Discovery of the Poly(ADP-ribose) Polymerase (PARP) Inhibitor 2-[(*R*)-2-methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide (ABT-888) for the Treatment of Cancer

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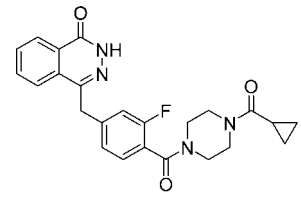
We have developed a series of cyclic amine-containing benzimidazole carboxamide PARP inhibitors with a methyl-substituted quaternary center at the point of attachment to the benzimidazole ring system. These compounds exhibit excellent PARP enzyme potency as well as single-digit nanomolar cellular potency. These efforts led to the identification of **3a** (2-[(*R*)-2-methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide, ABT-888), currently in human phase I clinical trials. Compound **3a** displayed excellent potency against both the PARP-1 and PARP-2 enzymes with a K_i of 5 nM and in a C41 whole cell assay with an EC_{50} of 2 nM. In addition, **3a** is aqueous soluble, orally bioavailable across multiple species, and demonstrated good in vivo efficacy in a B16F10 subcutaneous murine melanoma model in combination with temozolomide (TMZ) and in an MX-1 breast cancer xenograft model in combination with either carboplatin or cyclophosphamide.

Introduction

Poly(ADP-ribose) polymerase-1 (PARP-1)[a] is a nuclear enzyme involved in the detection and repair of DNA damage. The PARP family of enzymes share a catalytic PARP homology domain, but only PARP-1 and PARP-2 contain a DNA-binding domain that facilitates localization to the site of DNA damage.[1a] PARP-1 and PARP-2 catalyze the transfer of ADP-ribose units from intracellular nicotinamide adenine dinucleotide (NAD^+) to nuclear acceptor proteins, leading to the formation of ADP-ribose polymers. This is a key process for the repair of DNA caused by DNA damaging chemotherapeutic agents and also radiation,[1] and thus PARP-1 (and to a lesser extent, PARP-2) contributes to the resistance that often develops after cancer therapy.[2] Recently, several inhibitors of PARP-1 have been shown to block this intracellular DNA repair process in vivo and thus increase the maximum therapeutic benefit of several cytotoxic chemotherapeutics and radiation.[3−7] In addition, hyperactivation of PARP-1 as a response to more extensive DNA damage mediated by oxidative stress has been associated with several diseases, including stroke, myocardial ischemia, arthritis, colitis, and allergic encephalomyelitis.[1a] Several classes of PARP-1 inhibitors have been previously described, many of which are currently in clinical trials.[8] KuDOS has recently described a series of of phthalazinones, resulting in the identification of 4-(4-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-3-fluorobenzyl)phthalazin-1(2*H*)-one (AZD2281, **29**).[9] A series of benzimidazoles and azepinoindolones were disclosed by Pfizer, resulting in the discovery of 8-fluoro-5-(4-((methylamino)methyl)phenyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-one (AG014699, **30**).[10] Others, including Guilford and Inotek, have also described diverse series of PARP-1 inhibitors.[7,11] We have previously described optimization efforts on a series of potent benzimidazole-containing PARP inhibitors, culminating in the identification of a lead preclinical candidate **1** (A-620223).[12] This compound displayed good potency against both PARP-1 and PARP-2, along with oral efficacy in a number of preclinical mouse tumor models, potentiating the efficacy of cytotoxic agents such as temozolomide (TMZ) and cisplatin. In this report, we describe a series of benzimidazole carboxamide PARP-1 inhibitors in which a methyl-substituted quaternary center has been introduced at the point of attachment of a cyclic amine to the benzimidazole ring system. This modification of the benzimidazole system resulted in a significant improvement in enzyme and/or cellular potency relative to the analogous compounds where this methyl substituent is absent. These efforts resulted in the identification of the novel benzimidazole compound **3a** (ABT-888),[4a] a potent inhibitor



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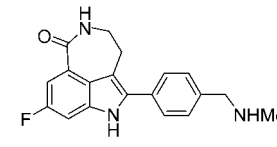

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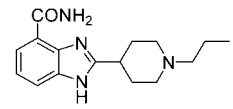

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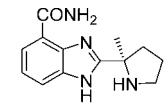

3a

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[a] Abbeviations: PARP, poly(ADP-ribose) polymerase; TMZ, temozolomide; CBZ, carbobenzyloxy; SIRT, silent information regulator protein; OMP, osmotic mini-pump; 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_{ss}, volume of distribution at steady state; CL, pharmacokinetic clearance.

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of the PARP-1 and PARP-2 enzymes ($K_i = 5$ nM) with good potency in C41 whole cells ($EC_{50} = 2$ nM). In addition, **3a**has excellent pharmaceutical and safety properties and has demonstrated good in vivo efficacy in several preclinical mouse tumor models in combination with cytotoxic agents such as temozolomide (TMZ), carboplatin, and cyclophosphamide. This data corroborates the excellent preliminary efficacy that has previously been reported for **3a** in various tumor models.[4] This lead molecule is currently undergoing evaluation in human phase I clinical trials for the treatment of a variety of cancers in combination with several cytotoxic chemotherapeutic regimens.

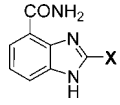
Chemistry

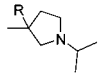
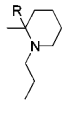
The benzimidazole ring system was constructed as described previously.[12,13] CBZ-protected cyclic amine carboxylic esters **29** were alkylated at the α-position of the ester, generally using an alkyl iodide and sodium bis(trimethylsilyl)amide, to give alkylated analogues **30**. Saponification of the ester gave acid **31**, which was coupled to a 2,3-diaminobenzamide hydrochloride under standard 1,1-carbonyldiimidazole (CDI) conditions to selectively give amide **32**. Refluxing in acetic acid provided benzimidazole **33**. Removal of the CBZ protecting group under hydrogenolysis conditions gave secondary amines **34**. Standard reductive amination conditions using sodium cyanoborohydride with a variety of aldehydes and ketones provided tertiary amines **35**.

Results and Discussion

The benzimidazole carboxamide series of PARP-1 inhibitors represents an attractive structural class due to its relatively low

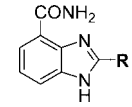
Table 1. Comparison of Methyl and Des-methyl Analogues

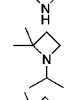
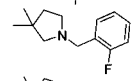
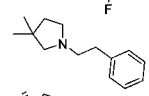
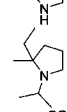
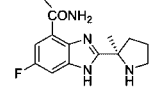
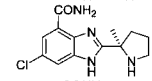
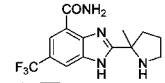
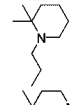
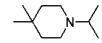
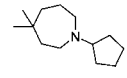


Compd	X	R	PARP-1 (K_i, μM)[a]	Cellular (EC_{50}, μM)[a]
2a		Me	0.004	0.14
b		H	0.006	0.61
3a		Me	0.005	0.002
b		H	0.007	0.018
4a		Me	0.005	0.003
b		H	0.03	0.016
5a		Me	0.006	0.003
b		H	0.015[b]	0.013
6a		Me	0.004	0.017
b		H	0.004	0.16
7a		Me	0.006	0.002
b		H	0.009	0.004
8a		Me	0.005	0.002
b		H	0.025	0.025
9a		Me	0.019	0.005
b		H	0.13	0.067
10a		Me	0.003	0.008
b		H	0.005	0.031

[a] Mean of two or more independent determinations. [b] Single determination.

Table 2. SAR of Quaternary Analogues



Compd	R	PARP-1 (K_i, μM)[a]	Cellular (EC_{50}, μM)[a]
11		0.013	0.12
12		0.042	0.018
2a		0.004	0.14
13		0.009	0.003
14		0.004	0.003
3a		0.005	0.002
4a		0.005	0.003
5a		0.006	0.003
15		0.017	0.004
16		0.031	0.006
6a		0.004	0.017
17		0.005	0.001
7a		0.006	0.002
18		0.009	0.004
19		0.01	0.002
20		0.023	0.028
21		0.013	0.007
22		0.069	0.020
23		0.003	0.002
24		0.010	0.004
25		3.3	>1
8a		0.005	0.002
9a		0.019	0.005
26		0.004	0.13
27		0.008	0.008[b]
10a		0.003	0.008
28		0.007	0.002

[a] Mean of two or more determinations. [b] Single determination.

Table 3. Mouse Pharmacokinetics

compd[a]	%*F*	$T_{1/2}$ (iv)[b]	AUC (po)[c]	C_{max} (po)[d]
3a	92	1.6	2.2	1.6
4a	66	1.2	1.1	0.8
5a	36	0.55	0.2	0.1
7a	100	1.4	1.0	0.5
8a	93	1.5	1.5	0.5
23	100	0.5	1.5	1.0
26	20	1.2	0.4	0.1

[a] 10 mg/kg po (2.5% EtOH, 1 drop TW-80, 25% PEG400, PBS), 3 mg/kg iv (2.5% EtOH, 5% DMSO, 1 drop TW-80, 25% PEG400, PBS). [b] h. [c] μg-h/mL. [d] μg/mL.

