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Hepatitis C Virus NS5A Replication Complex Inhibitors. Part 6: Discovery of a Novel and Highly Potent Biarylimidazole Chemotype with Inhibitory Activity Toward Genotypes 1a and 1b Replicons

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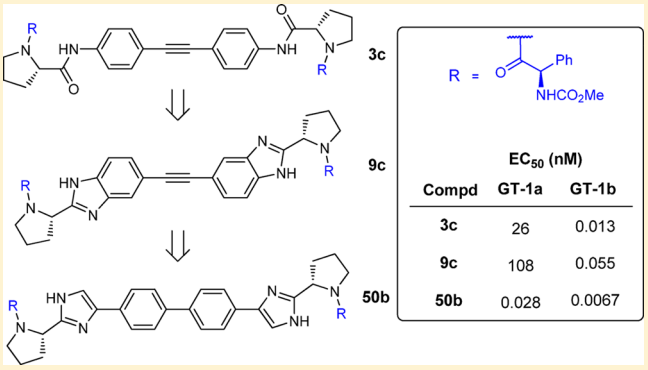
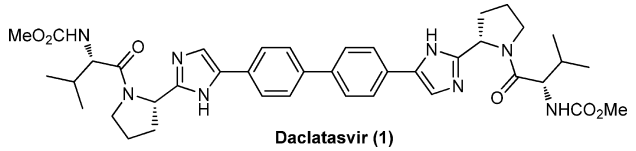
ABSTRACT: A medicinal chemistry campaign that was conducted to address a potential genotoxic liability associated with an aniline-derived scaffold in a series of HCV NS5A inhibitors with dual GT-1a/-1b inhibitory activity is described. Anilides **3b** and **3c** were used as vehicles to explore structural modifications that retained antiviral potency while removing the potential for metabolism-based unmasking of the embedded aniline. This effort resulted in the discovery of a highly potent biarylimidazole chemotype that established a potency benchmark in replicon assays, particularly toward HCV GT-1a, a strain with significant clinical importance. Securing potent GT-1a activity in a chemotype class lacking overt structural liabilities was a critical milestone in the effort to realize the full clinical potential of targeting the HCV NS5A protein.



INTRODUCTION

The hepatitis C virus (HCV) field is expected to experience a significant change in treatment paradigm over the next few years as a consequence of drug-discovery efforts sustained across both the pharmaceutical industry and academia during the past 2 decades.[1] A major focus of this endeavor has been the functional disruption of the virus' key nonstructural proteins, most notably, NS3/4A, NS5A, and NS5B, with direct-acting antiviral agents (DAAs). Various DAA combinations have reached late-stage clinical development and are exhibiting superior efficacy and tolerability compared to the current interferon-based regimens.[2]

Previously, we have disclosed the clinical validation of the NS5A protein as an antiviral target with daclatasvir (**1**)



Daclatasvir (1)

as well as various facets of the initial structure−activity relationship (SAR) investigations that, among others, uncovered a class of glycinamide cap derivatives that enhanced the genotype-1a (GT-1a) inhibitory potency of an early NS5A lead series (Figure 1, **3b** and **3c**).[3] Although the improved potency was encouraging, the significant disparity observed between GT-1a and GT-1b inhibition suggested that an additional gain in potency toward GT-1a was possible. In addition, although the stilbene core and its alkyne variant were useful scaffolds for exploring the SARs at the periphery of the molecule, there was

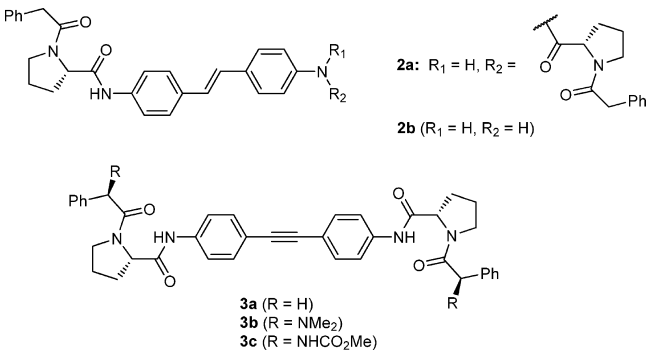


Figure 1. Selected analogues of anilide series.

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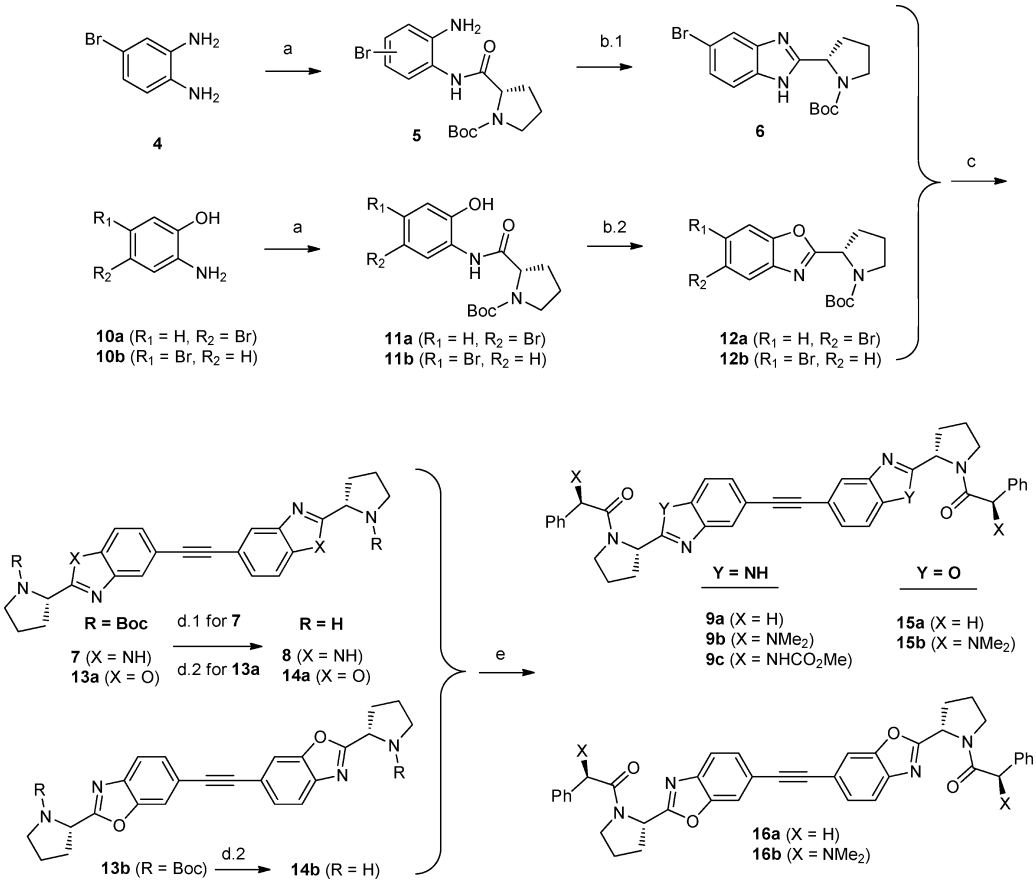
Scheme 1. Preparation of Analogues with Benzimidazole and Benzoxazole Scaffolds[a]



[a]Reagents and conditions: (a) *N*-Boc-L-proline, HOBT, EDCI, CH_2Cl_2; (b.1) AcOH, 65 °C; (b.2) DIAD, Ph_3P, THF; (c) $Me_3Sn{\equiv}SnMe_3$, $Pd(Ph_3P)_4$, DMF, 80 °C; (d.1) HCl/dioxane/MeOH; (d.2) 20% TFA/CH_2Cl_2; (e) RCO_2H, HATU, DIEA, DMF.

some concern about the embedded aniline moiety because it may pose a risk for genotoxicity in the event that it is released in vivo by hydrolytic enzymes and becomes activated by further metabolism in the liver.[4] For example, it was observed that although anilide **2a** was nonmutagenic in an Ames assay, both with and without rat liver S9 homogenate, aniline **2b** was mutagenic when assayed in the presence of rat liver S9 homogenate. Although the susceptibility of the anilide bond to hydrolysis, in vivo or otherwise, was not examined, we opted to explore structural replacements to eliminate the potential liability.[5,6] A compound with a phenylacetamide cap that lacked GT-1a inhibitory activity and two analogues with glycinamide caps, representing previously disclosed basic and nonbasic series exhibiting enhanced GT-1a inhibitory activities, were chosen for this exercise (see the caps of structure **3**).[3b] Herein, we describe the campaign that achieved these objectives through the discovery of a novel and potent biarylimidazole chemotype, the parental series of **1**, by capitalizing on a number of key SAR findings including an interesting interplay between GT-1a inhibitory potency and core topology.

CHEMISTRY, RESULTS, AND DISCUSSION

Single-crystal X-ray analyses of relevant proline−anilide structural fragments indicated that the amide bond of anilides is coplanar with the phenyl ring and thus, as part of an initial examination of replacements that would act as bioisosteres, the amide moiety was integrated onto the phenyl group, as exemplified by benzimidazole **9** or regioisomeric benzoxazoles **15** and **16**.[3b,7−9] It was reasoned that the benzimidazole group in **9** would retain both the H-bond accepting and H-bond donating properties of the anilide moiety in **3**, with its tautomers providing alternate modes of H-bond interactions with the NS5A protein, whereas benzoxazole variants **15** and **16** would be able to participate as only H-bond acceptors, likely through nitrogen, with defined but differing trajectories.[10]

The synthetic route to assemble the benzimidazole chemotype is outlined in Scheme 1. Diaminobenzene **4** was coupled with *N*-Boc-L-proline to afford anilide **5**, which was cyclized to benzimidazole **6** by heating in acetic acid. Coupling benzimidazole **6** with 1,2-bis(trimethylstannyl)ethyne followed by acid-mediated Boc deprotection afforded penultimate precursor **8**. Final products were prepared from **8** and the appropriate carboxylic acid cap precursors under standard HATU/DIEA-coupling conditions and purified by reverse-phase preparative HPLC.

The compounds were screened for their inhibitory activities in GT-1a and GT-1b replicons and cellular toxicity in a GT-1b replicon. In addition, specificity for HCV was assessed using a BVDV replicon that shared the same cellular background, Huh-7 cells, as that of the activity screens. A subset of the analogues were also assayed in a GT-1b LV/YH double-resistant mutant replicon to corroborate target specificity.[11]

Replicon evaluation of **9a−c** indicated that although the benzimidazole class still maintained subnanomolar levels of GT-1b inhibitory potency for the glycinamide cap analogues there was a loss in GT-1a inhibitory activity (Table 1). For

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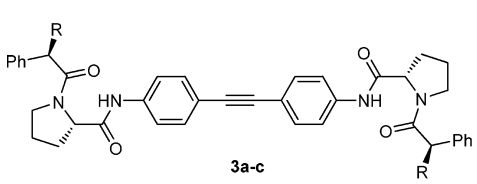
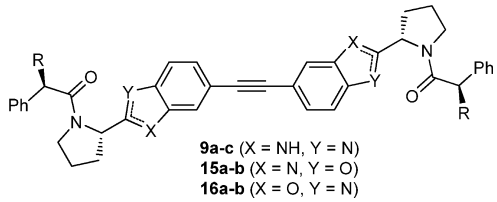
Table 1. Activity and Specificity of Anilides 3, Benzimidazoles 9, and Benzoxazoles 15 and 16[a,b]

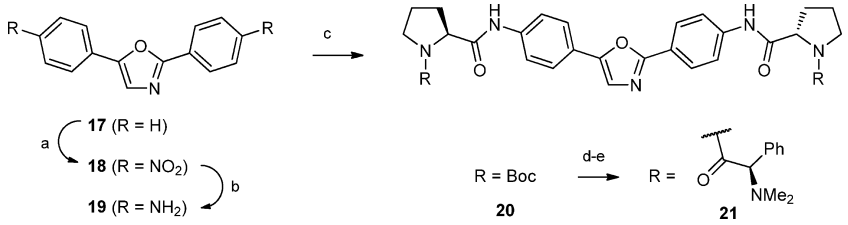




		HCV replicon inhibitory activity			
compd	R	GT-1a EC_{50} (nM)	GT-1b EC_{50} (nM)	GT-1b CC_{50} (nM)	BVDV EC_{50} (nM)
3a	H	>400	5.6	$>10^4$	$>10^4$
3b[c]	NMe_2	<4.6, 13	<4.6	5390	1900
3c[c]	$NHCO_2Me$	26	0.013	$>10^4$	$>10^4$
9a	H	>100	<4.6	$>10^4$	$>10^4$
9b	NMe_2	232	0.075	6390	3420
9c[d]	$NHCO_2Me$	108	0.055	$>10^4$	$>10^4$
15a	H	$>10^3$	$>10^3$	$>10^4$	412
15b	NMe_2	$>10^3$	$>10^3$	4450	1390
16a	H	$>10^3$	$>10^3$	$>10^4$	7980
16b[d]	NMe_2	$>10^3$	<4.6	2720	390

[a]Data represent mean values of at least two experiments. [b]Activity assessment: GT-1a, FRET (**3a** and **9a**) or ELISA (remaining set); GT-1b, FRET; and BVDV, luciferase. Cytotoxicity assessment: GT-1b, alamar blue. [c]Data disclosed previously in ref 3b. [d]EC_{50} in GT-1b LV/YH resistant replicon: **9c** (>3330 nM) and **16b** ($>10^3$ nM).

Scheme 2. Preparation of Compound 21[a]



[a]Reagents and conditions: (a) HNO_3/H_2SO_4; (b) 1 atm H_2, 20% $Pd(OH)_2/C$, MeOH/EtOAc; (c) *N*-Boc-L-proline, EEDQ, CH_2Cl_2; (d) HCl/dioxane/MeOH; (e) (*R*)-$PhCH(NMe_2)CO_2H$, HATU, DIEA, DMF.

example, **9b** and **9c** were 26- and 4.2-fold weaker than their anilide counterparts toward the GT-1a replicon, respectively. Although the maintenance of a potent inhibitory activity toward the GT-1b replicon with the benzimidazole chemotype was encouraging, the loss in GT-1a inhibitory potency foreshadowed the challenge encountered subsequently in maintaining and/or enhancing GT-1a coverage while optimizing other parameters.

Preliminary pharmacokinetic assessments of **9b** and **9c** in 4 h rat PK screens (PO: 5 mg/kg, PEG-400 vehicle, $n = 2$) indicated moderate-to-poor systemic exposure (AUC_{4h} < LLQ for **9b** and AUC_{4h} = 466 nM·h for **9c**). In a follow up 24 h rat PK study (IV/PO: 2/5 mg/kg, PEG-400 vehicle, $n = 3$), **9c** had a CL_{iv} of 1.1 mL/min/kg, a PO-AUC_{24h} of 539 ± 19 nM·h, and an oral bioavailability of <1%. Because **9c** had low clearance, it was postulated that the poor systemic exposure after oral dosing could be a reflection of poor permeability, with P-glycoprotein efflux likely making an additional contribution based on performance in a Caco-2 bidirectional assay (e.g., **9c**: B−A/A−B efflux ratio ≥ 7.2).

