give the imidazopyridine analogue **18**. A similar transformation involving **14** and 4-(trifluoromethyl)pyridin-2-amine provided **19**.

Scheme 3[a]

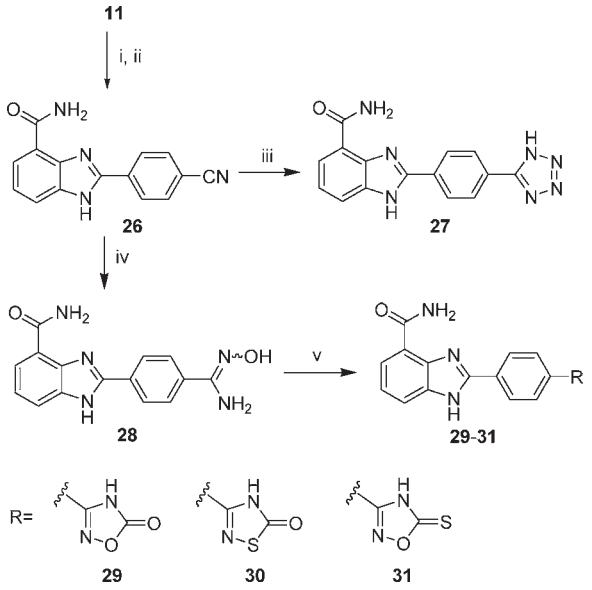


[a] Reagents and conditions: (i) 4-(methoxycarbonyl)benzoic acid, CDI, pyridine, DMF; (ii) AcOH; (iii) LiOH; (iv) acetamide oxime, TBTU, HOBT, Et_3N; (v) TFFH, NH_2NH_2, Et_3N; (vi) $HC(OMe)_3$; (vii) CDI.

The methods described in Scheme 3 were employed to synthesize **22**, **24**, and **25**. The benzoic acid intermediate **21** was produced after acylation of **11** followed by acid promoted cyclization and ester saponification with LiOH. The synthesis of **21** was reported by White et al.,[20] although we chose a different route to take advantage of an ample supply of the intermediate **11** in our lab that allowed us to pursue our targets more efficiently. Coupling of the acid moiety of **21** with acetamide oxime using TBTU, HOBT, and triethylamine led to cyclization to give the 3-methyl-1,2,4-oxadiazole **22**.[30] The initial attempt to make **23** by reacting the methyl ester precursor of **21** with hydrazine at an elevated temperature led to very poor yield. Intermediate **21** was alternatively treated with TFFH, hydrazine, and triethylamine to afford the benzohydrazide **23**. Subsequent condensation with methyl orthoformate at 160 °C under microwave irradiation gave the 1,3,4-oxadiazole derivative **24**. Treatment of **23** with CDI yielded the 5-oxo-1,3,4-oxadiazole **25**.

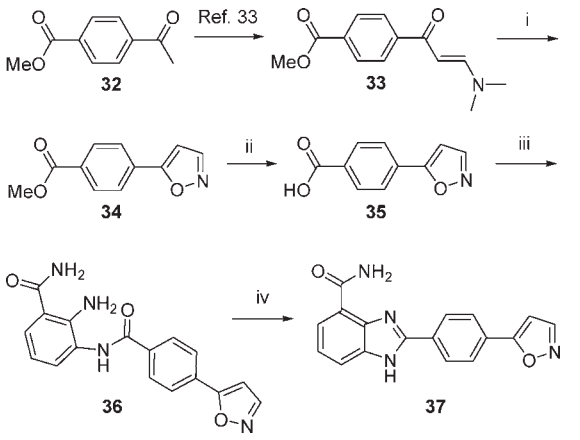
Preparation of compounds **29**−**31** is shown in Scheme 4. Although benzonitrile derivative **26** has been reported earlier,[20] we carried out our synthesis using intermediate **11**. The cyano moiety was transformed into a tetrazole by treatment of **26** with sodium azide and ammonium chloride in DMF at 80 °C to afford **27**. Meanwhile, addition of hydroxylamine into the cyano group produced the hydroxybenzamidine **28**, a convenient substrate labile to cyclization for analogue syntheses. Upon CDI treatment at 110 °C it was converted into the 1,2,4-oxadiazol-5-one **29**.[31] Treating **28** with 1,1′-thiocarbonyldiimidazole under either acidic (silica) or basic (DBU) conditions yielded the 1,2,4-thiadiazol-5-one **30** and the 1,2,4-oxadiazole-5-thione **31**, respectively.[32]

Scheme 4[a]



[a] Reagents and conditions: (i) 4-cyanobenzoic acid, CDI, pyridine, DMF; (ii) AcOH; (iii) NaN_3, NH_4Cl; (iv) $HONH_2 \cdot HCl$, K_2CO_3; (v) for **29**, CDI; (v) for **30**, TCDI, silica gel; (v) for **31**, TCDI, DBU.

Scheme 5[a]

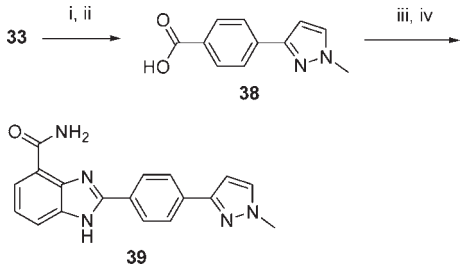


[a] Reagents and conditions: (i) hydroxylamine, MeOH, water; (ii) LiOH; (iii) **11**, CDI, pyridine, DMF; (iv) AcOH.

Treatment of **13** with DMF-dimethyl acetal failed to give the desired enamino ketone derivative for convergent syntheses of **37** and **39**. Thus, the heterocyclic rings were built before the benzimidazole core was assembled. Compound **37** was made according to Scheme 5. Following literature procedures,[33] enamino ketone **33** was obtained by the reaction of methyl 4-acetylbenzoate (**32**) with DMF-dimethyl acetal. Cyclization with hydroxylamine and subsequent saponification with LiOH provided **35**. The standard chemistry was performed to give the isoxazole **37**. As shown in Scheme 6, methylpyrazolylbenzoic acid **38**, derived from cyclization of the enamino ketone **33** in the presence of methylhydrazine and AcOH, was subjected to previously described conditions to afford the methylpyrazole **39**.

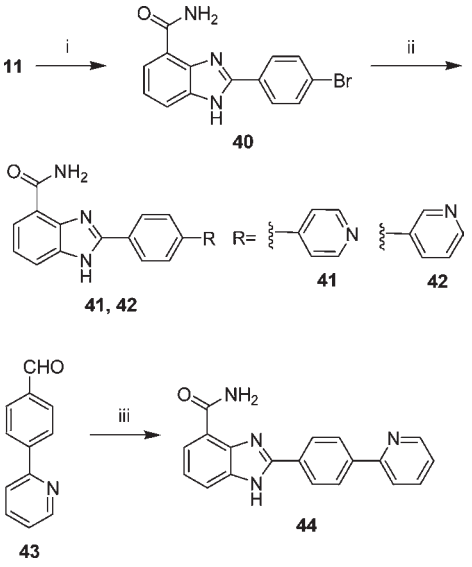
Scheme 7 provides the synthesis for compounds **41**, **42**, and **44**. 4-Bromobenzaldehyde was treated with **11** in the presence of Pd/C in refluxing methanol to yield the bromo derivative **40**.[34] An alternative method was to couple **11** with 4-bromobenzoic acid followed by an acidic ring closure. The

Scheme 6[a]



[a] Reagents and conditions: (i) methylhydrazine, AcOH; (ii) LiOH; (iii) **11**, CDI, pyridine, DMF; (iv) AcOH.