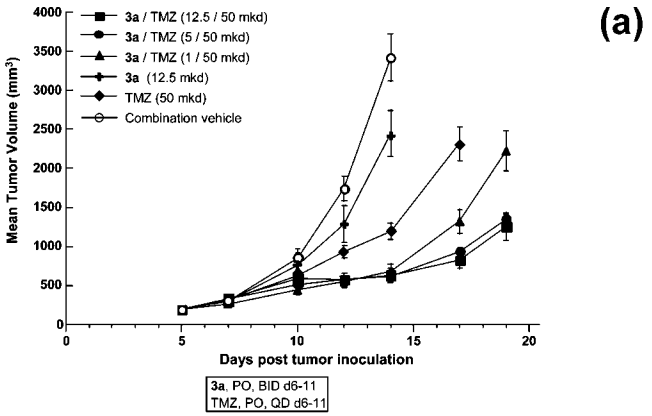
Table 4. Multispecies Pharmacokinetics for **3a** and **4a**

compd	species	dose	%*F*	$T_{1/2}$ (iv)[b]	AUC (po)[c]	C_{max} (po)[d]	V_{ss}[e]	CL[f]
3a	mouse	10	92	1.6	2.2	1.6	9.4	4.1
	rat	5	61	1.2	1.5	0.5	3.6	2.0
	dog	2.5	72	2.7	3.2	0.8	2.2	0.6
	monkey	2.5	56	1.9	1.3	0.3	3.1	1.1
4a	mouse	10	66	1.2	1.1	0.8	10.3	6.2
	rat	5	72	2.4	1.9	0.6	7.5	2.0
	dog	2.5	48	2.2	1.4	0.5	2.9	0.9
	monkey	2.5	39	1.5	0.7	0.2	3.0	1.4

[a] mg/kg. [b] h. [c] μg-h/mL. [d] μg/mL. [e] L/kg. [f] L/h/kg.

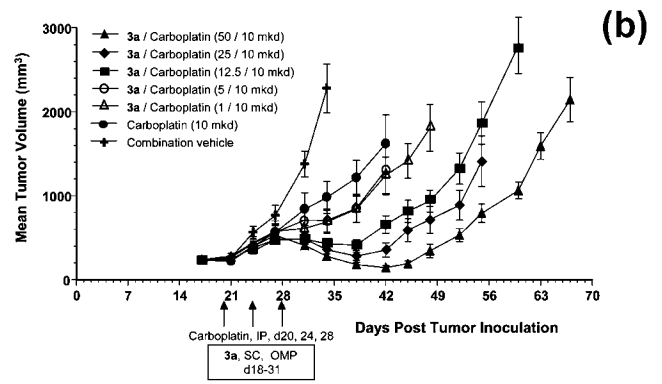
molecular weight and high intrinsic potency. An intramolecular hydrogen-bonded conformation closely mimics the nicotinamide binding interactions in the PARP-1 active site.[12] Contributing to this scaffold's potency are key hydrogen-bond interactions between the amide and two residues in the PARP-1 active site, Gly-863 and Ser-904, along with a π-stacking interaction with Tyr-907.[14] We previously described a series of potent benzimidazole-containing PARP-1 inhibitors, culminating in the identification of a lead preclinical candidate **1**.[12] We also demonstrated the advantages of incorporating a basic amine into this class of molecules for good cellular potency and reasonable pharmacokinetic properties. In this report, we describe a series of benzimidazole-containing PARP-1 inhibitors in which a methyl substituent has been introduced at the point of attachment of a cyclic amine to the benzimidazole ring system. Remarkably and quite unexpected, this modification resulted in a significant improvement in enzyme and cellular potency relative to the analogous compounds without this methyl substituent. Table 1 shows a comparison of several diverse analogues with the quaternary methyl group present (**2a**−**10a**) or absent (**2b**−**10b**). In many examples, the difference in enzyme potency is relatively small, although there are a few examples (i.e., **4a**/**b**, **8a**/**b**, **9a**/**b**) where the differences are more profound. However, quite to our surprise, we found that very consistently, the cellular potency of the methyl-containing analogues were 2−13 times more potent than the corresponding des-methyl analogues. On the basis of these results, we undertook a more detailed exploration of this class of PARP-1 inhibitors in order to optimize potency as well as other pharmaceutical properties. Table 2 highlights a variety of analogues made within this class. The azetidine analogues **11**, **12**, **2a**, and **13**, in general, demonstrated good to moderate enzyme potency. As we have seen previously, introducing larger groups at N-2 of 2-azetidine analogues (i.e., **12**) was detrimental to enzyme potency. Only N-alkylated 3-azetidine analogues such as **13** had good cellular potency, whereas the unalkylated analogues **11** and **2a** showed poor cellular potency. In contrast, unalkylated 2-pyrrolidine analogues showed excellent enzyme and cell potency, with no differentiation between individual enantiomers (**14**, **3a**, **4a**). This lack of enzyme potency differences between enantiomers is supported by X-ray crystallography studies of **3a** and **4a** showing the absence of any interactions that would allow one to predict greater potency of one enantiomer over the other. *N*-Methyl analogue **5a** demonstrated similar potencies to **14**, while larger substituents such as isopropyl and cyclobutyl (**15**, **16**) showed a moderate drop-off in enzyme potency, consistent with 2-azetidine analogues. The unsubstituted 3-pyrrolidine analogue **6a** showed similar enzyme potency to **14**, however, it was somewhat less potent in cells. N-Alkylation of the 3-pyrrolidine (i.e., **17**, **7a**, **18**, **19**) showed a significant improvement in cellular potency, demonstrating a tolerance for relatively larger groups such as benzyl and phenethyl, in contrast to the 2-pyrrolidine analogues. Consistent with what we have previously reported,[12] reducing the basicity of the cyclic amine as in **20** significantly impacted both enzyme and cellular potency. Likewise, introduction of slightly larger alkyl substituents at the quaternary center (i.e., ethyl in **21** and **22**) was also detrimental to potency. Consistent with X-ray crystallography data, small substituents were generally well tolerated at the 6-position of the benzimidazole ring, with 6-fluoro analogue **23** and 6-chloro analogue **24** demonstrating good potency. However, 6-trifluoromethyl analogue **25** showed essentially no enzyme or cellular activity. 2-Piperidine analogues showed a similar profile as the 2-pyrrolidine analogues, with the unalkylated **8a** showing excellent enzyme and cell potency and the alkylated analogue **9a** demonstrating a slight drop-off in potency. On the other hand, the unalkylated 4-piperidine analogue **26** showed good enzyme potency but very poor cellular potency. N-alkylation of the 4-piperidine (i.e, **27**) restored good cellular potency. Unalkylated 4-azepine analogue **10a** also showed good enzyme potency with reasonable cellular potency, while N-alkylation (i.e., **28**) moderately improved cellular potency. Selected compounds were also tested against the closely related PARP-2 enzyme and all had similar K_i values (i.e., 11, 5, 2, 2, 4, and 2 nM for **2b**, **3a**, **4a**, **6a**, **23**, and **26**, respectively). This is consistent with what we have previously reported that the majority of compounds within the benzimidazole class showed similar potencies against both enzymes.[12] Although it would be expected that most PARP-1 inhibitors would also inhibit PARP-2 to some extent based on sequence homology, there have been very limited reports detailing such selectivity data.[15]

To aid in the differentiation of a significant number of potent compounds, the pharmacokinetics of several analogues were profiled in CD1 mice (Table 3). With the exception of **5a** and **26**, all of these compounds showed oral bioavailabilities of >50% and good oral exposures. Most also had reasonable half-lives of >1 h. On the basis of their overall profile, enantiomers **3a** and **4a** were chosen for further pharmacokinetic assessment in Sprague−Dawley rats, beagle dogs, and cynomolgus monkeys (Table 4). Because of its superior oral bioavailability and exposure, *R*-enantiomer **3a** was identified for further characterization. The pharmacokinetic profile of **3a** is characterized by high plasma clearance and moderate volume of distribution in all species, with terminal elimination half-lives in the 1.2−2.7 h range. The oral bioavailability was >50% in all species, ranging from a low of 56% in the monkey to a high of 92% in the mouse, with low animal-to-animal variability across all species. In addition, **3a** partitioned slowly into the brain in both mouse and rat, with plasma to brain ratios of ∼3:1 during the first 3−6 h after dosing. Compound **3a** has high water solubility (>5 mg/mL) at physiological pH and did not inhibit several cytochrome P450s, including CYP1A2, 2A6, 2D6, 2C9, 2C19, 2E1, and 3A4 in human liver microsomes. Plasma protein binding (assessed in vitro as % bound at 5 μM) for **3a** was moderate in all species, ranging from 41−51% in various species, including human. As mentioned previously, **3a** was