Benzoxazoles **15** and **16** were assembled from aminophenols **10a** and **10b**, respectively, according to the route illustrated in Scheme 1. Capricious instability was observed during acid-catalyzed Boc deprotection and/or reverse-phase HPLC purification of the final products under acidic medium ($MeOH/H_2O/TFA$).[12] According to LC/MS analyses, the degradation products, formed as minor components, were consistent with the hydration of one of the benzoxazole moieties, accompanied in some instances by the cleavage of the putative aminobenzoate intermediate to afford aminophenol derivatives. Considering the fact that the primary objective for this exercise was to avoid a potential genotoxic liability by minimizing the formation of anilinic species, this instability issue was of some concern in the context of oral dosing. Nevertheless, final products with targeted purity (≥95%) were obtained through flash chromatography, and we opted to profile their HCV inhibitory activities for a fuller appreciation of the unfolding SAR while being mindful of the need to interpret the pertinent activity data carefully. Surprisingly, compounds **15a**, **15b**, and **16a** were essentially inactive in both GT-1a and GT-1b replicons, whereas **16b** exhibited potent inhibitory activity toward GT-1b replicon accompanied with a noticeable signal in the BVDV assay (Table 1). Although the stability of the benzoxazole analogues in the replicon medium was not examined closely, the possibility that the compounds may have degraded to variable extents during the course of the assay could not be ruled out.[13] Consequently, it is possible that the observed potency may not be a true reflection of the nature of the interaction that would have transpired between the targeted dimeric benzoxazoles and the NS5A protein.

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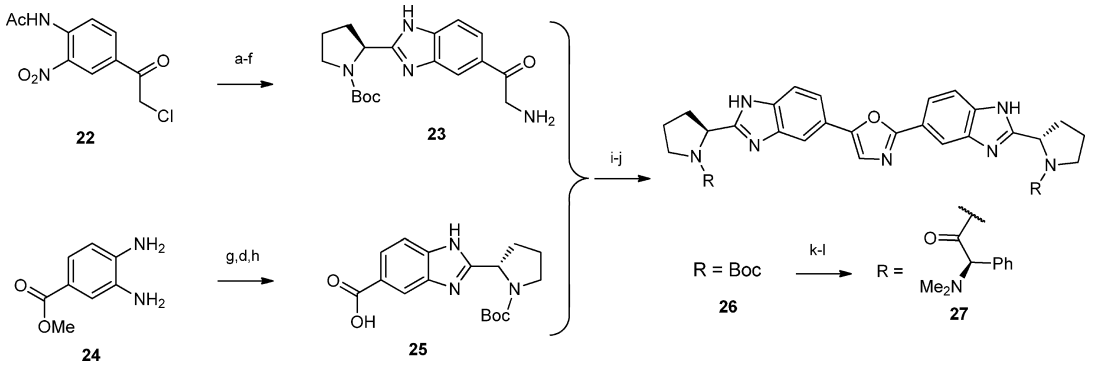
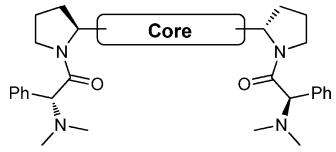
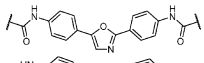
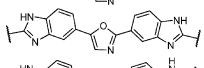
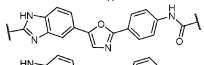
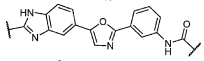
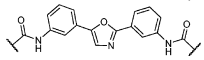
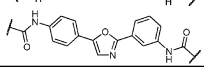
Scheme 3. Preparation Oxazole-Linked *bis*-Benzimidazole Analogues[a]



[a]Reagents and conditions: (a) 3 N HCl/H_2O, 80 °C; (b) $SnCl_2{\cdot}2H_2O$, MeOH, 70 °C; (c) *N*-Boc-L-proline, HATU, DIEA, DMF; (d) AcOH, 60 °C; (e) NaN_3, CH_3CN, 60 °C; (f) $SnCl_2{\cdot}2H_2O$, MeOH, 60 °C; (g) *N*-Boc-L-proline, *i*-BuO_2CCl, *N*-methylmorpholine, DIEA, THF; (h) NaOH, MeOH; (i) HATU, DIEA, DMF; (j) C_2Cl_6, Ph_3P, Et_3N, CH_2Cl_2; (k) HCl/MeOH/dioxane, 0 °C to rt; (l) (*R*)-$PhCH(NMe_2)CO_2H$, HATU, DIEA, DMF.

Table 2. Activity and Specificity of Oxazole-Linked Analogues[a,b]



Compd	Core	HCV Replicon Inhibitory Activity		GT-1b CC_{50} (nM)	BVDV EC_{50} (nM)
		GT-1a EC_{50} (nM)	GT-1b EC_{50} (nM)		
21		568	677	6010	1570
27		973	<4.6	$>10^4$	4960
31a		251	0.077	$>10^4$	>370
31b[c]		3.5	0.14	8610	3090
38a		738	0.16	4730	1160
38b		1.6	0.39	5760	1220

[a]Data represent mean values of at least two experiments. [b]Activity assessment: GT-1a, FRET (**21**, **38a**, **38b**) or ELISA (remaining set); GT-1b, FRET; and BVDV, luciferase. Cytotoxicity assessment: GT-1b, alamar blue. [c]EC_{50} in GT-1b LV/YH resistant replicon: $>10^3$ nM.

Evidently, the benzoxazole investigation was neither productive nor truly informative.

At this juncture, attention was redirected to the benzimidazole series, and consideration was given to the various factors that could have caused the potency to diminish, particularly toward GT-1a. It was apparent that tying back the amide unit in **3** onto the phenyl ring to afford benzimidazole **9** resulted in both a change in the vectorial disposition of the peripheral components and a localized conformational restriction around what appears to be an important H-bond donating/accepting element. To obtain a better understanding on how changes in these parameters may affect the GT-1a activity, two distinct SAR explorations were pursued: one approach focused on examining the ramifications of an anilide-to-benzimidazole conversion within the context of an oxazole-linked scaffold, providing topologies that are distinct from that of the original alkyne series, and the second approach focused on identifying an alternate replacement for the anilide moiety that, among others, was conformationally more flexible than benzimidazole.

Anilide-oxazole **21** was prepared readily from biphenyloxazole **17** through the adoption of a route communicated previously (Scheme 2).[14] The modular assembly of benzimidazole **27** from precursors **22** and **24** is illustrated in Scheme 3. A key step of the devised route involved the construction of the oxazole linker through the condensation of aminoketone **23** and carboxylic acid **25** followed by dehydration. Replacement of the alkyne linker in **3b** with an oxazole, as in **21**, resulted in >60-fold potency loss toward both the GT-1a and GT-1b replicons (Table 2).[15] The significant loss in potency, particularly toward GT-1b, was unexpected, and it was not apparent at this stage which of the modified molecular parameters, core vector or linker polarity, was the primary contributing factor. Interestingly, when both anilide moieties of **21** were replaced with benzimidazoles, as in **27**, the GT-1b activity improved by >100-fold, whereas the GT-1a activity

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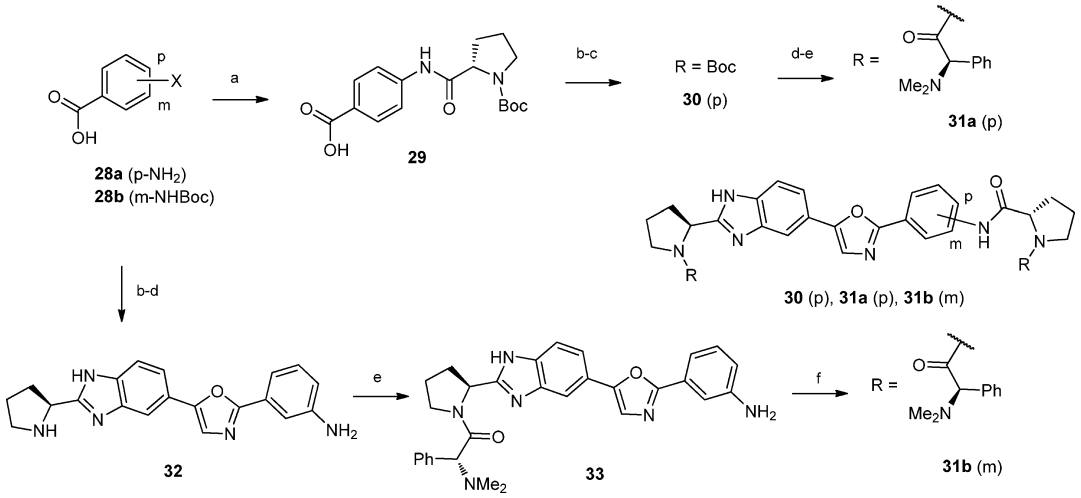
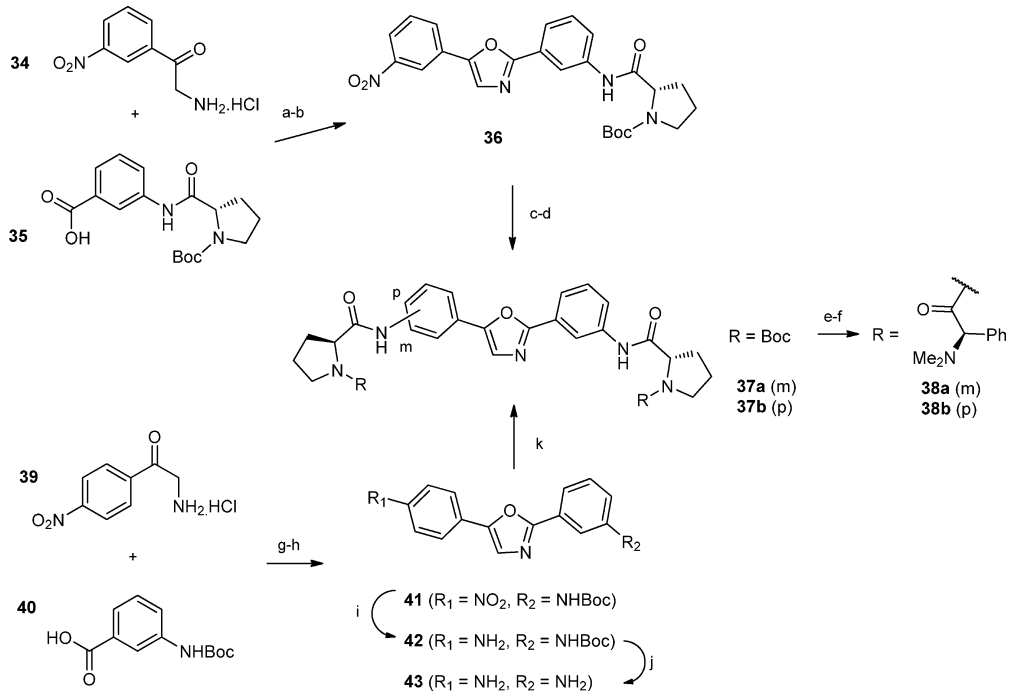
Scheme 4. Preparation of Oxazole-Linked Benzimidazole-Anilide Hybrid Analogues[a]



[a]Reagents and conditions: (a) *N*-Boc-L-proline, EDCI, CH_2Cl_2; (b) **23**, HATU, DIEA, DMF; (c) C_2Cl_6, Ph_3P, Et_3N, CH_2Cl_2; (d) HCl/MeOH/dioxane, 0 °C to rt; (e) (*R*)-PhCH(NMe_2)CO_2H, HATU, DIEA, DMF; (f) (2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxylic acid, HATU, DIEA, DMF.

Scheme 5. Preparation of Regioisomeric Oxazole-Linked Anilides 38a and 38b[a]



[a]Reagents and conditions: (a) HATU, DIEA, DMF; (b) C_2Cl_6, Ph_3P, Et_3N, CH_2Cl_2; (c) H_2 (20 psi), 10% Pd/C, MeOH; (d) *N*-Boc-L-proline, HATU, DIEA, DMF; (e) HCl/MeOH/dioxane, 0 °C to rt; (f) (*R*)-PhCH(NMe_2)CO_2H, HATU, DIEA, DMF; (g) EDCI, HOAT, *N*-methylmorpholine, DMF; (h) Burgess reagent, THF, 100 °C; (i) H_2 (1 atm), 10% Pd/C, EtOH/THF; (j) 20% TFA/CH_2Cl_2; (k) *N*-Boc-L-proline, EEDQ, CH_2Cl_2.

remained essentially unchanged. Although the oxazole-linked benzimidazole template appeared to provide no advantage over its alkyne counterpart from a GT-1a coverage perspective, an important insight was gleaned from subsequent SAR explorations where the oxazole linker was used to examine the activities of regioisomeric anilide-benzimidazole hybrid templates. The purpose here was to find out how inhibitory potency would be impacted if the topology that an oxazole linker introduces into the core region was offset by changing the substitution pattern of the attachments on the phenyl rings.

Activity assessment of hybrid analogues **31a** and **31b**, assembled from acid **28** as described in Scheme 4, indicated that whereas the GT-1a potency of *para*-regioisomer **31a** was within 3.9-fold of that of *bis*-benzimidazole **27**, *meta*-regioisomer **31b** exhibited a significantly enhanced GT-1a inhibitory potency.[16] It is noteworthy that regioisomers **31a** and **31b** had similar GT-1b potencies. The fact that a para-to-meta transposition of the anilide moiety in **31a**, to afford **31b**, resulted in ∼70-fold gain in GT-1a potency while having minimal impact on GT-1b activity not only illustrated the

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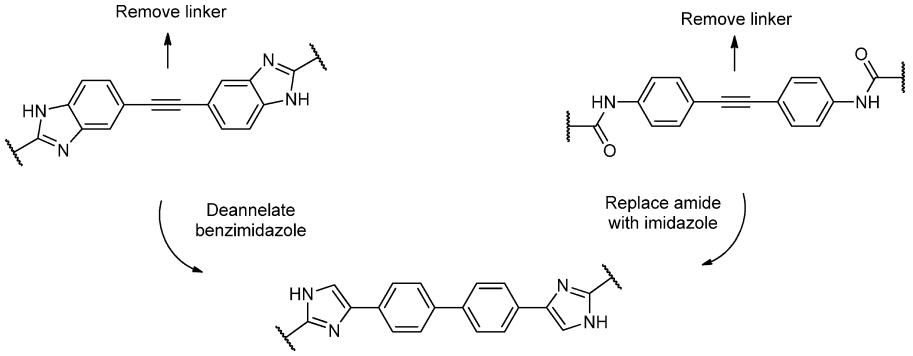
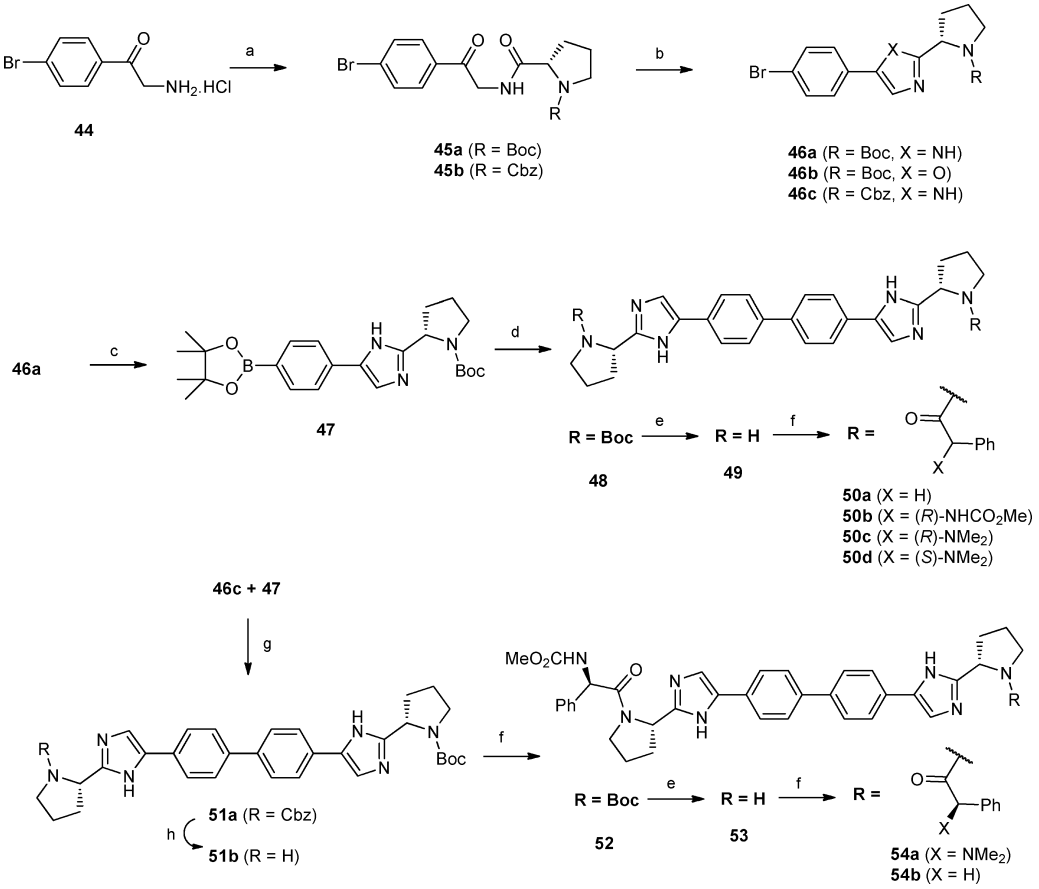


Figure 2. Bioisosteric design strategy.