Scheme 7[a]



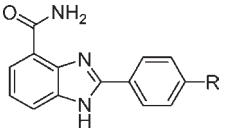
[a] Reagents and conditions: (i) 4-bromobenzaldehyde, Pd/C, MeOH; (ii) for **41**, 4-pyridineboronic acid, Pd $(dppf)_2Cl_2$, Na_2CO_3, dioxane; for **42**, 3-pyridineboronic acid, Pd $(dppf)_2Cl_2$, Na_2CO_3, dioxane; (iii) **11**, Pd/C, MeOH.

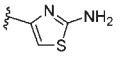
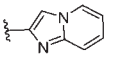
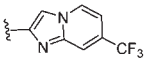
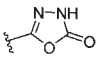
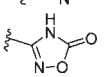
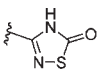
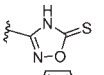
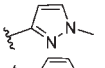
subsequent Suzuki reactions led to **41** and **42**. Compound **44** was synthesized from **43** following similar procedures described for **40**.

Results and Discussion

The fact that our earlier PARP-1 inhibitors with a benzimidazole core, exemplified by **4**, have demonstrated robust efficacy in multiple tumor models[17] prompted us to further investigate and diversify the benzimidazole-based inhibitors, one of the strategies we took to expand our portfolio of PARP-1 inhibitors. According to X-ray cocrystal structures we and others reported earlier,[20,22,35,36] the benzimidazole carboxamide scaffold is mainly responsible for enzyme inhibition through its network of hydrogen-bond and π-stacking interactions with the nicotinamide binding site of PARP-1, leaving the area off the 2-position of the benzimidazole a primary target for substantial modifications. Also, as discovered in the prior studies, the basic piperidyl (e.g., **3**) or pyrrolidinyl (e.g., **4**) moieties appeared necessary for good cellular potencies. For example, when the alkyl group on the nitrogen of the corresponding saturated rings was replaced by an acyl or a sulfonyl group, the resulting inhibitors suffered about 20- to 1000-fold decrease in cellular EC_{50} values.[22] This observation significantly limits the diversity of potential analogues to be explored. Facing this limitation and also knowing compound **5** to possess potent enzymatic inhibition, we decided to make more profound changes to the molecules. We thus turned our attention to investigating compounds with unsaturated heterocycles extended off the 2-phenyl group of the benzimidazole scaffold, replacing the previously described piperidyl or pyrrolidinyl moieties.

Table 1. Enzymatic and Cellular Activities



Compd.	R	PARP-1 Ki (nM)[a]	Cellular EC_{50} (nM)[b]
8		0.76	0.99
9		1.2	3.7
10		2.2	2.2
15		1.7	3.7
16		2.4	18
17		2.2	26
18		2.9	20
19		6.8	20
22		4.0	9.1
24		1.0	3.7[a]
25		1.6	64
27		20	---
29		16	---
30		5.2	461
31		3.8	328
37		10	>1000
39		4.5	20
41		3.1	12
42		0.95	9.0
44		1.9	7.8[a]

[a] Values are the mean of two experiments. [b] Single measurement except for **24** and **44**.

The activity data for our next-generation inhibitors are shown in Table 1. As expected, all the compounds synthesized were potent against PARP-1, since the heterocycle portion of the inhibitors was generally not involved in any key interactions with the enzyme according to X-ray cocrystal structures from early studies.[22] The K_i values ranged from 0.76 nM (**8**) to

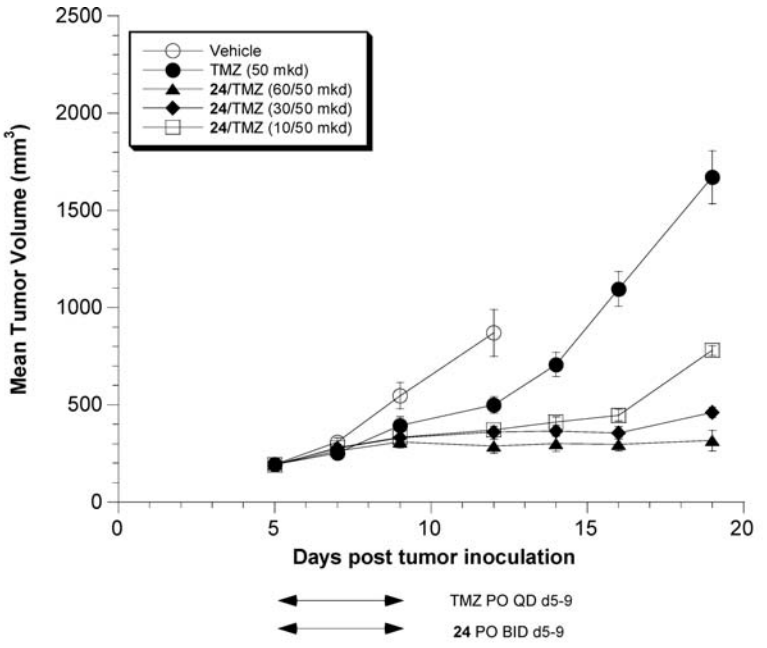
20 nM (**27**), in line with inhibitors (**2**) bearing piperidines or pyrrolidines.[22] The larger bicyclic moieties were also tolerated as **18** and **19** exhibited K_i values of 2.9 and 6.8 nM, respectively. More importantly, many of the these compounds also possessed high cellular potency as measured by their ability to inhibit H_2O_2-induced poly(ADP-ribosyl)ation in C-41 cervical carcinoma cells. Compounds **8**, **9**, **10**, **15**, **16**, **18**, **19**, **22**, **24**, **39**, **41**, **42**, and **44** all exhibited cellular EC_{50} values at 20 nM or lower with the most active (**8**) being 0.99 nM. The size of the heterocycles did not appear to be the main factor impacting cellular activity. Some monocyclic derivatives possessed EC_{50} values below 4 nM (**8**, **9**, **10**, **15**, and **24**), while others were above 300 nM (**30**, **31**, and **37**). Meantime, the values were 20 nM for the only two bicyclic inhibitors (**18** and **19**). It is noteworthy that any substitution on the carbon of the oxadiazole on **24** was detrimental to the potencies (data not shown). There was a general lack of correlation between enzymatic and cellular activities, an outcome commonly displayed by many enzyme inhibitors, since certain physicochemical properties such as cellular permeability is not reflected in an enzymatic assay. In contrast to our previous observations, the finding associated with the cellular EC_{50} values from this new generation of compounds, however, demonstrated that the more basic piperidyl or pyrrolidinyl derivative is not required for good cellular potency.