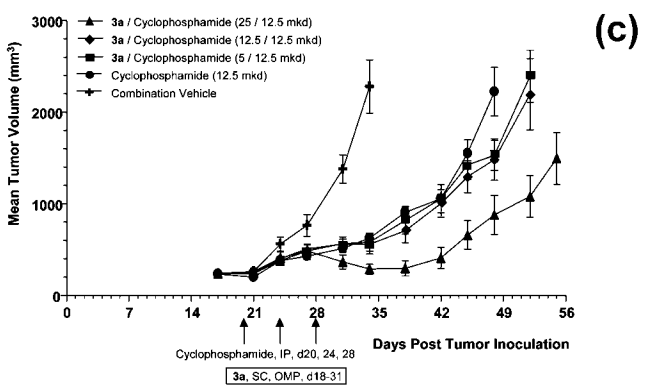
compd	dose (mg/kg/day)	tumor volume[a] (day 14)	%TGI vehicle[b] (day 14)	tumor volume[a] (day 17)	%TGI cytotoxic[c] (day 17)
3a/TMZ	12.5/50	632 ± 89	82***	827 ± 113	64***
	5/50	620 ± 72	82***	934 ± 98	60***
	1/50	679 ± 99	80***	1319 ± 155	43**
vehicle/TMZ	0/50	1198 ± 104	65***	2318 ± 212	--
3a/vehicle	12.5/0	2452 ± 297	28*	--	--
combination vehicle	0/0	3425 ± 303	--	--	--

* p <0.04; ** p <0.002; *** p<0.0001; [a] Mean (mm^3) ± SEM of 9-10 mice/group; [b] %TGI vs. combo vehicle control; [c] %TGI vs. TMZ control.



compd	dose (mg/kg/day)	tumor volume[a] (day 34)	%TGI vehicle[b] (day 34)	tumor volume[a] (day 42)	%TGI cytotoxic[c] (day 42)
3a/carboplatin	50/10	277± 30	88***	145 ± 22	91***
	25/10	358 ± 51	84***	353 ± 85	78**
	12.5/10	428 ± 59	81***	656 ± 105	58*
	5/10	703 ± 136	69***	1306 ± 291	17
	1/10	687 ± 137	70***	1243 ± 218	21
vehicle/carboplatin	0/10	980 ± 191	57**	1619 ± 343	--
combination vehicle	0/0	2279 ± 291	--	--	--

* p< 0.05, ** p< 0.01, *** p< 0.001; [a] Mean (mm^3) ± SEM of 8-9 mice/group; [b] %TGI vs. combo vehicle control; [c] %TGI vs. carboplatin control.

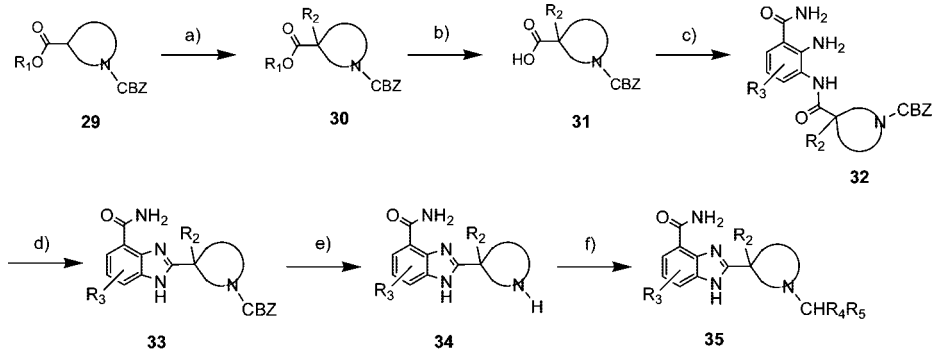


compd	dose (mg/kg/day)	tumor volume[a] (day 34)	%TGI vehicle[b] (day 34)	tumor volume[a] (day 48)	%TGI cytotoxic[c] (day 48)
3a/cyclophosphamide	25/12.5	289 ± 53	86***	878 ± 211	61**
	12.5/12.5	558 ± 104	77***	1482 ± 227	33
	5/12.5	582 ± 99	74***	1528 ± 165	31*
vehicle/cyclophosphamide	0/12.5	625 ± 49	73***	2223 ± 264	--
combination vehicle	0/0	2279 ± 291	--	--	--

* p< 0.05, ** p< 0.01, *** p< 0.001; [a] Mean (mm^3) ± SEM of 8-9 mice/group; [b] %TGI vs. combo vehicle control; [c] %TGI vs. cyclophosphamide control.

Figure 1. (A) B16F10 model: **3a** in combination with TMZ. (B) MX-1 model: **3a** in combination with carboplatin. (C) MX-1 model: **3a** in combination with cyclophosphamide.

Scheme 1[a]



[a] (a) R_2I, base, THF; (b) LiOH, H_2O, THF; (c) 2,3-diaminobenzamide-HCl, CDI, DMF, pyridine; (d) HOAc, heat; (e) H_2, 10% Pd/C; (f) $NaBH_3CN$, $R_4R_5C(O)$, MeOH.

equally potent against the related enzyme PARP-2 ($K_i = 5$ nM) but also does not inhibit ($K_i > 17$ μM) SIRT1 or SIRT2, regulatory proteins with reported mono ADP-ribosyltransferase activity.[16]

In vivo, **3a** showed excellent potentiation of cytotoxic agents in two subcutaneous, murine tumor models: with temozolomide (TMZ) in B16F10, a syngeneic melanoma model (Figure 1A), and with both carboplatin (Figure 1B) and cyclophosphamide (Figure 1C) in MX-1 human breast cancer xenograft model. The B16F10 model (Figure 1A), while relatively resistant to most chemotherapeutics, is moderately sensitive to TMZ, and this sensitivity can be enhanced with PARP inhibitors.[5,7] In this model, **3a** was administered orally on days 6−11 at doses of 1, 5, and 12.5 mg/kg/day, bid, while TMZ was administered at 50 mg/kg/day, po, qd, on days 6−11. Compound **3a** significantly potentiated the efficacy of TMZ as early as day 14 and continued to differentiate from the TMZ alone group out to day 17, with TGI values (vs. TMZ control) of 64, 60, and 43% for the 12.5, 5, and 1 mg/kg/day **3a** combination groups, respectively. The **3a**/TMZ combinations were well tolerated, with maximum body weight loss for all combination groups similar to the TMZ monotherapy group.

In the MX-1 in combination with carboplatin (Figure 1B), **3a** was dosed via sc osmotic minipump (OMP) at doses of 1, 5, 12.5, 25, and 50 mg/kg/day for 14 days starting on day 18 post-tumor inoculation, while carboplatin was given as a single dose on days 20, 24, and 28 at 10 mg/kg, ip. Significant potentiation was observed as early as day 34 for all five **3a** combination groups, with the three higher dosing groups continuing to differentiate from the carboplatin alone group out to day 42, with TGI values (vs TMZ control) of 91, 78, and 58% for the 50, 25, and 12.5 mg/kg/day **3a** combination groups, respectively. In the MX-1 model in combination with cyclophosphamide (Figure 1C), **3a** was dosed via sc OMP at doses of 5, 12.5, and 25 mg/kg/day for 14 days starting on day 18 post tumor inoculation, while cyclophosphamide was given as a single dose on days 20, 24, and 28 at 12.5 mg/kg, ip. Significant potentiation was observed as early as day 34 for the 25 mg/kg/day **3a** combination group and continued to differentiate from the cyclophosphamide alone group out to day 48, with a TGI value (vs TMZ control) of 61%. In the MX-1 model, both **3a** combinations were well tolerated, with maximum body weight loss for all combination groups similar to the cytotoxic monotherapy groups.

Although **3a** was dosed by OMP in the two MX-1 efficacy trials to help establish the steady state concentration necessary for in vivo activity, similar results were obtained when the compound was dosed by oral administration.[4]

Conclusion

In summary, the discovery and characterization of a novel clinical candidate **3a**, containing a methyl-substituted quaternary center, has been described. The addition of this quaternary methyl group provides a significant increase in potency, with **3a** demonstrating a K_i of 5 nM against both the PARP-1 and PARP-2 enzymes and an EC_{50} of 2 nM in whole cells. In addition, **3a** exhibited excellent pharmaceutical properties and pharmacokinetics in multiple species. In B16F10 melanoma and MX-1 breast cancer models, **3a** demonstrated significant efficacy in combination with a variety of cytotoxic agents, including temozolomide, carboplatin, and cyclophosphamide. This lead candidate has recently completed the first human oncology phase 0 clinical trial[17] and is currently undergoing evaluation in multiple phase I human clinical trials.

Experimental Section

NMR spectra were obtained on Varian M-300, Bruker AMX-400, Varian U-400, or Varian Unity Inova 500 magnetic resonance spectrometers with indicated solvent and internal standard. Chemical shifts are given in delta (δ) values and coupling constants (J) in hertz (Hz). The following abbreviations are used for peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Mass spectra were performed as follows: ESI (electrospray ionization) was performed on a Finnigan SSQ7000 MS run as a flow injection acquisition; DCI (desorption chemical ionization) was performed on a Finnigan SSQ7000 MS using a direct exposure probe with ammonia gas; APCI (atmospheric pressure chemical ionization) was performed on a Finnigan Navigator MS run as flow injection acquisition. Elemental analyses were performed by Quantitative Technologies Inc. Whitehouse, New Jersey. All manipulations were performed under nitrogen atmosphere unless otherwise noted. All solvents and reagents were obtained from commercial sources and used without further purification.