Scheme 6. Preparation of Biarylimidazole Analogues[a]



[a]Reagents and conditions: (a) *N*-Boc-L-proline, HATU, DIEA, DMF; (b) NH_4OAc, xylenes, 140 °C; (c) bis(pinacolato)diboron, $Pd(Ph_3P)_4$, KOAc, 1,4-dioxane; (d) **46a**, $Pd(Ph_3P)_4$, $NaHCO_3$, DME, 80 °C; (e) 25% TFA/CH_2Cl_2; (f) RCO_2H, HATU, DIEA, DMF; (g) $Pd(Ph_3P)_4$, $NaHCO_3$, DMF, 80 °C; (h) H_2 (60 psi), 10% Pd/C, K_2CO_3, MeOH.

differing tolerance of the two NS5A proteins to the modifications examined but also drew attention to a parameter that needed to be examined more closely to optimize the GT-1a activity further. To rule out the possibility that the anilide portion of **31b** might be responsible for the significant enhancement of the compound's GT-1a inhibitory potency, *bis*-anilide **38a** was prepared (Scheme 5), tested, and found to have weaker GT-1a inhibiting properties. It is noteworthy that *bis*-anilide **38b**, a regioisomer of **38a** or **21**, was very potent toward both GT-1a and GT-1b replicons.

The fact that hybrid chemotype **31b** exhibits a GT-1a activity that is significantly better than either of its pseudo-homodimeric counterparts (i.e., *bis*-benzimidazole **27** or *bis*-anilide **38a**) suggested that it might be feasible to identify a scaffold exhibiting the GT-1a/-1b inhibitory activity of anilides **3b**/**3c** but lacking their genotoxic liability through additional isosteric iteration, where the distance between the pharmacophoric elements and their relative topological disposition was varied. It was against this backdrop that deannelation of the benzimidazole moieties of **9** into phenylimidazoles was pursued, with concomitant removal of the alkyne linker to offset the core lengthening that such structural manipulation would entail. Alternatively, this approach would be equivalent to replacing the amide moieties of original aniline-based lead **3**

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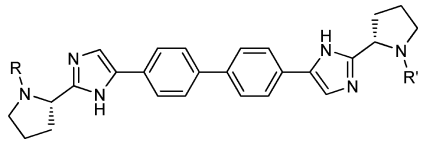
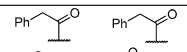
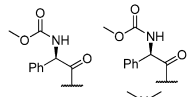
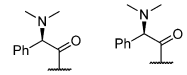
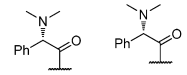
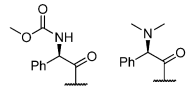
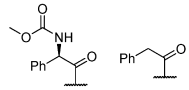
Table 3. Activity and Specificity of Biarylimidazoles[a,b]



Compd	R / R'	HCV Replicon Inhibitory Activity GT-1a EC_{50} (nM)	HCV Replicon Inhibitory Activity GT-1b EC_{50} (nM)	GT-1b CC_{50} (nM)	BVDV EC_{50} (nM)
50a		283	0.33	$>10^4$	596
50b[c]		0.028	0.0067	$>10^4$	1460
50c[c]		0.037	0.042	5860	2350
50d		704	5.4	3610	1270
54a		0.049	0.012	>9700	3440
54b		14.9	0.0040	$>10^4$	523
52	 Boc	203	0.011	$>10^4$	110
48	Boc Boc	901	102	9630	2760

[a]Data represent mean values of at least two experiments. [b]Activity assessment: GT-1a, FRET (**50a**, **52** and **48**) or ELISA (remaining set); GT-1b, FRET; and BVDV, luciferase. Cytotoxicity assessment: GT-1b, alamar blue. [c]EC_{50} in GT-1b LV/YH resistant replicon: **50b** (166 nM) and **50c** (233 nM).

with imidazole isosteres and making a compensatory length adjustment to the central scaffold region (Figure 2).[17] It was envisioned that such a chemotype would decrease conformational rigidity of the benzimidazole chemotype while providing an opportunity to survey vectorial trajectories that may not have been accessed thus far. This enterprise indeed proved fruitful.

The biphenylimidazole chemotype was assembled by the synthetic route illustrated in Scheme 6. Heating ketoamide **45a** with excess NH_4OAc afforded phenylimidazole **46a**, contaminated with a minor amount of oxazole **46b** that was readily removed under standard flash chromatography conditions.[18] A Suzuki–Miyaura coupling of bromide **46a** with its boronate derivative **47** afforded biphenylimidazole **48**, which was elaborated to final products **50a–d** under conditions noted for the chemotypes discussed above. Gratifyingly, glycinamide cap analogues **50b** and **50c** exhibited an unprecedented antiviral spectrum in the replicon assays, with GT-1a and GT-1b EC_{50} values <50 pM, accompanied by favorable antiviral specificity, as indicated by BVDV EC_{50} and GT-1b CC_{50} of >1 μM (Table 3). Both compounds exhibited weaker potency toward NS5A GT-1b LV/YH resistant replicon, which supports their specificity for the HCV NS5A protein. In line with the cap SAR uncovered with the lead alkyne-linked anilide template, phenylacetamide cap analogue **50a** exhibited a significant loss in GT-1a inhibitory potency, and the (R) stereoisomer of the dimethylamine cap was much more potent than its (S) counterpart (compare **50c** vs **50d**). As part of the preliminary cap-SAR survey of this new chemotype, heterodimeric cap analogues **54a** and **54b** were also prepared through the intermediacy of differentially protected precursor **51a** (Scheme 6). The GT-1a EC_{50} of **54a** was similar to that of its homodimeric cap variants **50b** and **50c**, which demonstrated that chemical symmetry is not a requirement for effecting potent GT-1a activity. Moreover, in going from homodimer **50b** to heterodimer **54b**, the GT-1b potency remained essentially unchanged, whereas the GT-1a potency eroded by ~530-fold. This finding, coupled with the differential activity exhibited by advanced synthetic precursor **52** toward GT-1a and -1b replicons, illustrates, yet again, that the GT-1a NS5A protein exhibits a more stringent pharmacophoric requirement for inhibition. Although it is clear that the biphenylimidazole chemotype was optimal for achieving potent GT-1a activity, the poor GT-1a and GT-1b inhibitory activity of the *bis*-Boc intermediate **48** coupled with the single-digit nanomolar potency exhibited by anilide **3b** toward GT-1a revealed, in general, that the cap region plays the more dominant role among the elements of the pharmacophore.

Carbamate **50b** and amine **50c** were characterized further to gather preliminary information on the chemotype's broader genotype coverage potential and on its in vitro and in vivo metabolism and pharmacokinetic (MAP) properties. Both compounds exhibited very potent inhibition toward a panel of HCV replicon strains (Table 4), with EC_{50} values <60 pM for all except a GT-3a YH resistant strain. Both had very good metabolic stability in human and rat liver microsomes (100% remaining after 10 min of incubation), whereas their PAMPA permeability at pH 7.4 was either poor (7 nm/s for **50c**) or inconclusive (null for **50b**). In a 4 h rat PK screen study (IV/PO dose: 2/5 mg/kg, PEG-400 vehicle, n = 2), **50b** and **50c**

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Table 4. Antiviral Activity of 50b and 50c toward a Panel of HCV Genotype Strains

HCV replicon strain[b]	EC_{50} (nM)[a]	
	50b	**50c**
GT-2a (J6)	0.023	0.032
GT-3a	0.0040	0.015
GT-3a YH	4.4	3.8
GT-4a	0.0057	0.013
GT-5a	0.014	0.032

[a]Data represent mean values of at least two experiments done with FRET assays. [b]All are hybrid replicons in either GT-2a JFH-1 backbone (for GT-2a J6 and GT-5a) or GT-1b Con1 backbone (for GT-3a, GT-3a YH and GT-4a).

exhibited low estimated clearance after IV dosing (11.1 and 17.4 mL/min/kg, respectively) but essentially no systemic exposure after oral dosing; only one plasma sample obtained at 0.17 h after PO dosing of **50c** indicated exposure, with a 20 nM concentration recorded. Although the poor PO exposure was disappointing, it can be rationalized when considering the fact that the structural composition of these prototypical molecules lies on the periphery of the chemical space historically deemed drug-like.[19] At this stage of the SAR exploration it became apparent that additional iterations of structural refinements were needed to attain targeted PK properties without compromising the gains in replicon inhibitory potency of this promising new chemotype class.

CONCLUSIONS

A novel, highly potent and pan-genotypic biphenylimidazole chemotype was discovered through an optimization campaign that was directed at addressing the potential genotoxic liabilities and nonoptimal virology properties of early program leads containing an anilide moiety. In an initial effort, the anilide was replaced with either benzimidazole or regioisomeric benzoxazoles, which resulted in various levels of inhibitory potency loss toward GT-1a and/or GT-1b replicons. Subsequently, an examination of regioisomeric benzimidazole/anilide hybrid cores with an oxazole central linker revealed the critical importance of core topology in determining GT-1a inhibitory activity, paving the way for consideration of deannelation of the benzimidazole chemotype to enhance GT-1a potency. This strategy succeeded and led to the identification of a biphenylimidazole chemotype that exhibited picomolar inhibitory potency toward a panel of clinically relevant strains. It is intriguing that securing potent GT-1a activity has been consistently problematic both in a previously disclosed cap investigation and the core study discussed here.[3b] The evidence gathered to date strongly suggests that potent inhibitory activity toward GT-1a correlates with a dimeric disposition of the pharmacophoric elements located on both the core and the peripheral regions of the inhibitor, whereas this is not necessarily the case for GT-1b.[20] Compounds **50b** and **50c** had poor systemic exposure after oral dosing in rat PK screens, and the subsequent ADME optimization effort that resulted in the discovery of **1** will be the subject of a forthcoming communication.

EXPERIMENTAL SECTION

Unless noted otherwise, all reactions were conducted under nitrogen and, where appropriate, under anhydrous conditions using commercially available substrates and solvents. Products were purified either by flash chromatography on silica gel or Shimadzu reverse-phase preparative HPLC. In cases where the HPLC eluting medium contained TFA additives, the TFA content of the final products was not determined. However, for purposes of yield and EC_{50} calculations, it was assumed that the mole equivalent of TFA was the same as the number of basic moieties present in the molecule. Compounds were characterized with a combination of LC/MS, HRMS, and ^1H and ^{13}C NMR. LC/MS analyses were performed on a Shimadzu LC instrument coupled to a Water Micromass ZQ instrument. All test compounds exhibited ≥95% purity under the LC conditions provided in Table 5 except for **27** (91%) and **31b** (90%, see ref 16). HRMS

Table 5. LC Conditions for the Characterization of Final Products

LC/MS condition[a]	Col[b]	GT[c]	FR[d]	Sol A[e]	Sol B[f]
method A	1	4	0.8	A1	B1
method B	2	4	0.8	A1	B1
method C	3	3	4	A2	B2
method D	4	3	3	A1	B1
method E	5	3	4	A1	B1
method F	2	4	0.8	A3	B3
method G	5	2	5	A1	B1
method H	4	2	4	A1	B1
method I	6	1.5	0.8	A1	B1
method J	7	2	5	A1	B1
method K	4	3	4	A1	B1

[a]Gradient: 0% B to 100% B. Wavelengh (λ): 200 nm. [b]Col: column, where column 1 = Xbridge Phenyl (2.1 × 50 mm, 2.5 μm), oven temp. 40 °C; column 2 = Phenomenex-Luna C18 (2.0 × 50 mm, 3.0 μm), oven temp. 40 °C; column 3 = XTERRA C18 (4.6 × 50 mm, S5); column 4 = Phenomenex-Luna C18 (3.0 × 50 mm, S10); column 5 = Phenomenex-Luna C18 (4.6 × 50 mm, S10); column 6 = Waters Aquity BEH C18 (2.1 × 50 mm, 1.7 μm), oven temp. 40 °C; and column 7 = XTERRA C18 (3.0 × 50 mm, S7). [c]GT: gradient time (min). [d]FR: flow rate (mL/min). [e]Sol A: solvent A, where solvent A1 = 0.1% TFA in 10% MeOH/90% H_2O; solvent A2 = 0.2% H_3PO_4 in 10% MeOH/90% H_2O; and solvent A3 = 0.1% TFA in 5% MeOH/95% H_2O. [f]Sol B: solvent B, where solvent B1 = 0.1% TFA in 90% MeOH/10% H_2O; solvent B2 = 0.2% H_3PO_4 in 90% MeOH/10% H_2O; and solvent B3 = 0.1% TFA in 95% MeOH/5% H_2O.

analyses were conducted on a Thermo Scientific Finnegan MAT900 or Fourier Transform Orbitrap spectrometers, calibrated daily. NMR spectra were recorded on a Bruker Ultrashield 400 MHz spectrometer or on a Bruker Advance-III 500 MHz spectrometer, each equipped with a 5 mm TXI cryoprobe. Residual protio-solvent was used as internal standard for chemical-shift assignments. Coupling constants are provided in Hz, with the following spectral pattern designations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad; app, apparent. ^1H NMR analyses of most intermediates and final products in DMSO-d_6 or CD_3OD at ambient temperature indicated the presence of rotamers and/or tautomers, and the chemical shift provided is for the dominant rotamer(s) and/or tautomer(s).