The difference in molecular properties derived from the unsaturated heterocycle portion appeared not to have a clear impact on the cellular potency. For instance, compounds **8** and **37** shared similar polar surface area (PSA) with values around 102 Å^2, yet **8** had the lowest EC_{50} value (0.99 nM) while **37** was not active (EC_{50} > 1000 nM). Meanwhile, compounds with a larger difference in PSA such as **15** and **24** (PSA = 87 and 118 Å^2, respectively) could be equally potent (EC_{50} = 3.7 nM for both). Compounds with the lowest and highest clogP values (1.2 for **24**; 5.0 for **19**) possessed cellular activity in the middle range of the spectrum. On the other hand, **15**, **17**, **31**, **37**, **41**, **42**, and **44** had similar lipophilicity (clogP value around 3) but their EC_{50} values ranged from 3.7 nM (**15**) to greater than 1000 nM (**37**). Relatively more basic heterocycles led to compounds with

Table 2. Mouse PK Data for Selected Inhibitors

	mouse iv[a]				mouse po[b]		
compd	CL[c]	V_d[d]	$T_{1/2}$ (h)	AUC[e]	C_{max}[f]	AUC[e]	F (%)
8	18	26	0.97	0.54	0.07	0.11	6
10	32	26	0.56	0.31	0	0	0
24	3.3	1.7	0.36	3.0	2.7	4.0	41
41	10	5.9	0.40	0.94	0.76	1.4	44
42	8.8	7.3	0.58	1.1	2.2	2.7	73
44	7.4	6.6	0.62	1.3	1.8	6.1	141

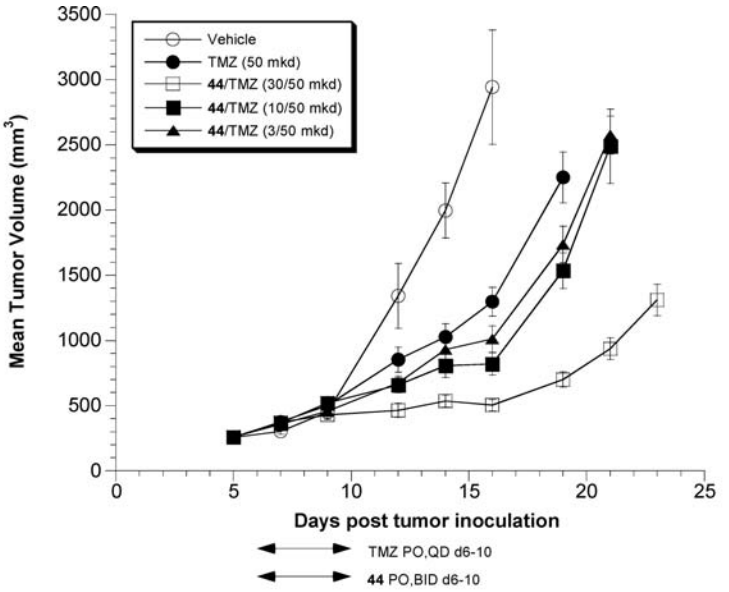
[a] 3.0 mg/kg. [b] 10 mg/kg. [c] (L/h)/kg. [d] L/kg. [e] μM·h. [f] μM.



Compound *Rx schedule*, Dose (mkd)	Mean Tumor Volume, mm^3 ± SEM	%TGI	Student's t-test *p*-value
Vehicle PO, BID/PO, QD, 0/0	870 ± 120 (d12)	-	-
TMZ PO, QD, 50	500 ± 43 (d12) 1670 ± 136 (d19)	43[a] -	0.001[a] -
24/TMZ PO, BID/ PO, QD, 60/ 50	288 ± 17 (d12) 317 ± 25 (d19)	67[a] 81[b]	0.0001[a] <0.0001[b]
24/TMZ PO, BID/ PO, QD, 30/ 50	361 ± 39 (d12) 462 ± 43 (d19)	59[a] 72[b]	0.0008[a] <0.0001[b]
24/TMZ PO, BID/ PO, QD, 10/ 50	372 ± 48 (d12) 779 ± 70 (d19)	57[a] 53[b]	0.001[a] <0.0001[b]

%TGI: percent tumor growth inhibition.
[a] compared to vehicle. [b] compared to TMZ.

Figure 1. In vivo efficacy of **24** in combination with temozolomide (TMZ) in the B16F10 murine melanoma model.



Compound *Rx schedule*, Dose (mkd)	Mean Tumor Volume, $mm^3 \pm SEM$	%TGI	Student's t-test *p*-value
Vehicle PO, BID/PO, QD, 0/0	2942 + 440 (d16)	-	-
TMZ PO, QD, 50	1297+ 111 (d16) 2250 + 195 (d19)	56[a] -	0.002[a] -
44/TMZ PO, BID/ PO, QD, 30/ 50	503 + 43 (d16) 670 + 58 (d19)	83[a] 70[b]	<0.0001[a] <0.0001[b]
44/TMZ PO, BID/ PO, QD, 10/ 50	818 + 84 (d16) 1535 + 137 (d19)	72[a] 32[b]	0.0002[a] 0.008[b]
44/TMZ PO, BID/ PO, QD, 3/ 50	1012 +100 (d16) 1736 + 141 (d19)	66[a] 23[b]	0.0005[a] <0.05[b]

%TGI: percent tumor growth inhibition.
[a] compared to vehicle. [b] compared to TMZ.

Figure 2. In vivo efficacy of **44** in combination with temozolomide (TMZ) in the B16F10 murine melanoma model.

EC_{50} values in the middle range between 2.2 and 20 nM (**9**, **10**, **18**, **19**, **41**, **42**, and **44**), while nonbasic species contributed to the most and least potent compounds (EC_{50} values being 0.99 nM for **8** and > 1000 nM for **37**). These observations indicated that there was no correlation between physicochemical properties and cellular activity.

Six compounds with better overall enzymatic and cellular activities were tested for pharmacokinetic (PK) properties in CD-1 mice. As shown in Table 2, the oxazole and imidazole derivatives **8** and **10** exhibited high clearance rates (at least 18 L/h/kg), high volumes of distribution (26 L/kg), and very poor oral exposure (AUC = 0 or 0.11 $\mu M \cdot h$, respectively). However, the oxadiazole compound **24** did possess greatly improved PK properties with a moderated clearance rate (3.3 (L/h)/kg) and volume of distribution (1.7 L/kg) and much higher oral AUC (4.0 $\mu M \cdot h$) and bioavailability (41%). When dosed via iv administration, the three pyridyl analogues **41**, **42**, and **44** displayed similar profiles. The clearance rates, volumes of distribution, and AUC values ranged from 7.4 to 10 (L/h)/kg, 5.9−7.3 L/kg, and 0.94−1.3 $\mu M \cdot h$, respectively. On the contrary, their oral exposures differed to a much larger degree. The oral AUC for **44** (6.1 $\mu M \cdot h$) was about twice as high as for **42** (2.7 $\mu M \cdot h$) and 4 times as high as for **41** (1.4 $\mu M \cdot h$).

The two compounds with the best oral PK properties, **24** and **44**, were further evaluated for their in vivo efficacy in potentiating temozolomide (TMZ) in a B16F10 murine melanoma model. Temozolomide is a DNA-alkylating agent and is used as a chemotherapy agent for melanoma and gliomas. In this study, temozolomide was dosed orally, q.d., at 50 mg/kg/day (mkd) for 5 consecutive days. Meanwhile, during the same time frame, **24** was administered orally, b.i.d., at doses of 10, 30, and 60 mkd. As shown in Figure 1, the effect of **24** in combination with TMZ started to differentiate from temozolomide monotherapy at day 12. At day 19, the relative tumor growth inhibition (TGI) of **24** in combination with TMZ at doses of 10, 30, and 60 mkd compared to TMZ monotherapy was 53%, 72%, and 81%, respectively, showing significant dose-dependent potentiation of TMZ by compound **24**. Compound **44** also demonstrated a clear TMZ-sensitizing effect (Figure 2) when dosed at 10 or 30 mkd starting at day 12. At day 16, TGI reached 83% and 72%, respectively. However, its efficacy retreated much more quickly after day 16 compared to **24**.