PARP Enzyme Assay.[4] Enzyme assay was conducted in 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 or 4 nM PARP-2 enzyme. Auto reactions 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 and DNA. These reactions were terminated by the addition of 150 μL of 1.5 mM benzamide (~1000-fold over its IC_{50}). Then 170 μL of the stopped reaction mixtures were transferred to streptavidin-coated flash plates, incubated for 1 h, and counted using a TopCount

microplate scintillation counter. K_i data was determined from inhibition curves at various substrate concentrations.

Cellular PARP Assay. C41 cells were treated with test compound 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 5 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 5 times, analysis was performed using an fmax Fluorescence Microplate Reader set at the excitation and emission wavelength for FITC or the excitation and emission wavelength for DAPI. PARP activity (FITC signal) was normalized with cell numbers (DAPI).

B16F10 Tumor Model. For B16F10 syngeneic studies, 6×10^4 cells were mixed with 50% matrigel (BD Biosciences, Bedford, MA) and inoculated by sc injection into the flank of 6−8 week old female C57BL/6 mice, 20 g (Charles River Laboratories, Wilmington, MA). Mice were injection-order allocated to treatment groups and PARP inhibitor therapy was initiated on day 6 following inoculation, with temozolomide treatment also starting on day 6.

MX-1 Tumor Model. A 0.2 cc of 1:10 MX-1 tumor brei was injected subcutaneously into the flank of female SCID mice (Charles River Laboratories) on study day 0. On day 15, tumors were size matched and animals placed into study groups ($N = 10$ mice/group). PARP inhibitor therapy began on day 18, with cisplatin or cyclophosphamide treatment starting on day 20. At various intervals following tumor inoculation, the individual tumor dimensions were serially measured using calibrated microcalipers and the tumor volumes calculated according to the formula $V = L \times W^2/2$ (V: volume; L: length, W: width). Mice were humanely euthanized when the tumor volumes reached a predetermined size.

Procedure A: 2-(2-Methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (14). Step 1: Preparation of 1-Benzyl 2-Methyl 2-Methylpyrrolidine-1,2-dicarboxylate (14-1). A solution of 1-benzyl 2-methyl pyrrolidine-1,2-dicarboxylate (15.0 g, 57 mmol) and iodomethane (7.11 mL, 114 mmol) in THF (100 mL) was treated with 1 M sodium bis(trimethylsilyl)amide in THF (114 mL, 114 mmol) at −75 °C. The mixture was warmed to −20 °C and stirred at −20 °C for 3 h. After quenching with water, the mixture was acidified with 2N HCl (100 mL) and partitioned between water and EtOAc. The organic phase was washed with brine and concentrated and the residue purified by flash chromatography on silica gel using EtOAc/hexane to give the title compound (15.15 g, 96%). ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 1.5H), 1.61 (s, 1.5H), 1.86−1.99 (m, 3H), 2.13−2.24 (m, 1H), 3.46 (s, 1.5H), 3.56−3.69 (m, 2H), 3.71 (s, 1.5H), 4.99−5.23 (m, 2H), 7.24−7.40 (m, 5H), as a mixture of two rotamers. MS (DCI/NH_3) m/z 278 $(M + H)^+$.

Step 2: Preparation of 1-[(Benzyloxy)carbonyl]-2-methylpyrrolidine-2-carboxylic Acid (14-2). A solution of **14-1** (15.15 g, 54.63 mmol) in THF (100 mL) and water (50 mL) was treated with a solution of LiOH (4.58 g, 109.26 mmol) in water (50 mL), and MeOH (60 mL) was added until homogeneous. The solution was heated at 60 °C overnight and the organic solvents removed. The aqueous solution was acidified to pH 2 with 2N HCl and partitioned between EtOAc and water. The organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated to give the title compound as a white solid (13.72 g, 95%). ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 1.5H), 1.45 (s, 1.5H), 1.80−1.96 (m, 3H), 2.02−2.19 (m, 1H), 3.43−3.53 (m, 2H), 4.94−5.11 (m, 2H), 7.24−7.41 (m, 5H), 12.51 (br s, 1H), as a mixture of two rotamers. MS (DCI/NH_3) m/z 264 $(M + H)^+$.

Step 3: Preparation of Benzyl 2-(([2-amino-3-(aminocarbonyl)-phenyl]amino)carbonyl)-2-methylpyrrolidine-1-carboxylate (14-3). A solution of **14-2** (13.7 g, 52 mmol) in pyridine (60 mL) and DMF (60 mL) was stirred with 1,1′-carbonyldiimidazole (CDI, 9.27 g, 57.2 mmol) at 45 °C for 2 h. 2,3-Diaminobenzamide dihydrochloride[13] (11.66 g, 52 mmol) was added and the mixture stirred at ambient temperature overnight. After concentration, the residue was partitioned between EtOAc and aqueous $NaHCO_3$. The solid was collected, washed with water and EtOAc, and dried to give 16.26 g of the title compound. Extraction of the aqueous phase with EtOAc, followed by concentration, filtration, and water and EtOAc wash, provided an additional 1.03 g of solid (84% overall). ^{1}H NMR (DMSO-d_6) δ 1.48 (s, 3H), 1.86−1.98 (m, 3H), 2.22 (dd, $J = 8.0$, 4.6 Hz, 1H), 3.48−3.58 (m, 1H), 3.66−3.76 (m, 1H), 4.97−5.20 (m, 2H), 6.40 (br s, 2H), 6.50 (t, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 6.8$ Hz, 1H), 7.13 (br s, 1H), 7.29−7.42 (m, 5H), 7.50 (d, $J = 6.4$ Hz, 1H), 7.79 (br s, 1H), 9.08 (br s, 1H). MS (APCI) m/z 397 $(M + H)^+$.

Step 4: Preparation of Benzyl 2-[4-(Aminocarbonyl)-1*H*-benzimidazol-2-yl]-2-methylpyrrolidine-1-carboxylate (14-4). A suspension of **14-3** (17.28 g, 43.6 mmol) in AcOH (180 mL) was heated at reflux for 2 h. After cooling, the solution was concentrated and the residue partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was washed with water and concentrated and the residue purified by flash chromatography on silica gel using 3−15% MeOH in 2:1 EtOAc/hexane to provide the title compound (16.42 g, 99%). ^{1}H NMR (DMSO-d_6) δ 1.86 (s, 1.5H), 1.88 (s, 1.5H), 1.91−2.03 (m, 3H), 2.13−2.26 (m, 1H), 3.59−3.71 (m, 1H), 3.74−3.84 (m, 1H), 4.77−5.09 (m, 2H), 6.68 (d, $J = 7.5$ Hz, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.30−7.39 (m, 2H), 7.58−7.68 (m, 2H), 7.80−7.84 (m, 1H), 9.26 (br s, 1H), 12.64 (br s, 0.5H), 12.73 (br s, 0.5H), as a mixture of two rotamers. MS (APCI) m/z 379 $(M + H)^+$.

Step 5: Preparation of 2-(2-Methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide. A solution of **14-4** (15 g, 40 mmol) in MeOH (250 mL) was treated with 10% Pd/C (2.8 g) under 60 psi of hydrogen overnight. Solid was filtered off and the filtrate concentrated. The residue was recrystallized from MeOH to give the free base, which was dissolved in warm MeOH, treated with 1 M HCl in Et_2O, and filtered to give 10.09 g (80%) of the title compound as the HCl salt. ^{1}H NMR (D_2O) δ 1.92 (s, 3H), 2.00−2.09 (m, 1H), 2.21−2.29 (m, 1H), 2.35−2.41 (m, 1H), 2.52−2.57 (m, 1H), 3.54−3.65 (m, 2H), 7.31 (t, $J = 7.9$ Hz, 1H), 7.68 (dd, $J = 8.2$, 0.9 Hz, 1H), 7.72 (dd, $J = 7.6$, 0.9 Hz, 1H). Anal. ($C_{13}H_{16}N_4O \cdot 2HCl$) C, H, N.

2-(2-Ethylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (21). The title compound was prepared according to procedure A using iodoethane in place of iodomethane in step 1 (25% yield). ^{1}H NMR (CD_3OD) δ 0.89 (t, $J = 7.4$ Hz, 3H), 1.90−2.05 (m, 1H), 2.16−2.30 (m, 2H), 2.31−2.48 (m, 2H), 2.59−2.73 (m, 1H), 3.48−3.71 (m, 2H), 7.43 (t, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 7.4$ Hz, 1H), 8.01 (d, $J = 7.4$ Hz, 1H). Anal. ($C_{14}H_{18}N_4O \cdot 1.34TFA$) C, H, N.

2-[(2*R*)-2-Methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide (3a). Step 1: Preparation of Benzyl (2*R*)-2-[4-(Aminocarbonyl)-1*H*-benzimidazol-2-yl]-2-methylpyrrolidine-1-carboxylate (3a-1). Benzyl 2-[4-(aminocarbonyl)-1*H*-benzimidazol-2-yl]-2-methylpyrrolidine-1-carboxylate (1.05 g, 2.8 mmol) was resolved by chiral HPLC (Chiralcel OD, 80/10/10 hexane/EtOH/MeOH). The faster eluting peak was collected and concentrated to provide the title compound (99.4% ee, 500 mg, 95%). MS (APCI) m/z 379 $(M + H)^+$.