2-Phenyl-1-[(2*S*)-2-[5-(2-{2-[(2*S*)-1-(2-phenylacetyl)-pyrrolidin-2-yl]-1*H*-1,3-benzodiazol-5-yl}ethynyl)-1*H*-1,3-benzodiazol-2-yl]pyrrolidin-1-yl]ethan-1-one (9a). To a mixture of 4-bromobenzene-1,2-diamine (5.00 g, 26.7 mmol), (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (5.75 g, 26.7 mmol), and HOBT (4.33 g, 32.1 mmol) in CH_2Cl_2 (135 mL) at rt was added EDCI (4.98 g, 26.0 mmol), and the mixture was stirred for 16.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (2×) followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brownish foam. The foam was treated with glacial acetic acid (100 mL) and heated at 65 °C for 3.5 h. The reaction mixture was removed from the heat, and the volatile component was removed in vacuo. The residue was taken up in EtOAc

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and washed with a sat. aq. solution of $NaHCO_3$ (2×) followed by brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; EtOAc) to afford benzimidazole **6** (second elute, tan foam, 3.98 g, 41%) and the *bis*-acylated side-product *tert*-butyl (2*S*)-2-({5-bromo-2-[(2*S*)-1-[(*tert*-butoxy)carbonyl]pyrrolidine-2-amido]phenyl}carbamoyl)pyrrolidine-1-carboxylate (brown foam, 1.3 g, 8%). Bromide **6**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (br s, 0.32H), 12.47 (br s, 0.27H), 12.44 (br s, 0.23H), 12.37 (br s, 0.18H), 7.75 (d, J = 1.8 Hz, 0.54H), 7.67−7.59 (m, 0.46H), 7.52 (d, J = 8.5 Hz, 0.45H), 7.42 (d, J = 8.5 Hz, 0.55H), 7.34−7.23 (m, 1H), 5.02−4.94 (m, 0.41H), 4.90 (dd, J = 7.8, 3.8 Hz, 0.59H), 3.69−3.50 (m, 1H), 3.50−3.38 (m, 1H), 2.46−2.15 (m, 1H), 2.12−1.77 (m, 3H), 1.41 (s, 3.64H), 1.07 (s, 5.36H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.0, 157.6, 157.3, 156.8, 153.1, 152.5, 144.0, 141.6, 141.6, 134.6, 134.5, 132.4, 123.5, 123.2, 120.1, 120.0, 119.4, 119.3, 113.2, 113.0, 112.9, 112.4, 112.3, 112.1, 78.2, 77.7, 54.9, 54.4, 54.4, 46.0, 45.7, 32.5, 31.1, 27.4, 27.0, 23.2, 22.5. LC/MS (ESI) m/z calcd for $C_{16}H_{21}N_3O_2Br$, 366.08; found, 366.21 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{16}H_{21}N_3O_2Br$, 366.0817; found, 366.0800 $[M + H]^+$. Side product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97−9.05 (m, 2H), 8.22−7.16 (m, 3H), 4.39−4.20 (m, 2H), 3.52−3.36 (m, 4H), 2.34−2.08 (m, 2H), 1.96−1.72 (m, 6H), 1.43 (s, 8H), 1.33 (s, 10H). LC/MS (ESI) m/z calcd for $C_{26}H_{37}N_4O_6BrNa$, 603.18; found, 603.24 $[M + Na]^+$.

To a reaction vessel containing a solution of 1,2-bis-(trimethylstannyl)ethyne (1.00 g, 2.84 mmol) and **6** (2.19 g, 5.97 mmol) in DMF (25 mL) was added $Pd(Ph_3P)_4$ (0.329 g, 0.284 mmol). The mixture was thoroughly flushed with N_2 before being sealed and heated at 80 °C for 23 h. After it was allowed to cool to rt, the volatile component was removed in vacuo. The residue was purified by flash chromatography (silica gel; EtOAc) to afford a light yellow foam (811.6 mg). The foam was dissolved in EtOH (6 mL) with heating and allowed to cool to rt to afford **7** as a light yellow solid (421 mg). The filtrate was heated and allowed to cool again to afford a second crop of **7** (120 mg), resulting in a combined yield of 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57−12.47 (series of s, 1.18H), 12.47−12.36 (series of s, 0.82H), 7.76 (app d, J = 6.0 Hz, 1H), 7.69−7.62 (m, 1H), 7.58 (dd, J = 8.3, 1.8 Hz, 1H), 7.49 (app d, J = 8.0 Hz, 1H), 7.42−7.27 (m, 2H), 5.06−4.97 (m, 0.81H), 4.97−4.87 (m, 1.19H), 3.70−3.53 (m, 2H), 3.53−3.39 (m, 2H), 2.48−2.17 (m, 2H), 2.16−1.82 (m, 6H), 1.42 (s, 7.26H), 1.08 (s, 10.74H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.1, 157.9, 157.4, 157.2, 153.1, 152.5, 142.7, 142.4, 133.5, 133.2, 124.6, 124.0, 120.6, 117.9, 114.9, 114.5, 113.5, 113.2, 111.0, 110.7, 88.4, 88.3, 87.9, 87.8, 78.2, 77.7, 55.0, 54.5, 46.1, 45.8, 32.6, 31.2, 27.4, 27.0, 23.2, 22.5. LC/MS (ESI) m/z calcd for $C_{34}H_{41}N_6O_4$, 597.32; found, 597.43 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{34}H_{41}N_6O_4$, 597.3189; found, 597.3184 $[M + H]^+$.

To a suspension of **7** (0.410 g, 0.687 mmol) in 4 N HCl in dioxane (80 mL) was added MeOH (20 mL), and the mixture was stirred at rt for 17 h. The volatile component was removed in vacuo, and the resultant solid was dissolved in MeOH (25 mL) and treated with Et_2O to cause precipitation. The solid was filtered and dried in vacuo to afford the HCl salt of **8** as a tan solid (315 mg, 85% assuming 4 equiv of HCl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (br s, 2H), 9.79 (br s, 2H), 9.68 (br s, 4H), 7.96 (s, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.59 (dd, J = 8.4, 1.4 Hz, 2H), 5.20−4.94 (m, 2H), 3.63−3.24 (m, 4H), 2.63−2.53 (m partially hidden under DMSO, 2H), 2.47−2.31 (m, 2H), 2.27−2.13 (m, 2H), 2.13−1.99 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.9, 135.3, 135.3, 126.5, 117.3, 116.8, 114.7, 88.4, 53.7, 44.6, 29.1, 22.9. LC/MS (ESI) m/z calcd for $C_{24}H_{25}N_6$, 397.21; found, 397.23 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{24}H_{25}N_6$, 397.2141; found, 397.2126 $[M + H]^+$.

To a solution of the HCl salt of **8** (60.0 mg, 0.111 mmol), 2-phenylacetic acid (0.033 g, 0.24 mmol), and DIEA (0.16 mL, 0.89 mmol) in DMF (2 mL) was added HATU (88.0 mg, 0.232 mmol). The reaction mixture was stirred at rt for 1.5 h. It was then diluted with MeOH (2 mL) and purified by reverse-phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of title compound **9a** as an off-white solid (42 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1.67H), 7.88−7.81 (m, 0.34H), 7.81−7.72 (m, 1.67H), 7.69−7.58 (m, 1.97H), 7.51 (dd, J = 8.4, 1.4 Hz, 0.33H), 7.38−7.27 (m, 3.54H), 7.27−7.20 (m, 4.97H), 7.20−7.08 (m, 0.90H), 7.08−7.00 (m, 0.61H), 5.52 (dd, J = 8.0, 2.0 Hz, 0.31H), 5.29 (dd, J = 8.4, 3.1 Hz, 1.69H), 3.98−3.87 (m, 1.63H), 3.79 (t, J = 1.0 Hz, 3.72H), 3.72−3.49 (m, 2.35H), 3.38 (d, J = 15.6 Hz, 0.30H), 2.50−2.28 (m, 2.12H), 2.26−2.01 (m, 5.15H), 2.01−1.77 (m, 0.73H). Note: signals for the two exchangeable NH protons were not observed. LC (method A): t_R = 3.38 min. LC/MS (ESI) m/z calcd for $C_{40}H_{37}N_6O_2$, 633.30; found, 633.35 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{40}H_{37}N_6O_2$, 633.2978; found, 633.2958 $[M + H]^+$.

(2*R*)-2-(Dimethylamino)-1-[(2*S*)-2-[5-(2-{2-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl] pyrrolidin-2-yl]-1*H*-1,3-benzodiazol-5-yl}ethynyl)-1*H*-1,3-benzodiazol-2-yl]pyrrolidin-1-yl]-2-phenylethan-1-one (9b). Title compound **9b** (TFA salt, light yellow solid) was prepared from **8** and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for **9a**. For purposes of comparing the activities of different forms in replicon medium, a portion of the sample was free-based with MCX cartridge (MeOH wash, 2.0 N NH_3/MeOH elution) to afford a light yellow solid. TFA salt: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (br s, 2H), 7.86 (s, 1.69H), 7.69 (s, 0.86H), 7.67 (s, 0.98H), 7.66−7.55 (m, 8.69H), 7.55−7.46 (m, 1.81H), 7.45−7.30 (m, 0.67H), 7.07−6.97 (m, 0.51H), 6.97−6.88 (m, 0.29H), 6.88−6.76 (m, 0.50H), 5.81 (d, J = 8.3 Hz, 0.24H), 5.54 (s, 1.70H), 5.47 (br s, 0.30H), 5.27 (dd, J = 8.4, 2.6 Hz, 1.76H), 4.18−4.02 (m, 1.73H), 3.95−3.81 (m, 0.27H), 3.76−3.63 (m, 0.24H), 3.18−3.07 (m, 1.76H), 3.05−2.69 (m, 6H), 2.46 (br s, 5H), 2.35 (app s, 1H), 2.31−2.20 (m, 1.78H), 2.19−2.01 (m, 3.85H), 2.01−1.77 (m, 2.37H). LC (method J): t_R = 0.99 min. LC/MS (ESI) m/z calcd for $C_{44}H_{47}N_8O_2$, 719.38; found, 719.38 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{47}N_8O_2$, 719.3822; found, 719.3799 $[M + H]^+$.

Methyl *N*-[(1*R*)-2-[(2*S*)-2-[5-(2-{2-[(2*S*)-1-[(2*R*)-2-[(Methoxycarbonyl)amino]-2-phenylacetyl]pyrrolidin-2-yl]-1*H*-1,3-benzodiazol-5-yl}ethynyl)-1*H*-1,3-benzodiazol-2-yl]-pyrrolidin-1-yl]-2-oxo-1-phenylethyl]carbamate (9c). Title compound **9c** (TFA salt, light yellow solid) was prepared from **8** and (*R*)-2-((methoxycarbonyl) amino)-2-phenylacetic acid according to the procedure described for **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1.59H), 7.94−7.83 (m, 0.54H), 7.78 (app d, J = 8.5 Hz, 1.66H), 7.73 (app d, J = 8.0 Hz, 1.80H), 7.69−7.60 (m, 1.62H), 7.51 (app s, 0.66H), 7.47−7.40 (m, 5.90H), 7.40−7.27 (m, 2.77H), 6.98−6.88 (m, 0.62H), 6.88−6.77 (m, 0.86H), 5.77 (app d, J = 8.0 Hz, 0.29H), 5.57 (d, J = 8.0 Hz, 1.63H), 5.40 (d, J = 7.8 Hz, 0.37H), 5.29 (dd, J = 8.4, 2.1 Hz, 1.71H), 4.07−3.89 (m, 1.80H), 3.88−3.66 (m, 0.46H), 3.65−3.54 (m, 3.40H), 3.51 (s, 3H), 3.30−3.19 (m, 1.34H), 2.46−2.20 (m, 1.85H), 2.20−2.02 (m, 3.84H), 2.01−1.80 (m, 2.31H). Note: signals for the two exchangeable NH protons were not observed. LC (method A): t_R = 3.40 min. LC/MS (ESI) m/z calcd for $C_{44}H_{43}N_8O_6$, 779.33; found, 779.45 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{43}N_8O_6$, 779.3306; found, 779.3273 $[M + H]^+$.

2-Phenyl-1-[(2*S*)-2-[5-(2-{2-[(2*S*)-1-(2-phenylacetyl)-pyrrolidin-2-yl]-1,3-benzoxazol-5-yl}ethynyl)-1,3-benzoxazol-2-yl]pyrrolidin-1-yl]ethan-1-one (15a). To a mixture of 2-amino-4-bromophenol (5.0 g, 27 mmol), (*S*)-1-(*tert*-butoxycarbonyl) pyrrolidine-2-carboxylic acid (5.72 g, 26.6 mmol), and HOBT (3.95 g, 29.3 mmol) in CH_2Cl_2 (130 mL) at rt was added EDCI (5.61 g, 29.3 mmol), and the mixture was stirred for 20 h. It was diluted with CH_2Cl_2 and washed with water (2×) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a tan foam. To a solution of the foam and Ph_3P (7.67 g, 29.3 mmol) in THF (150 mL) at rt was added DIAD (5.69 mL, 29.3 mmol) dropwise over a few minutes, and the mixture was stirred for 21 h. The volatile component was removed in vacuo, and the residue was triturated with Et_2O and hexanes (30:1 v/v), and the precipitate was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel; 15−25% EtOAc/hexanes) to afford **12a** as a viscous orange oil containing residual EtOAc in a 1.0:0.17 product/EtOAc mole ratio (7.44 g, ∼75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06−7.92 (m, 1H), 7.80−7.66 (m, 1H), 7.56 (dd, J = 8.5, 1.8 Hz, 1H), 5.09−5.01 (m, 0.38H), 4.99 (dd, J = 8.0, 4.5 Hz, 0.62H), 3.64−3.50 (m, 1H), 3.50−3.38 (m, 1H), 2.49−2.24 (m, 1H), 2.18−1.83 (m, 3H), 1.39 (s,

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3.36H), 1.10 (s, 5.64H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 167.9, 152.8, 152.0, 148.5, 141.8, 127.1, 127.0, 121.6, 121.5, 115.7, 115.7, 112.0, 111.9, 78.5, 78.1, 54.0, 53.8, 45.8, 45.6, 31.3, 30.3, 27.3, 26.9, 23.2, 22.5. LC/MS (ESI) m/z calcd for $C_{16}H_{19}N_2O_3BrNa$, 389.05/391.05; found, 389.05/391.05 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{16}H_{20}N_2O_3Br$, 367.0652; found, 367.0641 [M + H]$^+$.

To a solution of **12a** (1.90 g, 5.17 mmol) and 1,2-bis-(trimethylstannyl)ethyne (1.00 g, 2.84 mmol) in DMF (25 mL) was added Pd(Ph$_3$P)$_4$ (0.299 g, 0.259 mmol). The mixture was thoroughly flushed with N_2 before the reaction vessel was sealed and heated at 80 °C for 17.5 h. The volatile component was removed in vacuo, and the residue was purified by flash chromatography (silica gel; 25−100% EtOAc/hexanes) to afford **13a** as a light yellow solid (1.2 g) contaminated with Ph_3PO, as determined by LC/MS analysis. The product was recrystallized from EtOAc to afford a crop of **13a** as a light yellow solid (350 mg), and the filtrate was concentrated and repurified by flash chromatography (silica gel; EtOAc) to afford additional **13a** (570 mg, 59% combined yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04−7.91 (m, 2H), 7.89−7.73 (m, 2H), 7.70−7.55 (m, 2H), 5.13−5.03 (m, 0.73H), 5.01 (dd, J = 8.0, 4.8 Hz, 1.27H), 3.64−3.51 (m, 2H), 3.51−3.39 (m, 2H), 2.50−2.26 (m, 2H), 2.23−1.84 (m, 6H), 1.41 (s, 6.27H), 1.11 (s, 11.73H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.9, 167.7, 152.8, 152.1, 149.4, 149.3, 140.3, 128.0, 121.7, 117.9, 110.8, 110.7, 87.7, 78.5, 78.1, 54.1, 45.9, 45.7, 31.3, 30.3, 27.3, 26.9, 23.2, 22.6. LC/MS (ESI) m/z calcd for $C_{34}H_{39}N_4O_6$, 599.29; found, 599.35 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{34}H_{39}N_4O_6$, 599.2870; found, 599.2842 [M + H]$^+$.