Conclusion

In summary, we have replaced the piperidyl or pyrrolidinyl moieties on the benzimidazole-based PARP-1 inhibitors with unsaturated heterocycles extended off a 2-phenyl group in an attempt to further expand the scope of this class of inhibitors. Through diverse, yet often convergent synthetic schemes, a wide range of different heterocycles were installed, resulting in compounds not only with potent enzymatic potency but also with high cellular activity (EC_{50} as low as 1 nM). This finding broadened our earlier understanding regarding the necessity of an appropriate piperidine or pyrrolidine derivative for

cellular activity. Some compounds with balanced overall activities were assessed for their PK properties. Among them, compounds **24** and **44** showed reasonable oral exposure and bioavailability. In addition, both inhibitors, **24** in particular, demonstrated excellent oral in vivo efficacy in potentiating TMZ in the B16F10 murine melanoma model. Therefore, installation of an unsaturated heterocycle off the 2-phenyl group of the benzimidazole core proved to be another viable strategy for developing potent and orally efficacious PARP-1 inhibitors.

Experimental Section

All commercially available chemical reagents were used without further purification unless otherwise noted. Flash chromatography was carried out using an ISCO Companion flash system. Proton NMR data were recorded using a Varian Mercury 300 spectrometer or a Varian UNITY 400/500 spectrometer. Mass spectral data were collected using a Finnigan SSQ7000 GC/MS (ESI) or a Finnigan DCI/MS SSQ7000. Elemental analyses were performed by Quantitative Technologies, Inc. Preparative HPLC was performed on a Zorbax RX-C18 column (250 mm × 21.2 mm, 7 μm particle size) using a gradient of 10−100% acetonitrile/0.1% aqueous TFA over 40 min at a flow rate of 15 mL/min. LC/MS was run on an Agilent 1100/Finnigan Navigator system with a YMC C18 column (50 mm × 4.6 mm). Melting point was measured using a Mel-Temp II apparatus.

The purity of all final products was determined by HPLC (at least 95% pure unless otherwise noted). In addition, combustion analyses were conducted on eight of the final products (**8**, **18**, **22**, **24**, **27**, **29**, **39**, and **42**).

PARP-1 Enzyme Assay.[23] The enzyme assay was conducted in a buffer containing 50 mM Tris, pH 8.0, 1 mM DTT, and 4 mM $MgCl_2$. PARP reactions contained 1.5 μM [^{3}H]NAD^+ (1.6 μCi/mmol), 200 nM biotinylated histone H1, 200 nM slDNA, and 1 nM PARP-1 enzyme. Autoreactions utilizing SPA bead-based detection were carried out in 100 μL volumes in white 96-well plates. Reactions were initiated by adding 50 μL of 2× NAD^+ substrate mixture to 50 μL of 2× enzyme mixture containing PARP-1 and DNA. These reactions were terminated by the addition of 150 μL of 1.5 mM benzamide (∼1000-fold over its IC_{50} value). The stopped reaction mixtures (170 μL) were transferred to streptavidin-coated flash plates, incubated for 1 h, and counted using a TopCount microplate scintillation counter. K_i data were determined from inhibition curves at various substrate concentrations.

Cellular Assay.[23] C41 cells were treated with test compounds for 30 min in a 96-well plate. PARP was activated by damaging DNA with 1 mM H_2O_2 for 10 min. Cells were washed with ice-cold PBS once and fixed with prechilled methanol/acetone (7:3) at −20 °C for 10 min. After air-drying, plates were rehydrated with PBS and blocked using 5% nonfat dry milk in PBS-tween (0.05%) (blocking solution) for 30 min at room temperature. Cells were incubated with anti-PAR antibody 10H (1:50) in blocking solution at room temperature for 60 min followed by washing with PBS-Tween20 five times and incubation with goat antimouse fluorescein 5(6)-isothiocyanate (FITC)-coupled antibody (1:50) and 1 μg/mL 4′,6-diamidino-2-phenylindole (DAPI) in blocking solution at room temperature for 60 min. After washing with PBS-Tween20 five times, analysis was performed using an fmax fluorescence microplate reader set at the excitation and emission wavelengths for FITC or the excitation and emission wavelengths for DAPI. PARP activity (FITC signal) was normalized with cell numbers (DAPI).

Mouse PK Protocols. Male CD-1 mice weighing 26−30 g (Charles River Laboratories) were dosed iv via the tail vein or po by gavage with a metal feeder tube. Dosing solutions were prepared in 2.5% ethanol, 2.5% DMSO (iv only), 5% Tween-80, 25% PEG400, and pH 7.4 PBS for a dosing volume of 10 mL/kg. Blood samples were collected with a heparinized syringe by cardiac puncture following CO_2 asphixiation at specified times. Plasma samples were aliquoted into 96-well plates and proteins precipitated using acidified methanol. Supernatants were stored at −20 °C. Sample analyses were performed by LC−MS using a Shimadzu 10A-VP chromatography system with a Phenomenex Polar-RP column. The mobile phase consisted of various concentrations of acetonitrile and 0.1% acetic acid in water at a flow rate of 0.4 mL/min. Mass detection was accomplished with an ESI equipped LCQ-Duo by ThermoFinnigan. External standards were prepared from spiked control plasma and used to generate a response factor for every study. Limits of detection were between 20 and 50 nM. PK parameters were calculated using WinNonlin software (Pharsight).

B16F10 Tumor Model. For B16F10 syngeneic studies, 1.2×10^6 cells/mL were mixed with an equal volume of Matrigel (BD Biosciences, Bedford, MA) for a final cell concentration of 6×10^5 cells/mL. Mice were inoculated with 0.1 mL (6×10^4 cells/mouse) of cell suspension by sc injection into the flank of 6−8 week old female C57BL/6 mice, 18−20 g (Charles River Laboratories, Wilmington, MA). Mice were allocated into treatment groups by size-matching. PARP inhibitor therapy was initiated on day 5 (or 6) following inoculation, with temozolomide treatment also starting on day 5 (or 6).

2-(4-(Oxazol-5-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (8). To a suspension of 2-(4-formylphenyl)-1*H*-benzoimidazole-4-carboxylic acid amide **7**[21] (70.0 mg, 0.264 mmol) in MeOH (2.5 mL) was added sodium methoxide in MeOH (0.5 M, 2.1 mL, 1.1 mmol) followed by tosylmethyl isocyanide (61.8 mg, 0.317 mmol). The mixture was heated at reflux overnight. After cooling, the mixture was concentrated. The residue was treated with 50% $NaHCO_3$ and extracted with EtOAc (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was triturated with a small amount of MeOH and the solid was filtered, washed with MeOH and diethyl ether, and oven-dried to give 30.5 mg (38%) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.36 (t, J = 7.8 Hz, 1 H), 7.71−7.83 (m, 2 H), 7.84−7.91 (m, 2 H), 7.96 (d, J = 8.1 Hz, 2 H), 8.36 (d, J = 8.5 Hz, 2 H), 8.54 (s, 1 H), 9.34 (s, brd, 1 H), 13.47 (s, brd, 1 H). MS (DCI/NH_3) m/z 305.1 $(M + H)^+$. The sample was further purified by HPLC for combustion analysis. Anal. ($C_{17}H_{12}N_4O_2 \cdot 2TFA \cdot 0.15H_2O$) C, H, N.