Step 2: Preparation of 2-[(2*R*)-2-Methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide (3a-2). A solution of **3a-1** (500 mg, 1.32 mmol) in MeOH (10 mL) was treated with 10% Pd/C (150 mg) under 1 atm of hydrogen overnight. Solid was filtered off and the filtrate concentrated. The residue was purified by HPLC (Zorbax C-18, acetonitrile/water/0.1% TFA) and converted to the HCl salt as described for **14** to provide 254 mg (61%) of the title compound as a white solid. Absolute configuration was assigned by single crystal X-ray of the L-tartrate salt. $[\alpha]^{20}_{589}$ +15.6 ° (c 1.0, MeOH). ^{1}H NMR (D_2O) δ 2.00 (s, 3H), 2.10−2.19 (m, 1H), 2.30−2.39 (m, 1H), 2.45−2.51 (m, 1H), 2.61−2.66 (m, 1H), 3.64−3.73 (m,

2H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H). Anal. ($C_{13}H_{16}N_4O \cdot 2HCl$) C, H, N.

2-[(2*S*)-2-Methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide (4a). The slower-eluting fraction from the preparation of **3a** was converted to the title compound (248 mg, 59%) as described for the preparation of **3a**. $[\alpha]^{20}_{589}$ −13.5 ° (c 1.0, MeOH). ^{1}H NMR (D_2O) δ 1.99 (s, 3H), 2.09−2.19 (m, 1H), 2.30−2.38 (m, 1H), 2.44−2.50 (m, 1H), 2.61−2.66 (m, 1H), 3.63−3.73 (m, 2H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.77 (dd, $J = 8.1$, 0.9 Hz, 1H), 7.81 (dd, $J = 7.8$, 0.9 Hz, 1H). Anal. ($C_{13}H_{16}N_4O \cdot 2HCl$) C, H, N.

Procedure B: 2-(1,2-Dimethylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (5a). A solution of **14** as the free base (300 mg, 1.22 mmol) in MeOH (20 mL) was treated with formaldehyde (37 wt % in water, 228 μL, 3.07 mmol) at ambient temperature overnight. $NaBH_3CN$ (193 mg, 3.07 mmol) was added and the solution stirred at ambient temperature for 3 h. After concentration, the residue was purified by HPLC (Zorbax C-8, 0.1% TFA/acetonitrile/water) and the TFA salt converted to the HCl salt as described for **15** to give 317 mg (91%) of the title compound. ^{1}H NMR (D_2O) δ 1.94 (s, 3H), 2.25−2.43 (m, 2H), 2.49−2.56 (m, 1H), 2.61−2.68 (m, 1H), 2.91 (br s, 3H), 3.49−3.61 (m, 1H), 3.79−3.99 (m, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 7.7$ Hz, 1H). Anal. ($C_{14}H_{18}N_4O \cdot 1.7HCl$) C, H, N.

2-(1-Isopropyl-2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (15). The title compound was prepared according to procedure B using acetone in place of formaldehyde (13% yield). ^{1}H NMR (D_2O) δ 0.89 (d, $J = 4.9$ Hz, 3H), 1.42 (br s, 3H), 2.01 (br s, 3H), 2.34 (m, 2H), 2.43−2.53 (m, 1H), 2.55−2.65 (m, 1H), 3.54−3.63 (m, 1H), 3.71 (m, 1H), 3.97−4.07 (m, 1H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 7.7$ Hz, 1H). Anal. ($C_{16}H_{22}N_4O \cdot 2.7HCl$) C, H; N calcd 14.56, found, 13.69.

2-(1-Cyclobutyl-2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (16). The title compound was prepared according to procedure B using cyclobutanone in place of formaldehyde (66% yield). ^{1}H NMR (D_2O) δ 1.60−1.70 (m, 3H), 1.78−1.84 (m, 1H), 1.97 (br s, 3H), 2.08−2.16 (m, 1H), 2.24−2.38 (m, 3H), 2.45 (ddd, $J = 13.5$, 6.7, 6.7 Hz, 1H), 2.85 (q, $J = 8.9$ Hz, 1H), 3.44−3.53 (m, 1H), 3.69−3.85 (m, 2H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 7.7$ Hz, 1H). Anal. ($C_{17}H_{22}N_4O \cdot 2.8HCl$) C, H; N calcd 13.99, found 13.52.

2-(3-Methylpyrrolidin-3-yl)-1*H*-benzimidazole-4-carboxamide (6a). The title compound was prepared from 1-benzyl 3-methyl pyrrolidine-1,3-dicarboxylate according to procedure A (53% yield). ^{1}H NMR (CD_3OD) δ 1.73 (s, 3H), 2.29−2.36 (m, 1H), 2.69−2.76 (m, 1H), 3.40−3.48 (m, 2H), 3.55−3.62 (m, 1H), 4.21 (d, $J = 11.9$ Hz, 1H), 7.38 (t, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.94 (d, $J = 6.7$ Hz, 1H). Anal. ($C_{13}H_{16}N_4O \cdot 2TFA$) C, H, N.

2-(1-Isopropyl-3-methylpyrrolidin-3-yl)-1*H*-benzimidazole-4-carboxamide (7a). The title compound was prepared from **6a** and acetone according to procedure B (51% yield). ^{1}H NMR (CD_3OD) δ 1.43 (d, $J = 5.9$ Hz, 6H), 1.78(s, 3H), 2.29−2.48 (m, 1H), 2.72−2.91 (m, 1H), 3.33−3.66 (m, 3H), 3.69−3.92 (m, 1H), 4.17−4.57 (m, 1H), 7.37 (t, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.92 (d, $J = 7.2$ Hz, 1H). Anal. ($C_{16}H_{22}N_4O \cdot 2.4TFA$) C, H, N.

2-(2-Ethyl-1-isopropylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (22). The title compound was prepared from **21** and acetone according to procedure B (33% yield). ^{1}H NMR (CD_3OD) δ 0.58 (s, 2H), 0.96−1.28 (m, 4H), 1.46 (d, $J = 6.4$ Hz, 3H), 2.13−2.39 (m, 2H), 2.40−2.71 (m, 2H), 2.74−3.13 (m, 2H), 3.36−3.61 (m, 1H), 3.61−3.95 (m, 2H), 7.49 (t, $J = 7.2$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 8.05 (d, $J = 7.4$ Hz, 1H). Anal. ($C_{17}H_{24}N_4O \cdot 2HCl \cdot 1.8H_2O$) C, H, N.

2-[3-Methyl-1-(2-phenylethyl)pyrrolidin-3-yl]-1*H*-benzimidazole-4-carboxamide (19). The title compound was prepared from **6a** and phenylacetaldehyde according to procedure B (30% yield). ^{1}H NMR (CD_3OD) δ 1.75 (s, 3H), 2.44 (s, 1H), 2.75−2.89 (m, 1H), 3.02−3.17 (m, 2H), 3.50−3.64 (m, 3H), 3.78 (s, 2H), 4.37−4.80 (m, 1H), 7.23−7.42 (m, 6H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.93 (d, $J = 7.7$ Hz, 1H).Anal. ($C_{21}H_{24}N_4O \cdot 2TFA$) C, H, N.

2-(2-Methylazetidin-2-yl)-1*H*-benzimidazole-4-carboxamide (11). Step 1: Preparation of Dibenzyl Azetidine-1,2-dicarboxylate (11-1). A suspension of benzyl azetidine-2-carboxylate[18] (4.0 g, 21 mmol) and K_2CO_3 (5 g, 36 mmol) in 1,4-dioxane (25 mL) and water (30 mL) was treated with benzyl chloroformate (3 mL, 21 mmol) at ambient temperature for 6 h. Piperazine (5 drops) was added and the mixture stirred for 30 min. The mixture was concentrated and the residue partitioned between EtOAc and 2N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated to give 6.8 g (96%) of the title compound. ^{1}H NMR (CD_3OD) δ 2.07−2.29 (m, 1H), 2.41−2.77 (m, 1H), 3.80−4.16 (m, 2H), 4.76 (dd, $J = 9.5$, 5.4 Hz, 1H), 5.03 (s, 2H), 5.16 (s, 2H), 7.24−7.46 (m, 10H). MS (DCI/NH_3) *m*/*z* 278 $(M + H)^+$.

Step 2: Preparation of 2-(2-Methylazetidin-2-yl)-1*H*-benzimidazole-4-carboxamide. The title compound was prepared from **11-1** according to procedure A (10% yield). ^{1}H NMR (CD_3OD) δ 1.81 (s, 3H), 2.36−2.44 (m, 2H), 2.88−2.99 (m, 1H), 3.00−3.12 (m, 1H), 7.40 (t, $J = 7.7$ Hz, 1H), 7.77 (d, $J = 8.3$ Hz, 1H), 7.95 (d, $J = 7.7$ Hz, 1H). MS (APCI) *m*/*z* 231 $(M + H)^+$.

2-(1-Isopropyl-2-methylazetidin-2-yl)-1*H*-benzimidazole-4-carboxamide (12). The title compound was prepared from **11** and acetone according to procedure B (34% yield). ^{1}H NMR (CD_3OD) δ 1.30 (d, $J = 6.5$, 6H), 1.81 (s, 3H), 2.30−2.56 (m, 2H), 2.92−3.06 (m, 1H), 3.08−3.23 (m, 1H), 3.33−3.50 (m, 1H), 7.40 (t, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 7.94 (d, 1H). MS (APCI) *m*/*z* 305 $(M + H)^+$.