A solution of **13a** (0.50 g, 0.84 mmol) in 20% TFA/CH_2Cl_2 (15 mL) was stirred at rt for 4 h. The volatile component was removed in vacuo, and the residue was azeotroped with benzene and then free-based by MCX cartridge (MeOH wash; 2 N NH_3/MeOH elution). The resultant material was crystallized from MeOH to afford **14a** as an off-white solid (300 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98−7.90 (m, 2H), 7.83−7.73 (m, 2H), 7.60 (dd, J = 8.4, 1.6 Hz, 2H), 4.46 (dd, J = 8.0, 5.8 Hz, 2H), 3.11 (app br s, 2H), 2.96 (app t, J = 6.8 Hz, 4H), 2.28−2.03 (m, 4H), 1.97−1.84 (m, 2H), 1.84−1.70 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.7, 149.7, 140.2, 127.9, 121.7, 117.7, 110.6, 87.7, 54.2, 45.8, 29.5, 24.8. LC/MS (ESI) m/z calcd for $C_{24}H_{22}N_4O_6Na$, 421.16; found, 421.21 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_4O_2$, 399.1816; found, 399.1804 [M + H]$^+$.

To a mixture of **14a** (71.7 mg, 0.180 mmol), 2-phenylacetic acid (54.0 mg, 0.396 mmol), and DIEA (0.13 mL, 0.72 mmol) in DMF (2 mL) was added HATU (0.144 g, 0.378 mmol), and the reaction mixture was stirred at rt for 2.3 h. The volatile component was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and washed (2×) with a 10:1 mixture of H_2O and sat. aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; EtOAc) to afford title compound **15a** as a white foam (63.7 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01−7.97 (m, 0.38H), 7.97−7.91 (m, 1.45H), 7.83−7.74 (m, 1.98H), 7.68−7.57 (m, 1.98H), 7.38−7.29 (m, 3.38H), 7.29−7.21 (m, 4.89H), 7.21−7.15 (m, 0.78H), 7.15−7.04 (m, 1.16H), 5.62 (dd, J = 8.0, 1.8 Hz, 0.36H), 5.20 (dd, J = 8.3, 3.3 Hz, 1.64H), 3.90−3.79 (m, 1.75H), 3.77 (s, 3.16H), 3.75−3.66 (m, 1.90H), 3.66−3.47 (m, 1.19H), 2.49−2.26 (m, 2.42H), 2.25−1.82 (m, 5.58H). LC (method B): t_R = 4.16 min. LC/MS (ESI) m/z calcd for $C_{40}H_{35}N_4O_4$, 635.27; found, 635.30 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{40}H_{35}N_4O_4$, 635.2658; found, 635.2633 [M + H]$^+$.

(2*R*)-2-(Dimethylamino)-1-[(2*S*)-2-[5-(2-{2-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl]-1,3-benzoxazol-5-yl}ethynyl)-1,3-benzoxazol-2-yl]pyrrolidin-1-yl]-2-phenylethan-1-one (15b). Title compound **15b** (light yellow solid) was prepared from **14a** and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for **15a** with the exception that the flash chromatography used 5% MeOH/CH_2Cl_2 as eluant. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97−7.92 (m, 1.66H), 7.83 (app t, J = 1.0 Hz, 0.28H), 7.78 (d, J = 8.3 Hz, 1.73H), 7.63 (dd, J = 8.4, 1.6 Hz, 1.76H), 7.57 (app d, J = 0.8 Hz, 0.52H), 7.49−7.42 (m, 3.56H), 7.41−7.29 (m, 5.26H), 7.05−6.97 (m, 0.50H), 6.97−6.86 (m, 0.73H), 5.83 (dd, J = 8.2, 1.1 Hz, 0.25H), 5.13 (dd, J = 8.3, 3.8 Hz, 1.75H), 4.35 (br s, 0.39H), 4.30 (br s, 1.61H), 4.13−4.00 (m, 2H), 3.68−3.58 (m, 0.49H), 3.57−3.46 (m, 1.51H), 2.38−2.20 (m, 2.86H), 2.17 (br s, 2.18H), 2.15 (br s, 9.52H), 2.13−1.89 (m, 5.44H). LC (method B): t_R = 3.20 min. LC/MS (ESI) m/z calcd for $C_{44}H_{45}N_6O_4$, 721.35; found, 721.33 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{44}H_{45}N_6O_4$, 721.3502; found, 721.3477 [M + H]$^+$.

2-Phenyl-1-[(2*S*)-2-[6-(2-{2-[(2*S*)-1-(2-phenylacetyl)-pyrrolidin-2-yl]-1,3-benzoxazol-6-yl}ethynyl)-1,3-benzoxazol-2-yl]pyrrolidin-1-yl]ethan-1-one (16a). To a solution of 2-amino-5-bromophenol (1.0 g, 5.3 mmol) and (*S*)-1-(*tert*-butoxycarbonyl)-pyrrolidine-2-carboxylic acid (1.15 g, 5.32 mmol) in CH_2Cl_2 (25 mL) was added HOBT (0.791 g, 5.85 mmol) followed by EDCI (1.12 g, 5.85 mmol). The reaction mixture was stirred at rt for 7.5 h. It was diluted with CH_2Cl_2 and washed with water (2×) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a tan foam. The foam was dissolved in THF (30 mL), and Ph_3P (1.54 g, 5.86 mmol) was added followed by the dropwise addition of DIAD (1.14 mL, 5.85 mmol) over a few minutes. The reaction mixture was stirred at rt for 23.5 h. The volatile component was removed in vacuo, and the residue was dissolved in EtOAc and washed with H_2O (2×) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel; 25% EtOAc/hexanes) to afford a brownish-orange viscous oil that solidified upon standing (1.2 g). The solid was recrystallized from hexanes to afford two crops of **12b** as gray solid (770 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 1.5 Hz, 0.65H), 8.06 (app br s, 0.35H), 7.75−7.64 (m, 1H), 7.60−7.50 (m, 1H), 5.03 (dd, J = 8.0, 2.5 Hz, 0.38H), 4.98 (dd, J = 8.2, 4.4 Hz, 0.62H), 3.61−3.49 (m, 1H), 3.49−3.39 (m, 1H), 2.49−2.26 (m, 1H), 2.17−1.86 (m, 3H), 1.39 (s, 3.33H), 1.10 (s, 5.67H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.5, 167.2, 152.8, 152.0, 150.0, 149.8, 139.4, 127.0, 126.9, 120.3, 120.3, 116.3, 116.2, 113.5, 113.4, 78.5, 78.1, 54.0, 53.8, 45.8, 45.6, 31.3, 30.3, 27.3, 26.9, 23.2, 22.5. LC/MS (ESI) m/z calcd for $C_{16}H_{19}N_2O_3BrNa$, 389.05; found, 389.05 [M + Na]$^+$. HRMS (ESI) m/z calcd for $C_{16}H_{20}N_2O_3Br$, 367.0652; found, 367.0641 [M + H]$^+$.

To a solution of 1,2-bis(trimethylstannyl)ethyne (0.369 g, 1.048 mmol) and **12b** (0.77 g, 2.1 mmol) in DMF (8 mL) was added Pd(Ph$_3$P)$_4$ (0.121 g, 0.105 mmol). The reaction vessel was thoroughly flushed with N_2 before being capped and heated at 80 °C for 15.3 h. The reaction mixture was removed from the heat, and the volatile component was removed in vacuo. The residue was purified by flash chromatography (silica gel; EtOAc) to afford a solid, which was recrystallized from EtOAc to obtain two crops of **13b** as a light yellow solid (367 mg, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06−7.95 (m, 2H), 7.85−7.74 (m, 2H), 7.67−7.55 (m, 2H), 5.06 (dd, J = 8.2, 2.4 Hz, 0.74H), 5.01 (dd, J = 7.9, 4.6 Hz, 1.26H), 3.63−3.51 (m, 2H), 3.51−3.41 (m, 2H), 2.50−2.29 (m, 2H), 2.19−1.89 (m, 6H), 1.41 (s, 6.51H), 1.11 (s, 11.49H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 168.0, 152.8, 152.1, 149.2, 149.0, 140.6, 127.7, 127.6, 119.2, 119.1, 118.0, 113.1, 113.0, 88.6, 88.5, 78.5, 78.1, 54.1, 53.9, 45.9, 45.7, 31.4, 30.4, 27.4, 27.0, 23.2, 22.6. LC/MS (ESI) m/z calcd for $C_{34}H_{39}N_4O_6$, 599.29; found, 599.35 [M + H]$^+$. HRMS (ESI) m/z calcd for $C_{34}H_{39}N_4O_6$: 599.2864; found 599.2839 [M + H]$^+$.

Boc deprotection of **13b** (0.335g, 0.560 mmol) according to the procedure described in the preparation of **14a** afforded impure **14b** (213 mg), which was used in the next step without further purification. It is noteworthy that the impurities, which are believed to be derived from hydration and/or hydrolytic cleavage of the benzoxazole moiety, were observed after the MCX free-basing step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 0.8 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.58 (dd, J = 8.3, 1.5 Hz, 2H), 4.47 (dd, J = 7.8, 5.8 Hz, 2H), 3.36 (br s, 2H), 2.95 (t, J = 6.7 Hz, 4H), 2.27−2.02 (m, 4H), 1.97−1.83 (m, 2H), 1.83−1.71 (m, 2H). LC/MS (ESI) m/z calcd for $C_{24}H_{23}N_4O_2$, 399.18; found, 399.23 [M + H]$^+$.

To a solution of **14b** (70.0 mg, 0.176 mmol), 2-phenylacetic acid (53.0 mg, 0.389 mmol), and DIEA (0.12 mL, 0.70 mmol) in DMF (2 mL) was added HATU (0.140 g, 0.369 mmol), and the reaction mixture was stirred at rt for 1.5 h. Most of the solvent was removed in vacuo, and the residue was purified by reverse-phase HPLC (CH_3CN/

H_2O/NH_4OAc). The resultant material was dissolved in CH_2Cl_2 and washed with H_2O and sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford title compound **16a** as an off-white solid (26.6 mg, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (app d, J = 0.8 Hz, 0.37H), 7.98−7.94 (m, 1.45H), 7.84−7.73 (m, 1.98H), 7.65−7.56 (m, 1.96H), 7.38−7.29 (m, 3.36H), 7.29−7.24 (m, 4.60H), 7.24−7.15 (m, 1.14H), 7.15−7.07 (m, 1.14H), 5.63 (dd, J = 8.0, 1.5 Hz, 0.37H), 5.20 (dd, J = 8.3, 3.0 Hz, 1.63H), 3.90−3.79 (m, 1.69H), 3.77 (s, 3.26H), 3.75−3.67 (m, 1.84H), 3.66−3.48 (m, 1.21H), 2.49−2.27 (m, 2.36H), 2.24−1.87 (m, 5.64H). LC (method B): t_R = 4.15 min. LC/MS (ESI) m/z calcd for $C_{40}H_{35}N_4O_4$, 635.27; found, 635.35 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{40}H_{35}N_4O_4$: 635.2658; found 635.2634 $[M + H]^+$.

(2*R*)-2-(Dimethylamino)-1-[(2*S*)-2-[6-(2-{2-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl]-1,3-benzoxazol-6-yl}ethynyl)-1,3-benzoxazol-2-yl]pyrrolidin-1-yl]-2-phenylethan-1-one (16b). Title compound **16b** (light yellow solid) was prepared from **14b** and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for **16a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01−7.95 (m, 1.52H), 7.81−7.73 (m, 1.82H), 7.66−7.53 (m, 2.27H), 7.50−7.43 (m, 3.45H), 7.43−7.25 (m, 5.79H), 7.03−6.96 (m, 0.48H), 6.94−6.86 (m, 0.67H), 5.83 (app d, J = 9.0 Hz, 0.22H), 5.13 (dd, J = 8.2, 3.9 Hz, 1.78H), 4.33 (s, 0.29H), 4.29 (s, 1.71H), 4.13−3.99 (m, 2H), 3.67−3.58 (m, 0.47H), 3.56−3.47 (m, 1.53H), 2.37−2.18 (m, 2.74H), 2.18−2.13 (m, 10.93H), 2.13−1.89 (m, 6.33H). LC (method B): t_R = 3.16 min. LC/MS (ESI) m/z calcd for $C_{44}H_{45}N_6O_4$, 721.35; found, 721.39 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3476 $[M + H]^+$.

(2*S*)-1-[(2*R*)-2-(Dimethylamino)-2-phenylacetyl]-*N*-[4-(2-{4-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-amido]phenyl}-1,3-oxazol-5-yl)phenyl]pyrrolidine-2-carboxamide (21). H_2SO_4 (10 mL) was cooled to 0 °C, and 2,5-diphenyloxazole **17** (12.0 g, 54.0 mmol) was added in two portions. To the resultant orange suspension was added dropwise a 1:1 solution of concentrated HNO_3/H_2SO_4 acids over 10 min. The reaction mixture was stirred for 2.5 h at 0 °C and poured onto chopped ice, and the precipitate was filtered. The solid was washed with H_2O and Et_2O and dried in vacuo to afford **18** as a yellow solid (5.0 g). The cold filtrate was extracted with EtOAc (300 mL), and the extract was treated with hexanes (60 mL) and allowed to stand at rt for 16 h to afford additional **18** (2.0 g) as a yellow solid. Both samples were contaminated with an impurity believed to be a regioisomeric nitration product. For the major component: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46−8.38 (m, 6H), 8.32 (s, 1H), 8.22−8.18 (m, 2H). LC/MS (ESI) m/z calcd for $C_{15}H_9N_3O_5$, 312.05; found, 312.13 $[M + H]^+$.

A suspension of impure **18** (9.83 g) in MeOH (100 mL) and EtOAc (100 mL) was subjected to balloon hydrogenation over 20% $Pd(OH)_2/C$ (1.0 g) for 6 h at rt. The mixture was filtered through Celite and concentrated in vacuo to afford a red solid, which was recrystallized from MeOH to afford two crops of dianiline **19** as a brick red solid (4.6 g), each contaminated with an impurity believed to be a regioisomer. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.28 (s, 1H), 6.65 (d, J = 6.6 Hz, 2H), 6.63 (d, J = 6.6 Hz, 2H). Note: the NH_2 signals were too broad to make peak assignments. LC/MS (ESI) m/z calcd for $C_{15}H_{13}N_3O$, 252.11; found, 252.05 $[M + H]^+$.

EEDQ (6.2 g, 25.07 mmol) was added in one portion to a stirred mixture of the impure dianiline **19** (3.0 g) and *N*-Boc-L-proline (5.30 g, 24.5 mmol) in CH_2Cl_2 (120 mL), and the mixture was stirred at rt for 2 h. Additional *N*-Boc-L-proline (2.6 g) and EEDQ (3.1 g) were added, and stirring was continued for an additional 1.5 h at rt. Most of the volatile component was removed in vacuo, and the residue was subjected to flash chromatography (silica gel; 50% EtOAc/hexanes) to afford **20** (6.2 g) as an orange solid contaminated with an impurity believed to be a regioisomer. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.32−10.13 (3 s, 2H), 8.03 (m, 2H), 7.85−7.72 (m, 6H), 7.68 (m, 1H), 4.32−4.17 (m, 2H), 3.49−3.40 (m, 2H), 3.38−3.33 (m, 2H), 2.27−2.13 (m, 2H), 1.96−1.75 (m, 6H), 1.42 (s, 6.5H), 1.29 (s, 11.5H). LC/MS (ESI) m/z calcd for $C_{35}H_{44}N_5O_7$, 646.63; found, 646.51 $[M + H]^+$.