2-(4-(1*H*-Imidazol-5-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 9). To a suspension of **7**[21] (90.0 mg, 0.339 mmol) and tosylmethyl isocyanide (66.2 mg, 0.339 mmol) in ethanol (8 mL) was added sodium cyanide (1.7 mg, 0.034 mmol) at room temperature. The reaction mixture was heated at 40 °C for 1 h and then concentrated. The residue was treated with 6 mL of NH_3/MeOH (7 N), and the suspension was heated at 110 °C in a pressure tube overnight. The mixture was cooled and concentrated until most of the solvent was evaporated. The residue was treated with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by HPLC to give 30.1 mg (yellow solid, 29%) of the desired product as the TFA salt. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 7.42 (t, J = 7.8 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.91−8.00 (m, 3 H), 8.06 (d, J = 1.4 Hz, 1 H), 8.37 (d, J = 8.8 Hz, 2 H), 9.04 (d, J = 1.4 Hz, 1 H). MS (DCI/NH_3) m/z 304.1 $(M + H)^+$.

2-(4-(1*H*-Imidazol-2-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 10). To a suspension of **7**[21] (80.0 mg, 0.302 mmol) in ethanol (7 mL) was added glyoxal (40% in water, 0.15 mL, 3.3 mmol) and ammonium hydroxide (0.24 mL, 6.2 mmol). The reaction mixture was stirred overnight. Most of the solvent was evaporated. The residue was treated with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by HPLC to give 32.1 mg (off-white

solid, 35%) of the desired product as the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.36−7.44 (m, 1 H), 7.80 (d, J = 8.1 Hz, 2 H), 7.85 (s, 2 H), 7.91 (d, J = 8.5 Hz, 1 H), 8.21 (d, J = 8.8 Hz, 2 H), 8.50 (d, J = 8.8 Hz, 2 H), 9.22 (s, brd, 1 H). MS (DCI/NH_3) m/z 304.1 $(M + H)^+$.

2-(4-Acetylphenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (13). A solution of 4-acetylbenzoic acid (4.98 g, 30.3 mmol) in a mixture of pyridine (30 mL) and DMF (30 mL) was treated with CDI (5.41 g, 33.4 mmol). The reaction mixture was heated at 45 °C for 2 h. 2,3-Diaminobenzamide·2HCl (**11**,[28] 6.80 g, 30.3 mmol) was added, and the mixture was stirred at room temperature overnight. After concentration, the crude intermediate (**12**) was treated with acetic acid (70 mL) and the mixture heated at 90 °C for 6 h. After the mixture was cooled, the solvent was evaporated. The resulting oil was dissolved in EtOAc and treated with saturated $NaHCO_3$ until pH 8 was obtained. The solid that formed was filtered, washed with water, and oven-dried to give 7.46 g of the desired product (89%, 2 steps) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.66 (s, 3 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.80−7.84 (m, 1 H), 7.91 (d, J = 7.5 Hz, 1 H), 8.17 (d, J = 8.5 Hz, 2 H), 8.39 (d, J = 8.5 Hz, 2 H), 9.30 (s, 1 H), 13.61 (s, 1 H). MS (DCI/NH_3) m/z 280.1 $(M + H)^+$. Melting point: 285−286 °C.

2-(4-(2-Bromoacetyl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (14). To a solution of **13** (5.60 g, 20.1 mmol) in TFA (500 mL) were added *N*-bromosuccinimide (4.28 g, 24.1 mmol) and benzoyl peroxide (0.243 g, 1.00 mmol). After heating at 50 °C for 4 h, additional NBS (2 × 400 mg) was added at 1 h intervals. The reaction was continued for 1 h after the final addition of NBS. Water (10 mL) was added, and the mixture was concentrated. The residue was treated with EtOAc and washed with 50% $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was treated with warm MeOH and EtOAc, and the suspension was concentrated until most of the solvent was evaporated. The solid was filtered, washed with EtOAc, and oven-dried to give 1.87 g of the desired product as a yellow solid. The filtrate was loaded on silica and purified on an 80 g column using the ISCO Companion flash system eluting with CH_2Cl_2/EtOAc (6:4 to 4:6) to give an additional 0.614 g product. The total yield was 2.49 g (35%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 5.01 (s, 2 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.74−7.84 (m, 2 H), 7.87−7.98 (m, 1 H), 8.21 (d, J = 8.1 Hz, 2 H), 8.41 (d, J = 8.1 Hz, 2 H), 9.27 (s, 1 H), 13.63 (s, 1 H). MS (DCI/NH_3) m/z 358.0 $(M + H)^+$. Melting point: 78−79 °C.

2-(4-(Thiazol-4-yl)phenyl)-1*H*-benzo[d]imidazole-4-carboxamide (TFA Salt, 15). To a suspension of phosphorus pentasulfide (0.621 g, 2.79 mmol) in dioxane (7 mL) was added formamide (0.67 mL, 17 mmol). The mixture was heated at reflux for 2 h. The solution (thioformamide) was decanted. To **14** (0.100 g, 0.279 mmol) in 2.8 mL of dioxane were added $MgCO_3$ (0.235 g, 2.79 mmol) and the above-mentioned thioformamide solution. The mixture was heated at reflux for 2 h. After cooling, the reaction mixture was treated with 5% NaOH and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by HPLC to give 45 mg (light-yellow solid, 37%) of the desired product as the TFA salt (HPLC purity was 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.41 (t, J = 7.8 Hz, 1 H), 7.77 (s, 1 H), 7.80 (d, J = 7.1 Hz, 1 H), 7.91 (d, J = 7.4 Hz, 1 H), 8.24 (d, J = 8.3 Hz, 2 H), 8.32−8.36 (m, 2 H), 8.37 (d, J = 1.8 Hz, 1 H), 9.19 (s, brd, 1 H), 9.27 (d, J = 2.2 Hz, 1 H). MS (DCI/NH_3) m/z 321.0 $(M + H)^+$.

2-(4-(2-Methyloxazol-4-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (16). A mixture of **14** (60.0 mg, 0.168 mmol) and urea (40.2 mg, 0.670 mmol) in acetic acid (2 mL) was heated in a CEM microwave reactor at 160 °C for 15 min. The reaction mixture was concentrated. The resulting residue was treated with saturated $NaHCO_3$ and extracted with CH_2Cl_2/MeOH (9:1). The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified on a 4 g column using the ISCO Companion flash system eluting with CH_2Cl_2/MeOH (97:3 to 90:10) to give 7.2 mg (14%) of the desired product as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.53 (s, 3 H), 7.36 (t, J = 7.8 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 8.6 Hz, 2 H), 7.97 (d, J = 8.0 Hz, 1 H), 8.24 (d, J = 8.3 Hz, 2 H), 8.27 (s, 1 H). MS (DCI/NH_3) m/z 319.1 $(M + H)^+$.

2-(4-(2-Aminothiazol-4-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 17). A mixture of **14** (60.0 mg, 0.168 mmol) and thiourea (14.7 mg, 0.193 mmol) in EtOH (2.5 mL) and water (1.0 mL) was heated at 80 °C for 1 h. The solids were filtered, washed with EtOH and water, and purified by HPLC to give 35.0 mg (light-yellow solid, 46%) of the desired product as the TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.27 (s, 1 H), 7.38 (t, J = 7.8 Hz, 1 H), 7.72−7.82 (m, 2 H), 7.88 (d, J = 7.6 Hz, 1 H), 8.01 (d, J = 8.5 Hz, 2 H), 8.27 (d, J = 8.5 Hz, 2 H), 9.24 (s, brd, 1 H). MS (DCI/NH_3) m/z 336.1 $(M + H)^+$.