2-(3-Methylazetidin-3-yl)-1*H*-benzimidazole-4-carboxamide (2a). The title compound was prepared from 1-benzyl 3-methyl azetidine-1,3-dicarboxylate[19] according to procedure A (36% yield). ^{1}H NMR (CD_3OD) δ 1.91 (br s, 3H), 4.22 (d, $J = 11.5$ Hz, 2H), 4.69 (d, $J = 11.5$ Hz, 2H), 7.39 (t, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.95 (d, $J = 7.5$ Hz, 1H). MS (APCI) *m*/*z* 231 $(M + H)^+$.

2-(2-Methylpiperidin-2-yl)-1*H*-benzimidazole-4-carboxamide (8a). Step 1: Preparation of 1-Benzyl 2-Methyl Piperidine-1,2-dicarboxylate (8a-1). A solution of 1-[(benzyloxy)carbonyl]piperidine-2-carboxylic acid (5 g, 19 mmol) and iodomethane (2.5 mL, 40 mmol) in DMF (40 mL) was treated with K_2CO_3 (3.8 g) and stirred at ambient temperature for 18 h. The mixture was concentrated and the residue partitioned between EtOAc and water. The organic phase was concentrated and the residue purified by flash chromatography on silica gel using EtOAc/hexane to provide 4.88 g (93%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.21−1.34 (m, 1H), 1.37−1.51 (m, 1H), 1.62−1.75 (m, 3H), 2.16−2.28 (m, 1H), 2.90−3.13 (m, 1H), 3.74 (s, 3H), 4.01−4.16 (m, 1H), 4.81−5.00 (m, 1H), 5.16 (s, 2H), 7.30−7.41 (m, 5H). MS (DCI/NH_3) *m*/*z* 278 $(M + H)^+$.

Step 2: Preparation of 2-(2-Methylpiperidin-2-yl)-1*H*-benzimidazole-4-carboxamide. The title compound was prepared from **8a-1** according to procedure A (20% yield). ^{1}H NMR (CD_3OD) δ 1.53−1.63 (m, 1H), 1.83 (s, 3H), 1.84−1.90 (m, 2H), 1.91−1.99 (m, 1H), 2.14−2.26 (m, 1H), 2.45 (dd, $J = 14.9$, 7.2 Hz, 1H), 3.37−3.51 (m, 2H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 8.01 (d, $J = 6.7$ Hz, 1H). MS (DCI/NH_3) *m*/*z* 245 $(M + H)^+$.

2-(2-Methyl-1-propylpiperidin-2-yl)-1*H*-benzimidazole-4-carboxamide (9a). The title compound was prepared from **8a** and propionaldehyde according to procedure B (11% yield). ^{1}H NMR (CD_3OD) δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.79−1.93 (m, 4H), 2.01 (s, 3H), 2.02−2.07 (m, 2H), 2.16−2.25 (m, 2H), 2.83−2.98 (m, 1H), 3.02−3.18 (m, 1H), 3.33−3.49 (m, 1H), 3.73−3.84 (m, 1H), 7.45 (t, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 8.03 (d, $J = 7.7$ Hz, 1H). HRMS *m*/*z* 301.20307 (calcd for $C_{17}H_{24}N_4O$ (M + H), 301.20229).

2-(4-Methylpiperidin-4-yl)-1*H*-benzimidazole-4-carboxamide (26). The title compound was prepared from 1-benzyl 4-ethyl piperidine-1,4-dicarboxylate according to procedure A (33% yield). ^{1}H NMR (CD_3OD) δ 1.53 (s, 3H), 2.01−2.12 (m, 2H), 2.62−2.73 (m, 2H), 3.13−3.22 (m, 2H), 3.36−3.44 (m, 2H), 7.38 (t, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 7.7$ Hz, 1H), 7.94 (d, $J = 7.7$ Hz, 1H); Anal. ($C_{14}H_{18}N_4O \cdot 2.6TFA$) C, H, N.

2-(1-Isopropyl-4-methylpiperidin-4-yl)-1*H*-benzimidazole-4-carboxamide (27). The title compound was prepared from **26** and acetone according to procedure B (49% yield). ^{1}H NMR (pyridine-d_5) δ 1.20 (d, J = 6.4 Hz, 6H), 1.51 (s, 3H), 2.48−2.70 (m, 2H), 2.73−2.91 (m, 2H), 3.15−3.32 (m, 2H), 3.33−3.52 (m, 3H), 7.39 (t, J = 7.8 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 8.59 (d, J = 7.7 Hz, 1H), 9.88 (s, 1H). Anal. ($C_{17}H_{24}N_4O$·2.1TFA) C, H, N.

2-(4-Methylazepan-4-yl)-1*H*-benzimidazole-4-carboxamide (10a). Step 1: Preparation of 1-*tert*-Butyl 4-Ethyl 5-Hydroxyazepane-1,4-dicarboxylate (10a-1). To a solution of 1-*tert*-butyl 4-ethyl 5-oxoazepane-1,4-dicarboxylate (7.0 g, 24.56 mmol) in MeOH (60 mL) was added $NaBH_4$ (933 mg, 24.56 mmol) in portions. The mixture was stirred at 0 °C for 2 h and concentrated. The residue was partitioned between EtOAc and brine and the organic phase washed with brine and concentrated. Purification by flash chromatography on silica gel using 60% EtOAc in hexane provided 3.2 g (46%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.27 (q, J = 7.2 Hz, 3H), 1.46 (s, 9H), 1.59−1.85 (m, 1H), 1.81−1.98 (m, 1H), 2.16−2.40 (m, 1H), 2.44−2.68 (m, 1H), 3.09−3.30 (m, 1H), 3.29−3.42 (m, 2H), 3.42−3.60 (m, 1H), 3.61−3.80 (m, 1H), 4.07−4.26 (m, 3H). MS (DCI/NH_3) m/z 288 $(M + H)^+$.

Step 2: Preparation of 1-*tert*-Butyl 4-Ethyl 2,3,6,7-Tetrahydro-1*H*-azepine-1,4-dicarboxylate (10a-2). To a solution of **10a-1** (3.65 g, 12.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.8 mL, 25.44 mmol) in CH_2Cl_2 (50 mL) was added methylsulfonylchloride (1.48 mL, 19.08 mmol) and the mixture stirred at reflux for 2 h. After cooling, the mixture was concentrated and the residue purified by flash chromatography on silica gel using 30% EtOAc in hexanes to provide 3.2 g (94%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.27 (t, J = 7.1 Hz, 3H), 1.46 (s, 9H), 2.48 (q, J = 5.8 Hz, 2H), 2.60−2.75 (m, 2H), 3.25−3.36 (m, 2H), 3.41−3.57 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 7.11 (t, J = 5.9 Hz, 1H). MS (DCI/NH_3) m/z 270 $(M + H)^+$.

Step 3: Preparation of 1-*tert*-Butyl 4-Ethyl 4-Methylazepane-1,4-dicarboxylate (10a-3). A solution of **10a-2** (0.54 g, 2.0 mmol) in of MeOH (20 mL) was treated with 10% Pd/C (50 mg) under hydrogen overnight. The solid was filtered off and the filtrate concentrated. The residue was purified by flash chromatography on silica gel using 20% EtOAc in hexane to give the saturated azepane intermediate, which was methylated according to procedure A, step 1 to give the title compound (37% yield). ^{1}H NMR (CD_3OD) δ 1.19−1.29 (m, 3H), 1.46 (s, 9H), 1.59−1.68 (m, 2H), 1.77−2.06 (m, 5H), 2.43−2.53 (m, 1H), 3.30−3.37 (m, 1H), 3.38−3.68 (m, 4H), 4.06−4.16 (m, 2H). MS (DCI/NH_3) m/z 286 $(M + H)^+$.

Step 4: 1-Benzyl 4-Ethyl 4-Methylazepane-1,4-dicarboxylate (10a-4). A solution of **10a-3**(1.4 g, 5.6 mmol) in THF (50 mL) was treated with TFA (2 mL) at ambient temperature overnight. After concentration, the residue was dissolved in dioxane (25 mL) and water (50 mL) and stirred at ambient temperature with K_2CO_3 (3 g) and benzyl chloroformate (0.82 mL, 5.6 mmol) for 6 h. Piperazine (5 drops) was added and the mixture stirred for 30 min. The mixture was concentrated and the residue partitioned between EtOAc and 2N HCl. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 1.48 g (85%) of the title compound. ^{1}H NMR (CD_3OD) δ 0.72−0.84 (m, 3H), 1.11−1.26 (m, 3H), 1.33−1.42 (m, 1H), 1.41−1.56 (m, 1H), 1.56−1.65 (m, 1H), 1.64−1.72 (m, 1H), 1.71−1.86 (m, 1H), 2.01−2.11 (m, 1H), 2.19 (dd, J = 14.8, 3.3 Hz, 1H), 3.32−3.49 (m, 2H), 3.53−3.66 (m, 1H), 4.03−4.17 (m, 2H), 5.10 (s, 2H), 7.25−7.40 (m, 5H). MS (DCI/NH_3) m/z 306 $(M + H)^+$.