To a cold (0 °C) solution of **20** (6.2 g, 9.6 mmol) in MeOH (5 mL) was added 4 N HCl in dioxane (30 mL). The reaction mixture was allowed to warm to 25 °C, where it was stirred for 4 h before it was diluted with Et_2O (100 mL) and filtered. The solid was washed with excess Et_2O and dried in vacuo to afford the HCl salt of (2*S*)-*N*-[4-(5-{4-[(2*S*)-pyrrolidine-2-amido]phenyl}-1,3-oxazol-2-yl)phenyl]-pyrrolidine-2-carboxamide (4.9 g) as an orange solid contaminated with an impurity believed to be a regioisomer. According to ^{1}H NMR analysis, the product-to-impurity mole ratio was ∼96:4. The impurity was purged from the sample through recrystallization from MeOH. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 0.85H), 11.13/11.12/11.09 (3 s, 1.15H), 9.88 (m, 2H), 8.74 (m, 2H), 8.10 (d, J = 8.8 Hz, 2H), 7.87−7.78 (m, 7H), ∼4.90 (m, 2H, overlapped with water signal), 3.30 (m, 4H), 2.5−2.36 (m, 2H), 2.10−1.94 (m, 6H). Note: the chemical shifts of the signals at 9.88 and 8.74 ppm vary among different batches, likely because of concentration differences. LC/MS (ESI) m/z calcd for $C_{25}H_{28}N_5O_3$, 446.22; found, 446.50 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{25}H_{28}N_5O_3$, 446.2192; found, 446.2207 $[M + H]^+$.

HATU (39 mg, 0.10 mmol) was added in one portion to a solution of the HCl salt of (2*S*)-*N*-[4-(5-{4-[(2*S*)-pyrrolidine-2-amido]-phenyl}-1,3-oxazol-2-yl)phenyl]pyrrolidine-2-carboxamide (25 mg, 0.048 mmol), (*R*)-2-(dimethyl-amino)-2-phenylacetic acid·HCl (23.0 mg, 0.106 mmol), and DIEA (0.050 mL, 0.29 mmol) in DMF (1.5 mL), and the resultant mixture was stirred at rt for 90 min. The reaction mixture was purified by a reverse-phase HPLC (MeOH/H_2O/TFA) to afford title compound **21** as a light yellow solid (42 mg, 88% yield assuming *bis*-TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 10.47 (s, 1H), 10.31 (br s, 2H), 8.07 (d, J = 8.8 Hz, 2H), 7.83−7.74 (m, 7H), 7.62−7.57 (m, 10H), 5.57 (d, J = 2.9, 2H), 4.52−4.47 (m, 2H), 3.98−3.92 (m, 2H), 3.27−3.21 (m, 2H), 2.97 (d, J = 4.3 Hz, 6H), 2.47 (d, J = 4.3 Hz, 6H), 2.25−2.13 (m, 2H), 2.07−1.83 (m, 6H). Note: the ^{1}H NMR data is for the major rotamer because it was not feasible to capture the chemical shifts for the minor rotamer accurately. LC (method B): t_R = 2.96 min. LC/MS (ESI) m/z calcd for $C_{45}H_{50}N_7O_5$, 768.39; found, 768.44. HRMS (ESI) m/z calcd for $C_{45}H_{50}N_7O_5$, 768.3873; found, 768.3889 $[M + H]^+$.

(*S*)-*tert*-Butyl 2-(6-(2-Aminoacetyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (23). A suspension of *N*-(4-(2-chloroacetyl)-2-nitrophenyl)acetamide (25.7 g, 0.10 mol) in 3 N HCl (250 mL) was heated in a 1 L screw-top pressure vessel at 80 °C for 20 h. After it was allowed to cool to rt, 1-(4-amino-3-nitrophenyl)-2-chloro-ethanone·HCl (23.2 g, 92%) was isolated as a bright yellow solid by vacuum filtration. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, J = 2.1 Hz, 1H), 8.09 (br s, 2H), 7.92 (dd, J = 8.9, 2.1 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 5.09 (s, 2H). LC/MS (ESI) m/z calcd for $C_8H_7ClN_2O_3$, 215.02; found, 215.19 $[M + H]^+$.

1-(4-Amino-3-nitrophenyl)-2-chloroethanone·HCl (23.2 g, 0.090 mol) was suspended in MeOH (600 mL), and tin(II) chloride dihydrate (65 g, 0.29 mol) was added in one portion. The suspension was heated at 70 °C for 14 h while being vigorously stirred before an additional 20 g of tin(II) chloride dihydrate was added, and the reaction mixture was stirred further at 70 °C for 8 h. After being cooled to rt, most of the solvent was removed in vacuo, and the residue was poured into a beaker containing EtOAc and a sat. aq. $NaHCO_3$ solution (1.2 L, 1:1 by volume). **Caution:** *significant CO_2 evolution was observed*. The precipitate was removed by suction filtration, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2×), and the combined organic phase was washed with brine, dried (Na_2SO_4), and filtered. Concentration to one-quarter volume and filtration of the precipitate afforded 2-chloro-1-(3,4-diaminophenyl)ethanone as a brick red solid (10.0 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (dd, J = 8.3, 2.3 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.57 (br s, 2H), 4.85 (s, 2H), 4.78 (br s, 2H). LC/MS (ESI) m/z calcd for $C_8H_{10}ClN_2O$, 185.05; found, 185.02 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_8H_{10}ClN_2O$, 185.0482; found, 185.0480 $[M + H]^+$.

HATU (38.5 g, 101 mmol) was added portionwise to a vigorously stirred solution of 2-chloro-1-(3,4-diaminophenyl)ethanone (17.0 g, 92.0 mmol), *N*-Boc-L-proline (19.8 g, 92.0 mmol), and DIEA (17.6 mL, 101 mmol) in DMF (200 mL). After 6 h, the mixture was

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concentrated in vacuo to remove the solvent, and the residue was taken up in EtOAc, washed with a sat. aq. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a viscous brown oil that was taken up in glacial acetic acid (100 mL) and heated at 60 °C for 20 h. The solvent was removed in vacuo, and the residue was taken up in EtOAc, washed carefully with a sat. aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was then preadsorbed onto silica gel and subjected to flash chromatography (silica gel; 50−100% EtOAc/hexanes) to furnish *S*-*tert*-butyl 2-(6-(2-chloroacetyl)-1*H*-benzo[*d*]-imidazol-2-yl)pyrrolidine-1-carboxylate as a yellow foam (22.4 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.81 (dd, J = 8.3, 2.3 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 4.99/4.93 (s, 1H), 3.60 (br s, 1H), 3.46−3.41 (m, 1H), 2.36−2.30 (m, 1H), 2.01−1.89 (m, 3H), 1.39/1.06 (s, 9H). LC/MS (ESI) m/z calcd for $C_{18}H_{23}ClN_3O_3$, 364.14; found, 364.20 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{18}H_{23}ClN_3O_3$, 364.1415; found, 364.1428 $[M + H]^+$.

Sodium azide (1.79 g, 27.5 mmol) was added in one portion to a stirred solution of (*S*)-*tert*-butyl 2-(6-(2-chloroacetyl)-1*H*-benzo[*d*]-imidazol-2-yl)pyrrolidine-1-carboxylate (10.0 g, 27.5 mmol) in CH_3CN (200 mL), and the resultant mixture was stirred at 60 °C for 16 h. The reaction mixture was cooled to rt, and the solvent was removed in vacuo. The residue was diluted with EtOAc and washed with H_2O and brine prior to being dried over anhydrous Na_2SO_4 and filtered. Concentration of the filtrate afforded (*S*)-*tert*-butyl 2-(6-(2-azidoacetyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (6.8 g, 48%) as a golden-orange foam, which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 and 8.03 (2s, 1H), 7.80−7.75 (m, 1H), 7.65/7.56 (d, J = 8.5 Hz, 1H), 4.99−4.93 (m, 3H), 3.60 (br s, 1H), 3.46−3.41 (m, 1H), 2.38−2.27 (m, 1H), 2.01−1.89 (m, 3H), 1.40/1.06 (s, 9H). LC/MS (ESI) m/z calcd for $C_{18}H_{23}N_6O_3$, 371.19; found, 371.32 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{18}H_{23}N_6O_3$, 371.1832; found, 371.1825 $[M + H]^+$.

Tin(II) chloride dihydrate (3.84 g, 17.0 mmol) was added to a stirred solution of (*S*)-*tert*-butyl 2-(6-(2-azidoacetyl)-1*H*-benzo[*d*]-imidazol-2-yl)-pyrrolidine-1-carboxylate (2.10 g, 5.67 mmol) in MeOH (50 mL). The reaction mixture was heated at 60 °C for 8 h and stirred at rt for 12 h before it was concentrated in vacuo to afford title compound **23** contaminated with tin salts as a tan solid (5.96 g, above theoretical yield). It was used in the next step without further purification. LC/MS (ESI) m/z calcd for $C_{18}H_{25}N_4O_3$, 345.19; found, 345.37 $[M + H]^+$.

(*S*)-2-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]-imidazole-6-carboxylic acid (25). Isobutyl chloroformate (8.1 mL, 90.3 mmol) was added dropwise to a cold (0 °C), stirred solution of *N*-Boc-L-proline (19.4 g, 90.3 mmol) and *N*-methylmorpholine (9.9 mL, 90.3 mmol) in THF (150 mL). After 25 min at 0 °C, this suspension was cannulated into a cold (0 °C) solution of methyl 3,4-diaminobenzoate (**24**) (15.0 g, 90.3 mmol) and DIEA (15.7 mL, 90.3 mmol) in THF (250 mL). The reaction mixture was allowed to gradually warm to rt, where it was stirred for 18 h before additional *N*-Boc-L-proline (5.8 g), isobutyl chloroformate (2.4 mL), *N*-methylmorpholine (3.0 mL), and DIEA (4.2 mL) were added to ensure complete consumption of the starting material. After being stirred for an additional 2 h, the mixture was diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and filtered. Concentration of the filtrate gave a residue that was taken up in glacial acetic acid (200 mL) and heated at 60 °C for 6 h. The solvent was removed in vacuo, and the residue was diluted with EtOAc, washed carefully with a sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel; 10−100% EtOAc/hexanes) to afford (*S*)-methyl 2-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole-6-carboxylate as a tan foam (31.2 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.79 (dd, J = 8.4, 1.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 5.06−4.88 (2 m, 1H), 3.86 (s, 3H), 3.65−3.55 (m, 1H), 3.46−3.39 (m, 1H), 2.41−2.25 (m, 1H), 2.06−1.78 (m, 3H), 1.40 and 1.05 (2s, 9H). LC/MS (ESI) m/z calcd for $C_{18}H_{24}N_3O_4$, 346.18; found, 346.19 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{18}H_{24}N_3O_4$, 346.1761; found, 346.1749 $[M + H]^+$.

A solution of 5 N NaOH (18.1 mL, 90.5 mmol) was added to a stirred solution of (*S*)-methyl 2-(1-(*tert*-butoxy-carbonyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole-6-carboxylate (31.2 g, 90.3 mmol) in MeOH (90 mL), and the mixture was stirred for 16 h at rt. The mixture was washed with Et_2O followed by EtOAc. The aqueous phase was acidified with 6 N HCl to pH ∼5 and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Title compound **25** was retrieved as a tan foam (33.7 g, combined yield for two steps is above theoretical value) and was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.60−12.40 (br m, 2H), 8.08 (br s, 1H), 7.78 (dd, J = 8.4, 1.1 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 5.00−4.92 (2m, 1H), 3.65−3.54 (m, 1H), 3.47−3.40 (m, 1H), 2.43−2.20 (m, 1H), 2.06−1.80 (m, 3H), 1.39 and 1.05 (2s, 9H). LC/MS (ESI) m/z calcd for $C_{17}H_{22}N_3O_4$, 332.16; found, 332.14 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{17}H_{22}N_3O_4$, 322.1610; found, 322.1603 $[M + H]^+$.

(1*R*)-2-((2*S*)-2-(5-(2-(2-((2*S*)-1-((2*R*)-2-(Dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-benzimidazol-6-yl)-1,3-oxazol-5-yl)-1*H*-benzimidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine (27). HATU (0.74 g, 1.9 mmol) was added in one portion to a stirred solution of aminoketone **23** (0.62 g, ∼1.6 mmol), carboxylic acid **25** (0.54 g, 1.6 mmol), and DIEA (0.56 mL, 3.2 mmol) in anhydrous DMF (15 mL). The reaction mixture was stirred at rt for 2 h before it was diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel; 5−100% B/A, where A = CH_2Cl_2 and B = 10% MeOH in CH_2Cl_2) to afford (*S*)-*tert*-butyl 2-(6-(2-(2-((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-5-yl)-2-oxoethyl-carbamoyl)-1*H*-benzo[*d*]-imidazol-2-yl)pyrrolidine-1-carboxylate as a yellow oil (0.90 g, 84%), which was used in the next step directly. LC/MS (ESI) m/z calcd for $C_{35}H_{44}N_6O_7$, 658.34; found, 658.22 $[M + H]^+$.

A solution of crude (*S*)-*tert*-butyl 2-(6-(2-(2-((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-5-yl)-2-oxoethylcarbamoyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (0.88 g, 1.3 mmol), Ph_3P (0.70 g, 2.7 mmol), and Et_3N (0.85 mL, 6.1 mmol) in CH_2Cl_2 (90 mL) was stirred at rt for 5 min before hexachloroethane (0.60 g, 2.6 mmol) was added portion wise. The reaction mixture was stirred for 4 h before additional hexachloroethane (0.30 g) was added followed by an additional portion of Ph_3P (0.25 g) and hexachloroethane (0.20 g). After being stirred for an additional 16 h at rt, the solvent was removed in vacuo. The residue was then diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resultant residue was taken up in a minimal amount of CH_2Cl_2 and subjected to flash chromatography (silica gel; 0−10% B, where solvent A = EtOAc and solvent B = 10% MeOH/EtOAc) to afford **26** as a light yellow solid (432 mg, 42% for two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.53/12.44/12.34 (s, 2H), 8.26 (d, J = 7.0 Hz, 0.5H), 8.13 (br s, 0.5H), 8.03 (d, J = 5.8 Hz, 0.5H), 7.93−7.89 (m, 1H), 7.85 (br s, 0.5H), 7.74−7.54 (series of m, 3.5H), 5.01/4.94 (br s, 2H), 3.62 (br s, 2H), 3.44 (br s, 2H), 2.37−2.30 (m, 2H), 2.04−1.91 (m, 6H), 1.41 and 1.08 (2s, 18H). LC/MS (ESI) m/z calcd for $C_{35}H_{42}N_7O_5$, 640.32; found, 640.87 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{35}H_{42}N_7O_5$, 640.3247; found, 640.3231 $[M + H]^+$.

The HCl salt of 5-(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-5-yl)-2-(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)oxazole was prepared as a light yellowish-tan solid from **26** in a similar manner as described in the preparation of **8**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (br s, 2H), 9.61−9.33 (m, 2H), 8.34 (s, 1H), 8.11 (s, 1H), 8.06 (dd, J = 8.6, 1.5 Hz, 1H), 7.88 (s, 1H), 7.84−7.73 (m, 3H), 5.03 (d, J = 5.3 Hz, 2H), 3.56 (s, 2H), 3.49−3.30 (m, 4H), 2.30 (dt, J = 12.9, 7.6 Hz, 2H), 2.20−2.00 (m, 4H). LC/MS (ESI) m/z calcd for $C_{25}H_{26}N_7O$, 440.22; found, 440.12 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_7O$, 440.2199; found, 440.2218 $[M + H]^+$.

Title compound **27** (TFA salt, yellow solid) was prepared from the HCl salt of 5-(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-5-yl)-2-(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)oxazole and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure

described for the preparation of **9a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.16 (br s, 2H), 8.26−7.57 (series of m, 17H), 5.53−5.52 (m, 1H), 5.26−5.24 (m, 1H), 4.09 (br s, 2H), 3.18−3.14 (m, 1H), 2.95−2.95 (m, 3H), 2.45 (br s, 12H), 2.33 (m, 1H), 2.25−2.20 (m, 2H), 2.14−1.93 (m, 5H). LC (method D, except that column 3 was used): t_R = 1.73 min. LC/MS (ESI) m/z calcd for $C_{45}H_{48}N_9O_3$, 762.39; found, 762.31 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{45}H_{48}N_9O_3$, 762.3880; found, 762.3906 $[M + H]^+$.