2-(4-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 18). A suspension of **14** (0.0600 g, 0.168 mmol) and 2-aminopyridine (0.0170 g, 0.184 mmol) in ethanol (1.5 mL) was heated at 70 °C for 8 h. The solids were filtered, washed with EtOAc, and purified by HPLC to give 25 mg (tan solid, 32%) of the desired product as the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.28 (t, J = 6.7 Hz, 1 H), 7.38 (t, J = 7.7 Hz, 1 H), 7.63−7.72 (m, 1 H), 7.75−7.93 (m, 4 H), 8.19 (d, J = 8.7 Hz, 2 H), 8.42 (d, J = 8.7 Hz, 2 H), 8.72−8.83 (m, 2 H), 9.28 (s, brd, 1 H). MS (DCI/NH_3) m/z 354.1 $(M + H)^+$. Anal. ($C_{21}H_{15}N_5O \cdot 1.4TFA \cdot 0.35H_2O$) C, H, N.

2-(4-(7-(Trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 19). A suspension of **14** (0.0600 g, 0.168 mmol) and 4-(trifluoromethyl)pyridin-2-amine (0.0298 g, 0.184 mmol) in ethanol (1.5 mL) was heated at reflux for 24 h. The solids were filtered, washed with EtOAc, and purified by HPLC to give 0.0317 g (orange solid, 29%) of the desired product as the TFA salt (HPLC purity is 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.24 (dd, J = 7.1, 1.8 Hz, 1 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.74−7.82 (m, 2 H), 7.90 (d, J = 7.7 Hz, 1 H), 8.13 (s, 1 H), 8.24 (d, J = 8.3 Hz, 2 H), 8.37 (d, J = 8.3 Hz, 2 H), 8.78 (s, 1 H), 8.81 (d, J = 7.4 Hz, 1 H), 9.23 (s, brd, 1 H). MS (DCI/NH_3) m/z 422.1 $(M + H)^+$.

4-(4-Carbamoyl-1*H*-benzo[*d*]imidazol-2-yl)benzoic Acid (21). A solution of 4-(methoxycarbonyl)benzoic acid (4.47 g, 24.8 mmol) in a mixture of pyridine (25 mL) and DMF (25 mL) was treated with CDI (4.43 g, 27.3 mmol) at 45 °C for 2 h. Compound **11** (5.56 g, 24.8 mmol) was added to the mixture, and the mixture was stirred at room temperature overnight. After concentration, the crude product **20** in acetic acid (50 mL) was heated at 90 °C for 2.5 h. After the mixture was cooled, the solvent was evaporated and the resulting solids were treated with 8 mL of EtOAc and 300 mL of saturated $NaHCO_3$. The suspension was filtered, washed with water and diethyl ether, then oven-dried to give 6.98 g (95%, 2 steps) of the methyl 4-(4-carbamoyl-1*H*-benzo[*d*]imidazol-2-yl)benzoate intermediate as a white solid. To this intermediate (1.50 g, 5.08 mmol) in THF (30 mL) and MeOH (9 mL) was added an emulsion of lithium hydroxide (0.639 g, 15.2 mmol) in water (6 mL) at room temperature. The mixture was stirred overnight at room temperature. Most of the solvent was evaporated; the residue was treated with 5% citirc acid (~50 mL). The resulting precipitate was filtered, washed with water and diethyl ether, then oven-dried to give 1.56 g (quantitative yield) of the desired product as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.39 (t, J = 7.7 Hz, 1 H), 7.74−7.84 (m, 2 H), 7.90 (d, J = 7.5 Hz, 1 H), 8.14 (d, J = 8.7 Hz, 2 H), 8.36 (d, J = 8.3 Hz, 2 H), 9.30 (d, J = 3.2 Hz, 1 H), 13.60 (s, 1 H). MS (DCI/NH_3) m/z 282.0 $(M + H)^+$.

2-(4-(3-Methyl-1,2,4-oxadiazol-5-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 22). To a solution of **21** (0.0700 g, 0.249 mmol), HOBT (1.9 mg, 0.012 mmol), and triethylamine (0.17 mL, 1.2 mmol) in DMF (2 mL) were added TBTU (0.0840 g, 0.261 mmol) and acetamide oxime (0.0200 g, 0.274 mmol). The reaction mixture was stirred overnight and

then diluted with 50% brine. The resulting suspension was filtered, washed with water, and oven-dried to give 0.0320 g of an off-white solid as the intermediate. This solid was dissolved in DMF, and the solution was heated at 160 °C for 30 min in a Biotage microwave reactor. The crude material was purified by HPLC to give 0.0210 g (white solid, 19%) of the desired product as the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.46 (s, 3 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.75−7.83 (m, 2 H), 7.91 (d, J = 7.8 Hz, 1 H), 8.31 (d, J = 8.5 Hz, 2 H), 8.49 (d, J = 8.8 Hz, 2 H), 9.21 (s, brd, 1 H). MS (DCI/NH_3) m/z 320.2 (M + H)$^+$. Anal. ($C_{17}H_{13}N_5O_2 \cdot 0.65TFA \cdot 0.05H_2O$) C, H, N.

2-(4-(Hydrazinecarbonyl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (23). To a suspension of **21** (0.700 g, 2.49 mmol) and tetramethylfluoroformamidinium hexafluorophosphate (TFFH, 0.789 g, 2.99 mmol) in DMF (9 mL) at 0 °C were added triethylamine (0.69 mL, 5.0 mmol) and hydrazine (0.16 mL, 5.0 mmol). The mixture was stirred at room temperature for 6 h. Water was added to the reaction mixture. The resulting precipitate was filtered, washed with water, and oven-dried to give 0.35 g (48%) of the desired product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.57 (s, brd, 2 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.69−7.83 (m, 2 H), 7.89 (d, J = 7.5 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H), 8.32 (d, J = 8.3 Hz, 2 H), 9.31 (s, 1 H), 9.93 (s, 1 H), 13.49 (s, brd, 1 H). MS (DCI/NH_3) m/z 296.1 (M + H)$^+$. Melting point: 248−249 °C.

2-(4-(1,3,4-Oxadiazol-2-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 24). A mixture of **23** (75.0 mg, 0.254 mmol) and trimethyl orthoformate (1 mL) was heated in a CEM microwave reactor at 160 °C for 30 min. The reaction mixture was concentrated and purified by HPLC to give 43.0 mg (off-white solid, 41%) of the desired product as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, J = 7.8 Hz, 1 H), 7.74−7.84 (m, 2 H), 7.91 (d, J = 7.7 Hz, 1 H), 8.25 (d, J = 8.3 Hz, 2 H), 8.48 (d, J = 8.3 Hz, 2 H), 9.21 (s, brd, 1 H), 9.42 (s, 1 H). MS (DCI/NH_3) m/z 306.1 (M + H)$^+$. Anal. ($C_{16}H_{11}N_5O_2 \cdot 0.95TFA \cdot 0.05H_2O$) C, H, N (error for N, 0.43%).

2-(4-(5-Oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-1*H*-benzo[*d*]-imidazole-4-carboxamide (TFA Salt, 25). To a suspension of **23** (70.0 mg, 0.237 mmol) in dioxane (2.5 mL) was added CDI (46.1 mg, 0.284 mmol). The mixture was heated at reflux for 45 min. The suspension was concentrated and purified by HPLC to give 9.0 mg (off-white solid, 9%) of the desired product as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, J = 7.7 Hz, 1 H), 7.75−7.81 (m, 2 H), 7.90 (d, J = 7.7 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 2 H), 8.41 (d, J = 8.3 Hz, 2 H), 9.19 (s, brd, 1 H), 12.71 (s, 1 H). MS (DCI/NH_3) m/z 322.1 (M + H)$^+$.