Step 5: Preparation of 2-(4-Methylazepan-4-yl)-1*H*-benzimidazole-4-carboxamide. The title compound was prepared from **10a-4** according to procedure A (19% yield). ^{1}H NMR (CD_3OD) δ 1.56 (s, 3H), 1.88−1.97 (m, 1H), 1.97−2.05 (m, 1H), 2.05−2.13 (m, 1H), 2.16−2.26 (m, 1H), 2.57 (dd, J = 15.0, 8.1 Hz, 1H), 2.82 (dd, J = 16.2, 6.9 Hz, 1H), 3.22−3.29 (m, 1H), 3.29−3.33 (m, 1H), 3.34−3.49 (m, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 6.9 Hz, 1H). Anal. ($C_{15}H_{20}N_4O$·2.8TFA) C, H, N.

2-(1-Cyclopentyl-4-methylazepan-4-yl)-1*H*-benzimidazole-4-carboxamide (28). The title compound was prepared from **10a** and cyclopentanone according to procedure B (18% yield). ^{1}H NMR (CD_3OD) δ 1.50−1.53 (m, 3H), 1.54−1.60 (m, 1H), 1.62−1.78 (m, 4H), 1.85 (s, 2H), 1.90−2.07 (m, 3H), 2.07−2.28 (m, 3H), 2.30−2.67 (m, 1H), 2.69−3.02 (m, 1H), 3.11−3.28 (m, 1H), 3.35−3.49 (m, 1H), 3.50−3.79 (m, 2H), 7.40 (t, 1H), 7.74 (d, 1H), 7.94 (d, J = 6.9 Hz, 1H). HRMS m/z 341.23401 (calcd for $C_{20}H_{28}N_4O$ (M + H), 341.23359).

2-[1-(2-Fluorobenzyl)-3-methylpyrrolidin-3-yl]-1*H*-benzimidazole-4-carboxamide (18). The title compound was prepared from **6a** and 2-fluorobenzaldehyde according to procedure B (18% yield). ^{1}H NMR (CD_3OD) δ 1.74 (s, 3H), 2.43 (m, 1H), 2.82 (m, 1H), 3.62 (m, 2H), 3.70 (m, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.62 (s, 2H), 7.36 (m, 3H), 7.52 (m, 1H), 7.63 (m, 1H), 7.71 (d, J = 7.3 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H). HRMS m/z 353.17753 (calcd for $C_{20}H_{21}FN_4O$ (M + H), 353.17722).

2-(2-Methylpyrrolidin-2-yl)-6-trifluoromethyl-1*H*-benzimidazole-4-carboxamide (25). Step 1: Preparation of Benzyl 2-(4-Bromo-6-trifluoromethyl-1*H*-benzimidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (25-1). A solution of 1-[(benzyloxy)carbonyl]-2-methylpyrrolidine-2-carboxylic acid (1.0 g, 3.8 mmol) in pyridine (15 mL) and DMF (15 mL) was treated with CDI (739 mg, 4.6 mmol) at 40 °C for 30 min. 2,3-Diamino-1-bromo-5-trifluoromethylbenzene (969 mg, 3.8 mmol) was added and the mixture stirred at ambient temperature overnight. After concentration, the residue was stirred in AcOH (20 mL) at 80 °C overnight. After cooling and concentration, the residue was purified by flash chromatography on silica gel using EtOAc to give 500 mg (30%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.91 (s, 1.5H), 1.96 (s, 1.5H), 2.00−2.39 (m, 4H), 3.69−3.77 (m, 1H), 3.83−3.93 (m, 1H), 4.57−4.70 (m, 0.5H), 5.01−5.14 (m, 1.5H), 6.69 (t, J = 6.8 Hz, 1H), 6.88 (t, J = 6.8 Hz, 1H), 6.97−7.03 (m, 1H), 7.29−7.37 (m, 2H), 7.52 (s, 0.5H), 7.64 (s, 1H), 7.74 (d, J = 4.1 Hz, 0.5H), as a mixture of rotamers. MS (DCI/NH_3) m/z 483 $(M + H)^+$.

Step 2: Preparation of Benzyl 2-(4-Cyano-6-trifluoromethyl-1*H*-benzimidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (25-2). A mixture of **25-1** (482 mg, 1.0 mmol), zinc cyanide (293 mg, 1.2 mmol), and tetrakis(triphenylphosphine)palladium(0) (231 mg, 0.2 mmol) in DMF (15 mL) was heated at 90 °C overnight. After cooling, the mixture was partitioned between EtOAc and brine and the organic phase washed with brine and water. After concentration, the residue was purified by flash chromatography on silica gel using EtOAc to provide 320 mg (75%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H), 1.91−2.17 (m, 4H), 3.62 (t, J = 6.6 Hz, 2H), 5.21 (s, 2H), 7.32−7.41 (m, 5H), 7.82 (s, 1H), 8.06 (s, 1H). MS (DCI/NH_3) m/z 429 $(M + H)^+$.

Step 3: Preparation of 2-(2-Methylpyrrolidin-2-yl)-6-trifluoromethyl-1*H*-benzimidazole-4-carboxamide. A solution of **25-2** (50 mg, 0.12 mmol) in 38% HBr in AcOH (10 mL) was stirred at ambient temperature overnight. The mixture was concentrated and the residue purified by HPLC (Zorbax, C-18, 0.1% TFA/water/acetonitrile) to provide 24 mg (39%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.97 (s, 3H), 2.12 (m, 1H), 2.33 (m, 1H), 2.43 (m, 1H), 2.63 (m, 1H), 3.65 (m, 2H), 8.06 (s, 1H), 8.24 (s, 1H). Anal. ($C_{14}H_{15}F_3N_4O$·1.8TFA) C, H, N.

(*R*)-6-Chloro-2-(2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (24). Step 1: Preparation of 2-Amino-5-chloro-3-nitro-benzamide (24-1). A solution of 2-amino-3-nitrobenzamide[13] (4.0 g, 22.08 mmol) in acetonitrile (1250 mL) was treated with *N*-chlorosuccinimide (3.1 g, 23.18 mmol) at 60 °C overnight. After cooling, the orange solid was filtered, washed with acetonitrile, and dried to give 2.95 g of the title compound. The mother liquor was concentrated and the residue recrystallized from acetonitrile to give an additional 800 mg (79% total yield). ^{1}H NMR (DMSO-d_6) δ 7.75 (br s, 1H), 8.00 (d, J = 2.4 Hz, 1H), 8.19 (d, J = 2.7 Hz, 1H), 8.25 (br s, 1H), 8.47 (br s, 2H). MS (DCI/NH_3) m/z 216 $(M + H)^+$.

Step 2: Preparation of 2,3-Diamino-5-chlorobenzamide (24-2). A solution of **24-1** (650 mg, 3.0 mmol) in THF (100 mL) and EtOH (100 mL) was treated with Raney nickel (50% in water, 300

mg) under hydrogen at ambient temperature for 3 h. Solid was filtered off and the filtrate treated with 1 M HCl in Et_2O (6 mL) and concentrated to give 780 mg (100%) of the title compound. ^{1}H NMR (DMSO-d_6) δ 4.88 (br s, 4H), 7.21 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.57 (br s, 1H), 8.12 (br s, 1H). MS (DCI/NH_3) m/z 186 $(M + H)^+$.

Step 3: Preparation of (*R*)-6-Chloro-2-(2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide. To a solution of (*R*)-2-methylpyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (**23-4**, 500 mg, 1.9 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.17 mL, 1.9 mmol) followed by addition of 2 drops of DMF and the mixture stirred at ambient temperature for 1 h. The mixture was concentrated and the residue dissolved in CH_2Cl_2 (10 mL). This solution was added to a solution of **24-2** (353 mg, 1.9 mmol) and triethylamine (2 mL) in THF (20 mL) and the mixture stirred at ambient temperature overnight. The mixture was partitioned between EtOAc and 0.5 M NaOH and the organic layer separated, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in AcOH (50 mL) and heated at 80 °C overnight. The mixture was cooled and concentrated and the residue purified by flash chromatography on silica gel using EtOAc to give benzyl (*R*)-2-(4-carbamoyl-6-chloro-1*H*-benzimidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (690 mg, 88%). The protected intermediate was stirred in TFA (50 mL) at 50 °C for 6 h, cooled, and concentrated. The residue was purified by HPLC (Zorbax C-18, 0.1% TFA/acetonitrile/water) to give 180 mg (30%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.95 (s, 3H), 2.10 (m, 1H), 2.28 (m, 1H), 2.40 (m, 1H), 2.60 (m, 1H), 3.65 (m, 2H), 7.73 (s, 1H), 7.88 (s, 1H). Anal. ($C_{13}H_{15}ClN_4O \cdot 1.5TFA$) C, H, N.