(*S*)-1-((*S*)-2-(Dimethylamino)-2-phenylacetyl)-*N*-(4-(5-(2-((*S*)-1-((*R*)-2-(dimethylamino)-2-phenyl-acetyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)-oxazol-2-yl)phenyl)pyrrolidine-2-carboxamide (31a). EDCI (4.22 g, 22.0 mmol) was added to a mixture of **28a** (2.74 g, 20.0 mmol) and *N*-Boc-L-proline (4.73 g, 22.0 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at rt for 16 h, diluted with CH_2Cl_2 (30 mL), washed with 1 N HCl and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was preadsorbed onto silica gel and purified by flash chromatography (silica gel; 20−100% B/A, where solvent A = 1% acetic acid/hexanes and solvent B = 1% acetic acid/EtOAc) to yield **29** as a white solid (2.97 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78−12.45 (m, 1H), 10.44−10.19 (m, 1H), 7.95−7.83 (m, 2H), 7.78−7.63 (m, 2H), 4.21 (dd, J = 8.1, 4.5 Hz, 1H), 3.53−3.21 (m, 2H), 2.27−2.13 (m, 1H), 1.97−1.72 (m, 3H), 1.39 and 1.25 (2s, 9H). LC/MS (ESI) m/z calcd for $C_{17}H_{23}N_2O_5$, 335.16; found, 335.25 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_5$, 333.1450; found, 333.1467 $[M - H]^-$.

HATU (0.45 g, 1.2 mmol) was added in one portion to a stirred solution of aminoketone **23** (0.34 g, 1.0 mmol), acid **29** (0.33 g, 1.0 mmol), and DIEA (0.70 mL, 4.0 mmol) in DMF (10 mL). Note: a second coupling reaction was performed in tandem on 160 mg (0.42 mmol) of **23** using proportionally the same amount of reagents. The reaction mixtures were stirred at rt for 16 h. They were then combined, diluted with EtOAc, washed with a sat. aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated to afford crude (*S*)-*tert*-butyl 2-(4-(2-(2-((*S*)-1-(*tert*-butoxycarbonyl)-pyrrolidin-2-yl)-1*H*-benzo[*d*]-imidazol-6-yl)-2-oxoethylcarbamoyl)-phenylcarbamoyl)-pyrrolidine-1-carboxylate as a brown viscous oil (1.65 g, above theoretical yield), which was submitted to the next step without further purification. LC/MS (ESI) m/z calcd for $C_{35}H_{45}N_6O_7$, 661.34; found, 661.42 $[M + H]^+$.

A solution of crude (*S*)-*tert*-butyl 2-(4-(2-(2-((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]-imidazol-6-yl)-2-oxoeth-yl-carbamoyl)phenylcarbamoyl)pyrrolidine-1-carboxylate (1.65 g), Ph_3P (1.31 g, 5.0 mmol), and Et_3N (1.40 mL, 10.0 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 5 min before hexachloroethane (1.18 g, 5.0 mmol) was added in one portion. The reaction mixture was stirred for 4 h and then preadsorbed onto silica gel and purified by flash chromatography (silica gel; 50−100% EtOAc/hexanes followed by 0−10% MeOH/EtOAc) to afford **30** as a brown foam, which was submitted to the next step directly. LC/MS (ESI) m/z calcd for $C_{35}H_{43}N_6O_6$, 643.32; found, 643.41 $[M + H]^+$.

A cold (0 °C) solution of 4 N HCl in dioxane (10 mL) was added to a stirred solution of biscarbamate **30** in MeOH (5 mL), the resultant mixture was allowed to warm to rt and stirred for 2 h before Et_2O was added, and the suspension was suction-filtered and dried in vacuo to afford the HCl salt of (*S*)-*N*-(4-(5-(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)oxazol-2-yl)phenyl)pyrrolidine-2-carboxamide as a brown solid (127.2 mg, 9.0%). The filtrate was purified by flash chromatography (silica gel; 1:9:90 mixture of NH_4OH/MeOH/CH_2Cl_2) to yield an additional mass of the product in a free-base form as a tan solid (68.2 mg, 6.2%). For the purpose of characterization, a portion of the free-base form was further purified by reverse-phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of the product as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 9.82 (br s, 1H), 9.40 (br s, 2H), 9.27 (br s, 1H), 8.73 (br s, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.05 (s, 1H), 7.84−7.78 (m, 3H), 7.75−7.72 (m, 2H), 5.04−4.96 (m, 2H), 4.43−4.35 (m, 2H), 3.50−3.21 (m, 4H), 2.27−1.87 (series of m, 6H). LC/MS (ESI) m/z calcd for $C_{25}H_{27}N_6O_2$, 443.22; found, 443.31 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{25}H_{27}N_6O_2$, 443.2195; found, 443.2206 $[M + H]^+$.

Title compound **31a** (TFA salt, reddish-tan solid) was prepared from the HCl salt of (*S*)-*N*-(4-(5-(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo-[*d*]imidazol-5-yl)oxazol-2-yl)phenyl)-pyrrolidine-2-carboxamide and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for the preparation of **9a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.52/10.44 (two s, 1H), 10.25 (br s, 1H), 8.46 (s, 1H), 8.08−7.56 (series of m, 17H), 5.55−5.52 (m, 1H), 5.24−5.22 (m, 1H), 4.51−4.48 (m, 1H), 4.09 (br s, 1H), 3.97−3.92 (m, 2H), 3.24−3.15 (m, 2H), 2.95 (br s, 6H), 2.45 (br s, 6H), 2.36−2.09 (m, 3H), 2.02−1.86 (m, 5H). LC (Method E): t_R = 1.92 min. LC/MS (ESI) m/z calcd for $C_{45}H_{49}N_8O_4$, 765.39; found, 765.53 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{45}H_{49}N_8O_4$, 765.3877; found, 765.3843 $[M + H]^+$.

(2*R*)-1-[(2*S*)-2-{5-[2-(3-Aminophenyl)-1,3-oxazol-5-yl]-1*H*-1,3-benzodiazol-2-yl}pyrrolidin-1-yl]-2-(dimethylamino)-2-phenylethan-1-one (33). *tert*-Butyl (2*S*)-2-{6-[2-(3-{[(*tert*-butoxy)-carbonyl]amino}phenyl)-1,3-oxazol-5-yl]-1*H*-1,3-benzodiazol-2-yl}-pyrrolidine-1-carboxylate was prepared in two steps as a light yellow solid from aminoketone **23** and acid **28b** in a similar manner as described in the preparation of benzimidazole **30**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.35 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 5.30/5.08 (br s, 1H), 3.62 (br s, 1H), 3.49−3.46 (m, 1H), 2.46−2.41 (m, 1H), 2.11−2.08 (m, 1H), 2.02−1.97 (m, 2H), 1.51 (s, 9H), 1.41/1.10 (s, 9H). LC/MS (ESI) m/z calcd for $C_{30}H_{36}N_5O_5$, 546.27; found, 546.10 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{30}H_{36}N_5O_5$, 546.2716; found, 546.2728 $[M + H]^+$.

Compound **32** was prepared from the above precursor as a yellowish-orange solid in a similar manner as described in the preparation of **8**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.41 (br s, 1H), 9.45 (br s, 1H), 8.07 (s, 1H), 8.01 (s, 1H), 7.99 (s, 1H), 7.90 (s, 1H), 7.77 (s, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 5.02 (t, J = 7.3 Hz, 1H), 3.46−3.41 (m, 1H), 3.39−3.35 (m, 1H), 2.55−2.52 (m, 1H), 2.33−2.26 (m, 1H), 2.17−2.11 (m, 1H), 2.10−2.04 (m, 1H). LC/MS (ESI) m/z calcd for $C_{20}H_{20}N_5O$, 346.17; found, 346.00 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_5O$, 346.1668; found, 346.1672 $[M + H]^+$.

Title compound **33** was prepared as an off-white solid from **32** and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl (1.0 equiv) in a similar manner as described in the preparation of **9a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (br s, 1H), 7.72 (s, 1H), 7.62 (m, 6H), 7.32 (s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 6.93/6.76 (m, 1H), 6.71 (d, J = 7.6 Hz, 1H), 5.38 (br s, 1H), 5.21−5.19 (m, 1H), 4.10−4.07 (m, 1H), 3.20−3.17 (m, 1H), 2.89 (br s, 6H), 2.24−2.16 (m, 1H), 2.15−2.09 (m, 1H), 2.03−2.00 (m, 1H), 1.96−1.90 (m, 1H). LC/MS (ESI) m/z calcd for $C_{30}H_{29}N_6O_2$, 505.24; found, 505.26 $[M - H]^-$. HRMS (ESI) m/z calcd for $C_{30}H_{29}N_6O_2$, 505.2352; found, 505.2358 $[M - H]^-$.

(*S*)-1-((*R*)-2-(Dimethylamino)-2-phenylacetyl)-*N*-(3-(5-(2-((*S*)-1-((*R*)-2-(dimethylamino)-2-phenylacetyl)pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)-oxazol-2-yl)phenyl)pyrrolidine-2-carboxamide (31b). HATU (12.6 g, 33.0 mmol) was added in one portion to a stirred suspension of (*R*)-2-(dimethylamino)-2-phenyl-acetic acid·HCl (7.13 g, 33.2 mmol), (*S*)-*tert*-butyl pyrrolidine-2-carboxylate (2.15 g, 10.0 mmol), and *N*-methylmorpholine (7.30 mL, 66.0 mmol) in anhydrous DMF (100 mL). The reaction mixture was stirred at rt for 16 h and was then diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resultant crude material was purified by flash chromatography (silica gel; 10% MeOH/EtOAc) to afford two batches of *tert*-butyl (2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-pyrrolidine-2-carboxylate: pure material (light yellow foam, 1.20 g, 10.2%) and slightly impure material (orange solid, 7.15 g, 65.2%). The later material was advanced to the next step. LC/MS (ESI) m/z calcd for $C_{15}H_{21}N_2O_3$, 333.22; found, 333.12 $[M + H]^+$.

The slightly impure product (7.15 g, 21.5 mmol) was taken up in dioxane (20 mL) and treated with a cold (0 °C) solution of 4 N HCl in dioxane (50 mL). The mixture was allowed to warm to rt and stirred for 4 h. Et_2O (50 mL) was added, and the resultant

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heterogeneous mixture was stirred for 0.5 h. The precipitate was suction-filtered and rinsed with Et_2O to furnish (2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxylic acid as a peach-colored, hygroscopic solid (3.12 g, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (br s, 1H), 10.38/10.29 (two overlapping br s, 1H), 7.61−7.57 (m, 1.9H), 7.54−7.52 (m, 2.7H), 7.49−7.43 (m, 0.4H), 5.65 (d, J = 8.8 Hz, 0.94H), 5.55 (d, J = 8.1 Hz, 0.06H), 4.95 (d, J = 8.0 Hz, 0.05H), 4.29 (dd, J = 8.7, 2.8 Hz, 0.95H), 3.95−3.90 (m, 1H), 3.13−3.07 (m, 1H), 2.93/2.88 (two overlapping d, J = 4.2 and 5.9 Hz, 3H), 2.45/2.40 (two overlapping d, J = 4.4 and 4.6 Hz, 3H), 2.13−2.03 (m, 1H), 1.93−1.79 (m, 3H). LC/MS (ESI) m/z calcd for $C_{15}H_{21}N_2O_3$, 277.16; found, 277.02 $[M + H]^+$.

Title compound **31b** (TFA salt, straw-colored solid) was prepared from aniline **33** and (2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-pyrrolidine-2-carboxylic acid according to the procedure described for the preparation of **9a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46/10.36 (s, 1H), 10.26 (br s, 1H), 8.46 (s, 1H), 8.05−7.39 (series of m, 17H), 5.55−5.52 (m, 1H), 5.43 and 5.23 (two dd, J = 7.9, 2.4, 1H), 4.51−4.48 (m, 1H), 4.09−4.06 (m, 1H), 3.97−3.83 (m, 2H), 3.61−3.56 (m, 1H), 3.23−3.14 (m, 1H), 2.96 (br s, 6H), 2.46 (br s, 6H), 2.23−2.09 (m, 3H), 2.04−1.87 (m, 5H). LC (method E): t_R = 1.91 min. LC/MS (ESI) m/z calcd for $C_{45}H_{49}N_8O_4$, 765.39; found, 765.35 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{45}H_{49}N_8O_4$, 765.3877; found, 765.3887 $[M + H]^+$.

(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-[3-(2-{3-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-amido]phenyl}-1,3-oxazol-5-yl)phenyl]pyrrolidine-2-carboxamide (38a). HATU (1.14 g, 2.99 mmol) was added in one portion to a stirred solution of aminoketone **34** (0.65 g, 3.0 mmol), acid **35** (1.0 g, 3.0 mmol), and DIEA (1.1 mL, 6.0 mmol) in DMF (10 mL). The mixture was stirred for 1 h before additional **35** (100 mg), HATU (140 mg), and DIEA (0.1 mL) were added. The mixture was stirred further for 1 h before the solvent was removed in vacuo. The residue was taken up in EtOAc and was washed with 0.1 N HCl, sat. aq. $NaHCO_3$ solution, and brine. The organic phase was dried over anhydrous $MgSO_4$ and evaporated in vacuo to afford (*S*)-*tert*-butyl 2-(3-(2-(3-nitrophenyl)-2-oxoethylcarbamoyl)phenylcarbamoyl)-pyrrolidine-1-carboxylate (2.22 g) as a yellow foam, which was submitted to the next step without further purification. LC/MS (ESI) m/z calcd for $C_{25}H_{29}N_4O_7$, 397.15; found, 397.50 $[M + H\text{-Boc}]^+$.

A solution of crude (*S*)-*tert*-butyl 2-(3-(5-(3-nitrophenyl)oxazol-2-yl)phenylcarbamoyl)-pyrrolidine-1-carboxylate (2.22 g), Ph_3P (1.57 g, 5.98 mmol), and Et_3N (1.7 mL, 12 mmol) in CH_2Cl_2 (15 mL) was stirred at rt for 5 min before hexachloroethane (1.42 g, 5.98 mmol) was added in one portion. The reaction mixture was stirred for 16 h before it was diluted with CH_2Cl_2 and washed with 0.1 N HCl, sat. aq. $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (silica gel; 2−100% EtOAc/hexanes) to afford **36** as a tan foam (0.34 g, 24% for two steps). The product was slightly impure but was carried forward directly to the next step. For the purpose of characterization, a portion of the product was purified by reverse-phase HPLC ($CH_3CN/H_2O/NH_4OAc$) to yield a more pure sample of the target product as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (br s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 8.20 (dd, J = 8.1, 1.2 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.86 (br s, 1H), 7.72 (br s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.60 (s, 1H), 7.45 (br s, 1H), 4.54 (br s, 1H), 3.51 (br s, 1H), 3.42 (br. s, 1H), 2.04−1.97 (m, 3H), 1.67 (br s, 1H), 1.55 (s, 9H). LC/MS (ESI) m/z calcd for $C_{25}H_{27}N_4O_6$, 501.19; found, 501.68 $[M + Na]^+$.