2-(4-Cyanophenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (26). A solution of 4-cyanobenzoic acid (1.641 g, 11.16 mmol) in a mixture of pyridine (12 mL) and DMF (12 mL) was treated with CDI (1.990 g, 12.27 mmol) and stirred at 45 °C for 2 h. After the mixture was cooled, compound **11** (2.500 g, 11.16 mmol) was added and the mixture was stirred at room temperature overnight. After concentration, the residue was suspended in AcOH (20 mL) and the mixture was heated at 80 °C for 4 h. The reaction mixture was cooled and concentrated. The resulting residue was treated with saturated $NaHCO_3$, and the mixture was stirred for 15 min. The suspension was filtered. The solids were washed with water and diethyl ether, then oven-dried to give 2.726 g (93%) of the desired product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.40 (t, J = 7.7 Hz, 1 H), 7.75−7.83 (m, 2 H), 7.90 (d, J = 7.5 Hz, 1 H), 8.07 (d, J = 8.3 Hz, 2 H), 8.44 (d, J = 8.3 Hz, 2 H), 9.23 (s, brd, 1 H). MS (DCI/NH_3) m/z 263.0 (M + H)$^+$. Melting point: 323−324 °C.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (27). To a solution of **26** (43.3 mg, 0.165 mmol) in DMF (1.5 mL) were added ammonium chloride (44.2 mg, 0.825 mmol) and sodium azide (53.7 mg, 0.825 mmol). The mixture was heated at 60 °C overnight, then at 80 °C for 24 h. After cooling, the reaction mixture was treated with 5% citric acid and water until a suspension formed. The solids were filtered, washed with water, and oven-dried to give 29.4 mg (58%) of the desired product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.39 (t, J = 7.8 Hz, 1 H), 7.71−7.85 (m, 2 H,) 7.91 (d, J = 7.1 Hz, 1 H), 8.26 (d, J = 8.1 Hz, 2 H), 8.47 (d, J = 8.1 Hz, 2 H), 9.31 (s, 1 H), 13.58 (s, 1 H). MS (DCI/NH_3) m/z 306.1 (M + H)$^+$. Anal. ($C_{15}H_{11}N_7O \cdot 2H_2O$) C, H, N.

2-(4-(*N*′-Hydroxycarbamimidoyl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (28). A mixture of **26** (0.500 g, 1.91 mmol), potassium carbonate (1.317 g, 9.53 mmol), and hydroxylamine hydrochloride (0.199 g, 2.86 mmol) in EtOH (30 mL) was heated at reflux. After 5 h, more hydroxylamine hydrochloride (0.199 g) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled and the suspension filtered. The solids were washed with EtOH, stirred in water for 30 min, filtered, washed with water, and oven-dried to give 0.209 g of the desired product as a white solid. The initial filtrate was concentrated, and the residue was triturated with a small amount of MeOH. The solids were filtered, washed with MeOH, and dried to give 0.0800 g of the desired product. The total yield was 0.289 g (51%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 5.92 (s, 2 H), 7.35 (t, J = 7.8 Hz, 1 H), 7.75 (d, J = 7.1 Hz, 2 H), 7.83−7.94 (m, 3 H), 8.24 (d, J = 8.5 Hz, 2 H), 9.35 (s, brd, 1H), 9.81 (s, 1 H). MS (DCI/NH_3) m/z 296.1 (M + H)$^+$. Melting point: 255−256 °C.

2-(4-(5-Oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 29). To a suspension of **28** (40.0 mg, 0.135 mmol) in dioxane (2 mL) was added CDI (26.4 mg, 0.163 mmol). The mixture was heated at reflux for 40 min. The suspension was filtered and washed with diethyl ether. The solids were stirred in water for 20 min, filtered, washed with water and diethyl ether, and dried. The crude material was purified by HPLC to give 29.0 mg (white solid, 50%) of the desired product as the TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.40 (t, J = 7.8 Hz, 1 H), 7.79−7.81 (m, 2 H), 7.91 (d, J = 6.7 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 2 H), 8.44 (d, J = 8.2 Hz, 2 H), 9.20 (s, brd, 1 H), 13.12 (s, brd, 1 H). MS (DCI/NH_3) m/z 322.1 (M + H)$^+$. Anal. ($C_{16}H_{11}N_5O_3 \cdot 1.4TFA \cdot 1.25H_2O$) C, H, N.

2-(4-(5-Oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)phenyl)-1*H*-benzo[*d*]-imidazole-4-carboxamide (TFA Salt, 30). A mixture of **28** (40.0 mg, 0.135 mmol), and 1,1′-thiocarbonyldiimidazole (30.0 mg, 0.149 mmol) in THF (5 mL) was heated at 50 °C for 1 h. Silica gel (0.6 g) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added to the reaction at room temperature, and the reaction mixture was stirred overnight. Silica gel was filtered and washed with MeOH. The filtrate was purified by HPLC to give 10.0 mg (light-yellow solid, 16%) of the desired product as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.40 (t, J = 7.8 Hz, 1 H), 7.73−7.82 (m, 2 H), 7.91 (d, J = 8.6 Hz, 1 H), 8.16 (d, J = 8.6 Hz, 2 H), 8.40 (d, J = 8.6 Hz, 2 H), 9.20 (s, brd, 1 H), 13.54 (s, brd, 1 H). MS (DCI/NH_3) m/z 338.1 (M + H)$^+$.

2-(4-(5-Thioxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (31). A mixture of **28** (40.0 mg, 0.135 mmol), 1,1′-thiocarbonyldiimidazole (36.0 mg, 0.203 mmol), and DBU (0.082 mL, 0.54 mmol) in acetonitrile (4 mL) was stirred at 80 °C for 1.5 h. The reaction mixture was cooled, diluted with 5% citric acid, and extracted with EtOAc. The suspension staying between two clear layers was filtered, washed with water and EtOAc, and dried to give 35.0 mg (76%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (t, J = 7.7 Hz, 1 H), 7.74−7.81 (m, 2 H), 7.90 (d, J = 8.6 Hz, 1 H), 8.10 (d, J = 8.6 Hz, 2 H), 8.44 (d, J = 8.6 Hz, 2 H), 9.21 (s, brd, 1 H). MS (DCI/NH_3) m/z 338.0 (M + H)$^+$.

2-(4-(Isoxazol-5-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 37). A suspension of **36** (60.0 mg, 0.186 mmol) in acetic acid (2 mL) was heated at 90 °C for 90 min. The solids were filtered, washed with AcOH, diethyl ether, and oven-dried to give 44.0 mg of a white solid. The material was further purified by HPLC to give 23.5 mg (30%) of the desired product

as the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.83 (s, 2 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.72−7.86 (m, 2 H), 7.90 (t, J = 7.0 Hz, 1 H), 8.14 (d, J = 8.1 Hz, 2 H), 8.42 (d, J = 8.5 Hz, 2 H), 9.26 (s, brd, 1 H), 13.64 (s, 1 H). MS (DCI/NH_3) m/z 305.1 $(M + H)^+$.