(*R*)-6-Fluoro-2-(2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (23). Step 1: Preparation of 2-Amino-5-fluoro-3-nitrobenzonitrile (23-1). A suspension of 2-bromo-4-fluoro-6-nitrophenylamine (35 g, 0.15 mol), zinc cyanide (34.98 g, 0.3 mol), and tetrakis(triphenyphosphine)palladium(0) (12.05 g, 10 mmol) in DMF (420 mL) was heated under nitrogen at 95 °C for 22 h. After cooling, insoluble material was filtered off and the filtrate partitioned between EtOAc and brine. The organic phase was washed with water and concentrated and the residue recrystallized from MeOH to provide 24 g (89%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 6.63 (br s, 2H), 7.53 (dd, J = 6.4, 3.1 Hz, 1H), 8.15 (dd, J = 8.5, 3.1 Hz, 1H). MS (DCI/NH_3) m/z 182 $(M + H)^+$.

Step 2: Preparation of 2-Amino-5-fluoro-3-nitrobenzamide (23-2). Compound **23-1** (13.95 g, 77 mmol) and polyphosphoric acid (200 g) were stirred at 115 °C for 3 h. After cooling, water and CH_2Cl_2 were added and the precipitate filtered and recrystallized from MeOH to yield 11.3 g (74%) of the title compound. ^{1}H NMR (CD_3OD) δ 7.78 (dd, J = 8.5, 3.0 Hz, 1H), 8.04 (dd, J = 8.8, 3.0 Hz, 1H). MS (DCI/NH_3) m/z 200 $(M + H)^+$.

Step 3: Preparation of 2,3-Diamino-5-fluorobenzamide (23-3). A solution of **23-2** (11.2 g, 56.28 mmol) in 1:1 THF/EtOH (100 mL) and Raney Ni (11 g) was stirred under hydrogen for 16 h. The catalyst was filtered off, and the filtrate concentrated to provide 9.1 g (96%) of the title compound. ^{1}H NMR (DMSO-d_6) δ 5.00 (br s, 2H), 5.94 (br s, 2H), 6.45 (dd, J = 10.3, 2.9 Hz, 1H), 6.68 (dd, J = 10.5, 2.7 Hz, 1H), 7.07 (br s, 1H), 7.64 (br s, 1H). MS (DCI/NH_3) m/z 170 $(M + H)^+$.

Step 4: Preparation of (*R*)-2-Methylpyrrolidine-1,2-dicarboxylic Acid 1-Benzyl Ester (23-4). A solution of (*R*)-2-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester[20] (20 g, 87 mmol) in CH_2Cl_2 (150 mL) was treated with TFA (80 mL) at 0 °C and the mixture stirred at ambient temperature for 3 h. Acetonitrile was added and the mixture concentrated. To a solution of the residue in THF (150 mL) and water (150 mL) was added cesium carbonate (170.5 g) and benzyl chloroformate (14.7 mL) and the mixture stirred at ambient temperature for 16 h. After concentration, the residue was diluted with 0.5N NaOH and extracted with 20% Et_2O in hexane. The aqueous layer was acidified to pH 3 with 2N HCl and the solution extracted with EtOAc. The combined organic extracts were concentrated and the residue purified by flash chromatography on silica gel using 5−90% EtOAc in hexane to provide 22.7 g (99%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.61−1.70 (m, 3H), 1.83−1.95 (m, 2H), 2.41−2.59 (m, 1H), 3.50−3.73 (m, 3H), 5.16 (s, 2H), 7.28−7.39 (m, 5H). MS (DCI/NH_3) m/z 264 $(M + H)^+$.

Step 5: Preparation of Benzyl 2-(4-Cyano-6-fluoro-1*H*-benzimidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (23-5). To a solution of **23-4** (389 mg, 1.48 mmol) in CH_2Cl_2 (5 mL) was added oxalyl chloride (0.2 mL, 2.22 mmol) and one drop of DMF and the mixture stirred at ambient temperature for 1 h. The mixture was concentrated, dissolved in CH_2Cl_2 (5 mL), and added to a solution of **23-3** (250 mg, 1.48 mmol) in THF (8 mL). Triethylamine (0.25 mL, 1.78 mmol) was added and the mixture stirred for 18 h. The mixture was concentrated and stirred in AcOH (15 mL) at reflux for 2 h. The mixture was cooled and concentrated and the residue partitioned between EtOAc and $NaHCO_3$ solution. The organic phase was washed with water and concentrated and the residue purified by flash chromatography on silica gel using 60% EtOAc in hexanes to provide 387 mg (66%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.90 (s, 3H), 2.02−2.12 (m, 2H), 2.16−2.40 (m, 2H), 3.67−3.90 (m, 2H), 5.07 (d, J = 3.7 Hz, 2H), 6.71 (d, J = 7.8 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.22 (dd, J = 8.3, 2.5 Hz, 1H), 7.30−7.39 (m, 2H), 7.63 (dd, J = 10.7, 2.5 Hz, 1H). MS (DCI/NH_3) m/z 397 $(M + H)^+$.

Step 6: Preparation of (*R*)-6-Fluoro-2-(2-methylpyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide. A mixture of **23-5** (1 g) and 10% Pd/C (150 mg) in 2:1 MeOH/CH_2Cl_2 was stirred under hydrogen at ambient temperature for 18 h. Solid material was filtered off and the filtrate concentrated. The residue was washed with Et_2O and dried to provide 593 mg (90%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.96 (s, 3H), 2.05−2.14 (m, 1H), 2.26−2.36 (m, 1H), 2.38−2.47 (m, 1H), 2.56−2.65 (m, 1H), 3.57−3.63 (m, 1H), 3.64−3.70 (m, 1H), 7.52 (dd, J = 8.2, 2.4 Hz, 1H), 7.72 (dd, J = 10.4, 2.4 Hz, 1H). Anal. ($C_{13}H_{15}FN_4O \cdot 2.4HCl \cdot 0.3\ H_2O$) C, H, N.

(*R*)-2-(2-Methyl-5-*oxo*-pyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide (20). Step 1: Preparation of (*R*)-2-Methyl-5-*oxo*-pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester (20-1). To a solution of (*R*)-2-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (3.48 g, 15.2 mmol) in acetonitrile (30 mL), CCl_4 (30 mL), and water (46 mL) was added sodium periodate (13 g, 60.8 mmol) and ruthenium(III) chloride hydrate (640 mg, 3.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and at ambient temperature for 2 d. Solid material was filtered off and the filtrate concentrated. The residue was partitioned between EtOAc and brine and the organic phase washed with brine and concentrated. The residue was purified by flash chromatography on silica gel using 0−15% MeOH in 2:1 EtOAc/hexane to give 2.46 g (67%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 1.69 (s, 3H), 1.92−2.04 (m, 1H), 2.26−2.37 (m, 1H), 2.51−2.72 (m, 2H). MS (DCI/NH_3) m/z 244 $(M + H)^+$.

Step 2: Preparation of (*R*)-2-(2-Methyl-5-*oxo*-pyrrolidin-2-yl)-1*H*-benzimidazole-4-carboxamide. A solution of **20−1** (120 mg, 0.49 mmol) in pyridine (3 mL) and DMF (3 mL) was stirred with CDI (88 mg, 0.54 mmol) at 45 °C for 2 h. 2,3-Diaminobenzamide dihydrochloride[13] (110 mg, 0.49 mmol) was added and the mixture stirred at ambient temperature overnight. After concentration, the residue was heated at 80 °C in AcOH (6 mL) for 3 h, cooled, and concentrated. The residue was purified by flash chromatography on silica gel using 0−15% MeOH in CH_2Cl_2, followed by purification by HPLC (Zorbax, C-18, 0.1% TFA/water/acetonitrile) to provide 80 mg (36%) of the title compound. ^{1}H NMR (CD_3OD) δ 1.88 (s, 3H), 2.41−2.48 (m, 1H), 2.50−2.55 (m, 2H), 2.58−2.66 (m, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H). Anal. ($C_{13}H_{14}N_4O_2 \cdot 1.75TFA$) C, H, N.

2-(1-Isopropyl-3-methylazetidin-3-yl)-1*H*-benzimidazole-4-carboxamide (13). The title compound was prepared from **2a** and acetone according to procedure B (21% yield). ^{1}H NMR (CD_3OD) δ 1.30 (d, J = 6.4 Hz, 6H), 1.73−2.06 (br, 3H), 3.47−3.69 (m, 1H), 4.35 (d, J = 10.7 Hz, 2H), 4.73 (t, 2H), 7.39 (t, J = 8.0 Hz,

1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.95 (d, $J = 7.7$ Hz, 1H). Anal. ($C_{15}H_{20}N_4O \cdot 2.5$TFA) C, H, N.

2-(1,3-Dimethylpyrrolidin-3-yl)-1*H*-benzimidazole-4-carboxamide (17). The title compound was prepared from **6a** according to procedure B (14% yield). ^{1}H NMR (CD_3OD) δ 1.74 (s, 3H), 2.22−2.55 (m, 1H), 2.66−2.86 (m, 1H), 3.06 (s, 3H), 3.35−3.54 (m, 1H), 3.60−3.92 (m, 1H), 4.08−4.29 (m, 1H), 4.44−4.65 (m, 1H), 7.37 (t, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.93 (d, $J = 7.5$ Hz, 1H). Anal. ($C_{14}H_{18}N_4O \cdot 2.7$TFA) C, H, N.

Supporting Information Available: Microanalytical data for target compounds **3a**, **4a**, **5a**, **6a**, **7a**, **10a**, **13**−**17**, and **19**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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