4-(1-Methyl-1*H*-pyrazol-3-yl)benzoic Acid (38). A mixture of methylhydrazine (carcinogen! 0.201 g, 4.37 mmol) and **33** (1.02 g, 4.37 mmol) in AcOH (12 mL) was heated at 70 °C for 1 h. After concentration, the residue was treated with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was dried, concentrated, and purified on a 40 g column using the ISCO Companion flash system eluting with CH_2Cl_2/EtOAc (97.5:2.5 to 90:10) to give the desired isomeric intermediate (0.525 g, 56%). To a solution of this intermediate (0.500 g, 2.31 mmol) in THF (10 mL) and MeOH (3 mL) was added an emulsion of lithium hydroxide (0.291 g, 6.94 mmol) in water (2 mL). After 2 h at room temperature, the mixture was heated at 40 °C for 3 h. Most of the solvent was evaporated. The remaining material was treated with 5% citric acid. The resulting precipitate was filtered, washed with water, and oven-dried to give 0.415 g (50%, two steps) of the desired product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.91 (s, 3 H), 6.80 (d, J = 2.0 Hz, 1 H), 7.78 (d, J = 2.4 Hz, 1 H), 7.93 (q, J = 8.8 Hz, 4 H), 12.87 (s, brd, 1 H). MS (DCI/NH_3) m/z 203.0 $(M + H)^+$. Melting point: 235−236 °C.

2-(4-(1-Methyl-1*H*-pyrazol-3-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (HCl Salt, 39). A solution of **38** (0.150 g, 0.742 mmol) in a mixture of pyridine (1.5 mL) and DMF (1.5 mL) was treated with CDI (0.132 g, 0.816 mmol) at 45 °C for 2 h. Compound **11** (0.166 g, 0.742 mmol) was added, and the mixture was stirred at room temperature for 4.5 h. After concentration, the residue was treated with 20% brine and extracted with EtOAc (2×). The suspension in the aqueous layer was filtered, washed with water, and oven-dried to give 0.161 g (65%) of clean intermediate as a yellow solid. A suspension of this intermediate (0.110 g, 0.328 mmol) in acetic acid (3 mL) was heated at 90 °C for 90 min. The reaction mixture was concentrated. The residue was suspended in 3 mL of MeOH and sonicated. To this suspension was added 1 N HCl in ether. The precipitate was filtered, washed with diethyl ether, and oven-dried to give 0.114 g (tan solid, 89%) of the desired product as the HCl salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.93 (s, 3 H), 6.86 (d, J = 2.4 Hz, 1 H), 7.44 (t, J = 7.9 Hz, 1 H), 7.75−7.86 (m, 2 H), 7.91 (d, J = 7.5 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 2 H), 8.30 (d, J = 8.7 Hz, 2 H), 9.07 (s, brd, 1 H). MS (DCI/NH_3) m/z 318.1 $(M + H)^+$. Anal. ($C_{18}H_{15}N_5O \cdot 2HCl \cdot 1.75H_2O$) C, H, N.

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (40). A mixture of 2,3-diaminobenzamide (0.500 g, 2.23 mmol), 4-bromobenzaldehyde (0.454 g, 2.45 mmol), and 10% Pd/C (0.130 g) in MeOH (25 mL) was heated at reflux overnight. The reaction mixture was filtered through Celite. The filtrate was concentrated and purified on a 40 g silica column using the ISCO Companion flash system eluting with CH_2Cl_2/MeOH (95:5 to 90:10) to give 0.185 g (26%) of the desired product as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.39 (t, J = 7.8 Hz, 1 H), 7.74−7.86 (m, 4 H), 7.89 (dd, J = 7.5, 1.02 Hz, 1 H), 8.17−8.24 (m, 2 H), 9.14 (s, brd, 1 H). MS (ESI) m/z 316.1 $(M + H)^+$. Melting point: 219−220 °C.

2-(4-(Pyridin-4-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 41). A mixture of **40** (50.0 mg, 0.158 mmol), pyridin-4-ylboronic acid (23.3 mg, 0.190 mmol), bis(triphenylphosphine)palladium(II) dichloride (5.6 mg, 7.9 μmol), and 1 M Na_2CO_3 (0.19 mL, 0.19 mmol) in 1.8 mL of DME/EtOH/H_2O (7:2:3) was heated at 160 °C for 15 min in a Biotage microwave reactor. The reaction mixture was diluted with brine and water and extracted with EtOAc/MeOH (9:1). The organic layer was dried, concentrated, and purified by HPLC to give 27.0 mg (light-yellow solid, 32%) of the desired product as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.37−7.44 (m, 1 H), 7.81 (d, J = 7.9 Hz, 2 H), 7.91 (d, J = 7.6 Hz, 1 H), 8.24 (d, J = 8.6 Hz, 2 H), 8.36 (d, J = 6.7 Hz, 2 H), 8.48 (d, J = 8.9 Hz, 2 H), 8.96 (d, J = 6.7 Hz, 2 H), 9.23 (s, brd, 1 H). MS (ESI) m/z 315.2 $(M + H)^+$.

2-(4-(Pyridin-3-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (TFA Salt, 42). A mixture of **40** (40.0 mg, 0.127 mmol), pyridin-3-ylboronic acid (18.7 mg, 0.152 mmol), bis(triphenylphosphine)palladium(II) dichloride (4.4 mg, 6.3 μmol), and 1 M Na_2CO_3 (0.15 mL, 0.152 mmol) in 1.5 mL of DME/EtOH/H_2O (7:2:3) was heated at 160 °C for 15 min in a Biotage microwave reactor. The reaction mixture was diluted with brine and water and extracted with EtOAc/MeOH (9:1). The organic layer was dried, concentrated, and purified by HPLC to give 43.5 mg (white solid, 63%) of the desired product as the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.38 (t, J = 7.8 Hz, 1 H), 7.72−7.82 (m, 2 H), 7.83−7.92 (m, 2 H), 8.05 (d, J = 8.6 Hz, 2 H), 8.41 (d, J = 8.6 Hz, 2 H), 8.60 (d, J = 10.1 Hz, 1 H), 8.79 (dd, J = 5.2, 1.2 Hz, 1 H), 9.15−9.25 (m, 2 H). HR/MS (FAB) calculated for $C_{19}H_{15}N_4O$: 315.1240; found, 315.1237.

2-(4-(Pyridin-2-yl)phenyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (44). A mixture of **11** (2.00 g, 8.90 mmol), 4-(pyridin-2-yl)benzaldehyde (**43**, 1.64 g, 8.96 mmol), and 10% Pd/C (0.600 g) in MeOH (60 mL) was heated at reflux overnight. After cooling, the reaction mixture was filtered through Celite. The filtrate was concentrated and purified by recrystallization from MeOH to give 1.20 g (43%) of the desired product as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.48 (t, J = 7.8 Hz, 1 H), 7.62−7.68 (m, 1 H), 7.83 (s, 1 H), 7.87 (d, J = 7.9 Hz, 1 H), 7.94 (d, J = 7.6 Hz, 1 H), 8.20 (t, J = 7.6 Hz, 1 H), 8.25−8.31 (m, 1 H), 8.36 (d, J = 8.5 Hz, 2 H), 8.49 (d, J = 8.5 Hz, 2 H), 8.82 (d, J = 5.2 Hz, 1 H), 9.04 (s, brd, 1 H). MS (ESI) m/z 315.1 $(M + H)^+$.

Supporting Information Available: Combustion analysis data for compounds **8**, **18**, **22**, **24**, **27**, **29**, **39**, and **42** and experimental procedures for **34**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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