A suspension of impure **36** (1.43 g, ~2.99 mmol) in MeOH (15 mL) was subjected to Parr hydrogenation at 20 psi H_2 over 10% Pd/C (318 mg) for 16 h at rt before it was suction-filtered through Celite and concentrated in vacuo. The resultant material was purified by reverse-phase HPLC ($CH_3CN/H_2O/NH_4OAc$) to afford (*S*)-*tert*-butyl 2-(3-(5-(3-aminophenyl)oxazol-2-yl)phenylcarbamoyl)-pyrrolidine-1-carboxylate as light yellow solid (32.0 mg, 2.3% for three steps from **34** and **35**). ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.93 (br s, 1H), 7.84−7.79 (m, 1H), 7.74−7.69 (m, 1H), 7.51−7.45 (m, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.15−7.15 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 6.7 Hz, 1H), 4.41−4.40/4.34−4.31 (m, 1H), 3.63−3.58 (m, 1H), 3.53−3.49 (m, 1H), 2.39−2.31 (m, 1H), 2.11−2.04 (m, 2H), 1.95−1.91 (m, 1H), 1.50/1.40 (s, 9H). LC/MS (ESI) m/z calcd for $C_{25}H_{29}N_4O_4$, 449.22; found, 449.68 $[M + H]^+$.

HATU (30.1 mg, 0.079 mmol) was added in one portion to a stirred mixture of (*S*)-*tert*-butyl 2-(3-(5-(3-aminophenyl)oxazol-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate (32.3 mg, 0.072 mmol), *N*-Boc-L-proline (17.1 mg, 0.079 mmol), and DIEA (0.05 mL, 0.3 mmol) in DMF (1 mL). The mixture was stirred at rt for 1 h before the solvent was removed with a stream of N_2, and the residue was purified by reverse-phase HPLC ($CH_3CN/H_2O/NH_4OAc$) to afford **37a** as a light tan solid (18.0 mg, 37%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 10.19 (s, 1H), 8.41−8.36 (m, 1H), 8.10−8.05 (m, 1H), 7.81−7.73 (m, 3H), 7.64−7.58 (m, 1H), 7.54 (m, 2H), 7.47−7.44 (m, 1H), 4.34−4.29/4.25−4.22 (m, 2H), 3.48−3.45 (m, 2H), 3.39−3.34 (m, 2H), 2.26−2.18 (m, 2H), 1.96−1.86 (m, 4H), 1.85−1.80 (m, 2H), 1.41/1.30 (s, 18H). LC/MS (ESI) m/z calcd for $C_{35}H_{44}N_5O_7$-Boc, 546.27; found, 546.78 $[M + H\text{-Boc}]^+$.

To a cold (0 °C) solution of **37a** (18.0 mg, 0.028 mmol) in MeOH (0.5 mL) was added 4 N HCl in dioxane (1 mL). The reaction mixture was allowed to warm to rt and stirred for 2 h before it was evaporated to dryness. The HCl salt of (2*S*)-*N*-[3-(2-{3-[(2*S*)-pyrrolidine-2-amido]phenyl}-1,3-oxazol-5-yl)phenyl]pyrrolidine-2-carboxamide was isolated as a light yellow solid (15.0 mg, 100%) and was carried forward directly. LC/MS (ESI) m/z calcd for $C_{25}H_{28}N_5O_3$, 446.22; found, 446.61 $[M + H]^+$.

Title compound **38a** (off-white solid) was prepared from the HCl salt of (2*S*)-*N*-[3-(2-{3-[(2*S*)-pyrrolidine-2-amido]phenyl}-1,3-oxazol-5-yl)phenyl]pyrrolidine-2-carboxamide and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for the preparation of **9a** with the exception that the reverse-phase HPLC purification used a different solvent system ($CH_3CN/H_2O/NH_4OAc$). ^{1}H NMR (500 MHz, MeOH-d_4) δ 10.34 (s, 1H), 10.29 (s, 1H), 8.41 (s, 1H), 8.12 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.65−7.58 (m, 13H), 7.54 (t, J = 8.1 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 5.37 (d, J = 1.7 Hz, 2H), 4.61−4.58 (m, 2H), 3.97−3.92 (m, 2H), 3.27−3.22 (m, 2H), 3.10 (br s, 6H), 2.58 (br s, 6H), 2.31−2.24 (m, 2H), 2.21−2.07 (m, 4H), 1.95−1.90 (m, 2H). LC (method F): t_R = 3.29 min. LC/MS (ESI) m/z calcd for $C_{45}H_{50}N_7O_5$, 768.39; found, 768.28. HRMS (ESI) m/z calcd for $C_{45}H_{50}N_7O_5$, 768.3873; found, 768.3848 $[M + H]^+$.

(2*S*)-1-[(2*R*)-2-(Dimethylamino)-2-phenylacetyl]-*N*-[4-(2-{3-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-amido]phenyl}-1,3-oxazol-5-yl)phenyl]pyrrolidine-2-carboxamide (38b). *N*-Methylmorpholine (2.54 mL, 23.1 mmol) was added to a solution of aminoketone **39** (1.00 g, 4.62 mmol), benzoic acid **40** (1.21 g, 5.08 mmol), and HOAT (0.691 g, 5.08 mmol) in DMF (30 mL), and, 5 min later, EDCI (1.33 g, 6.92 mmol) was added in one portion. The reaction mixture was stirred at rt for 4 h, diluted with EtOAc, and washed sequentially with H_2O, 1 N HCl, sat. aq. $NaHCO_3$, H_2O, and brine. After drying over $MgSO_4$, the mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel; 30−100% EtOAc/hexanes) to afford *tert*-butyl *N*-(3-{[2-(4-nitrophenyl)-2-oxoethyl]carbamoyl}phenyl)-carbamate as a dark orange solid (0.131 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.85 (t, J = 5.4 Hz, 1H), 8.39−8.35 (m, 2H), 8.29−8.23 (m, 2H), 8.01 (s, 1H), 7.55 (app dd, J = 7.9, 1.3 Hz, 1H), 7.47 (app dt, J = 8.0, 1.1 Hz, 1H), 7.36 (app t, J = 7.9 Hz, 1H), 4.80 (d, J = 5.5 Hz, 2H), 1.48 (s, 9H). LC/MS (ESI) m/z calcd for $C_{20}H_{22}N_3O_6$, 400.15; found, 400.33 $[M + H]^+$.

THF (3 mL) was added to a mixture of Burgess reagent (0.156 g, 0.656 mmol) and the above product (0.131 g, 0.328 mmol) in a pressure vial, and the deep-orange solution heated at 100 °C under microwave radiation (Biotage Initiator) for 15 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel; 10−30% EtOAc/hexanes) to afford **41** as an orange solid (0.1 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.37 (d, J = 8.8 Hz, 2H), 8.34 (s, 1H), 8.16 (s, 1H), 8.08 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.4 Hz,

1H), 7.50−7.43 (m, 1H), 1.51 (s, 9H). LC/MS (ESI) m/z calcd for $C_{20}H_{20}N_3O_5$, 382.14; found, 382.28 $[M + H]^+$.

Compound **41** (0.10 g, 0.26 mmol) was dissolved in a mixture of EtOH (5 mL) and THF (5 mL), and the yellow solution was hydrogenated on an H-Cube hydrogenator over 10% Pd/C (1 bar, 25 °C, 1 mL/min flow rate). After the solution passed through the system, THF was used to purge the line. The solution was concentrated under reduced pressure to afford carbamate **42** as a yellow oil (90 mg), which was used in the next step without further purification. LC/MS (ESI) m/z calcd for $C_{20}H_{22}N_3O_3$, 352.11; found, 352.34 $[M + H]^+$.

TFA (2.0 mL, 26 mmol) was added to a solution of carbamate **42** (90.0 mg, 0.256 mmol) in CH_2Cl_2 (10 mL), and the resulting orange solution was stirred at rt for 30 min. The volatile component was removed under reduced pressure, and the residue was free-based using an MCX cartridge (MeOH wash; 2 N NH_3/MeOH elution) to afford dianiline **43** as yellow gum (54 mg), which was used in the next step without further purification. LC/MS (ESI) m/z calcd for $C_{15}H_{14}N_3O$, 252.11; found, 252.30 $[M + H]^+$.

A mixture of dianiline **43** (54.0 mg, 0.215 mmol), *N*-Boc-L-proline (95.0 mg, 0.441 mmol), and EEDQ (112 mg, 0.451 mmol) in CH_2Cl_2 (5 mL) was stirred at rt overnight. The volatile component was removed under reduced pressure, and the residue was purified by reverse-phase HPLC (MeOH/water/TFA) to afford *bis*-carbamate **37b** as a yellow solid (120 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.24/10.20 (two s, 2H), 8.41−8.37 (m, 1H), 7.81−7.71 (m, 7H), 7.53−7.49 (m, 1H), 4.31−4.28 (m, 0.72H), 4.25−4.21 (m, 1.28H), 3.49−3.42 (m, 2H), 3.39−3.34 (m, 2H), 2.30−2.13 (m, 2H), 1.99−1.75 (m, 6H), 1.42/1.41 (two s, 6.3H), 1.30/1.29 (two s, 11.7H). LC/MS (ESI) m/z calcd for $C_{35}H_{44}N_5O_7$, 646.32; found, 646.50 $[M + H]^+$.

HCl (4 N in dioxane) (1.0 mL, 4.0 mmol) was added to a solution of biscarbamate **37b** (117 mg, 0.181 mmol) in CH_2Cl_2 (8 mL), and the resulting yellow suspension was stirred at rt for 1.5 h. The solvent was removed under reduced pressure to afford the HCl salt of (2*S*)-*N*-[3-(5-{4-[(2*S*)-pyrrolidine-2-amido]phenyl}-1,3-oxazol-2-yl)phenyl]-pyrrolidine-2-carboxamide as a yellow solid (72 mg), which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (br s, 2H), 9.61 (br s, 2H), 8.73 (m, 2H), 8.43 (br s, 1H), 7.86−7.76 (m, 7H), 7.56 (t, J = 8.0 Hz, 1H), 4.41 (app br s, 2H), 3.31 (m, 4H), 2.48−2.39 (m, 2H), 2.08−1.94 (m, 6H). LC/MS (ESI) m/z calcd for $C_{25}H_{28}N_5O_3$, 446.22; found, 446.40 $[M + H]^+$.

Title compound **38b** (TFA salt, off-white solid) was prepared from the HCl salt of (2*S*)-*N*-[3-(5-{4-[(2*S*)-pyrrolidine-2-amido]phenyl}-1,3-oxazol-2-yl)phenyl]pyrrolidine-2-carboxamide and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for the preparation of **9a**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.50/10.46 (two s, 2H), 10.28 (br s, 2H), 8.38 (s, 1H), 7.82−7.75 (m, 7H), 7.61−7.52 (m, 11H), 5.56 (m, 2H), 4.49 (m, 2H), 3.95 (m, 2H), 3.23 (m, 2H), 2.96 (m, 6H), 2.47 (app d, J = 4.1 Hz, 6H), 2.24−2.15 (m, 2H), 2.07−1.84 (m, 6H). LC (method I): t_R = 1.25 min. LC/MS (ESI) m/z calcd for $C_{45}H_{50}N_7O_5$, 768.39; found, 768.50 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{45}H_{50}N_7O_5$, 768.3873; found, 768.3851 $[M + H]^+$.

2-[(2*S*)-Pyrrolidin-2-yl]-5-[4-(4-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)phenyl]-1*H*-imidazole (49). For the preparation of title compound **49**, see the supplemental section of ref 3a.

2-Phenyl-1-[(2*S*)-2-{5-[4-(4-{2-[(2*S*)-1-(2-phenylacetyl)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]ethan-1-one (50a). Title compound **50a** (TFA salt, white foam) was prepared from **49** and phenylacetic acid according to the procedure described for the preparation of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.51 (very br s, ∼2H), 8.12 (s, 2H), 7.97−7.88 (m, 8H), 5.50/5.22−5.19 (2 m, 2H, likely rotamers), 3.92−3.87 (m, 2H), 3.80−3.63 (m, 6H), 2.43−2.23 (m, 2H), 2.12−2.02 (m, 6H). LC (method G): t_R = 1.67 min. LC/MS (ESI) m/z calcd for $C_{42}H_{41}N_6O_2$, 661.33; found 661.53 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{42}H_{41}N_6O_2$, 661.3291; found 661.3264 $[M + H]^+$.

Methyl *N*-[(1*R*)-2-[(2*S*)-2-{5-[4-(4-{2-[(2*S*)-1-[(2*R*)-2-[(Methoxycarbonyl)amino]-2-phenylacetyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl]carbamate (50b). Title compound **50b** (TFA salt, off-white solid) was prepared from **49** and (2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetic acid according to the procedure described for the preparation of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.48 (app br s, ∼2H), 8.18 (br s, 1.79H), 8.10 (br s, 0.21H), 7.99−7.91 (m, 7H), 7.89−7.70 (2 overlapping br m, 3H), 7.42−7.28 (m, 9H), 7.05 (m, 1H), 5.74 (br m, 0.17H), 5.54−5.49 (m, 1.68H), 5.41 (m, 0.32H), 5.21 (m, 1.83H), 3.93 (br m, 1.72H), 3.81 (br m, 0.28H), 3.54/3.53 (2 overlapping s, 6H), 3.20−3.15 (m, 2H), 2.31−2.21 (br m, 2H), 2.10−1.85 (2 overlapping m, 6H). LC (method H): t_R = 1.36 min. LC/MS (ESI) m/z calcd for $C_{46}H_{47}N_8O_6$, 807.36; found 807.40 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{46}H_{47}N_8O_6$, 807.3619; found 807.3587 $[M + H]^+$.

(2*R*)-2-(Dimethylamino)-1-[(2*S*)-2-{5-[4-(4-{2-[(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-phenylethan-1-one (50c). Title compound **50c** (TFA salt, off-white foam) was prepared from **49** and (2*R*)-2-(dimethylamino)-2-phenylacetic acid according to the procedure described for the preparation of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (very broad s, ∼2H), 8.09 (br m, 2H), 7.99−7.88 (m, 7.44), 7.74 (br m, 0.56H), 7.68−7.56 (m, 9.12H), 7.24−7.10 (m, 0.88H), 5.80 (m, 0.2H), 5.51 (s, 0.2H), 5.47 (s, 1.8H), 5.23 (m, 1.8H), 4.03 (m, 1.8H), 3.85 (m, 0.2H), 3.60 (m, 0.2H), 3.06 (m, 1.8H), 2.97−1.76 (overlapping br s and m, 20H). Note that it was not feasible to provide segmented integration for the upfield region because the signal for the dimethylamine moiety (∼2.88 ppm) was very broad and overlapped with other signals, including that of the solvent. LC (method B): t_R = 2.34 min. LC/MS (ESI) m/z calcd for $C_{46}H_{51}N_8O_2$, 747.41; found 747.46 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{46}H_{51}N_8O_2$, 747.4135; found, 747.4107 $[M + H]^+$.

(2*S*)-2-(Dimethylamino)-1-[(2*S*)-2-{5-[4-(4-{2-[(2*S*)-1-[(2*S*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-phenylethan-1-one (50d). Title compound **50d** (TFA salt, off-white foam) was prepared from **49** and (2*S*)-2-(dimethylamino)-2-phenylacetic acid according to the procedure described for the preparation of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (br s, 2H), 8.04−7.72 (m, 10H), 7.61−7.32 (m, 10H), 5.52/5.27/5.00/4.91 (4 m, 4H, the first two signals were relatively dominant), 3.91−3.78 (m, 2H), 3.43/3.20 (2 m, 2H, the later signal was dominant), 2.93 (app br s, ∼5H), 2.58−1.71 (collection of m, 15H, partially overlapped with solvent signal). Note that for some regions individual integration was not feasible because of baseline shift and signal broadening. LC (method G): t_R = 1.28 min. LC/MS (ESI) m/z calcd for $C_{46}H_{51}N_8O_2$, 747.41; found, 747.64 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{46}H_{51}N_8O_2$,747.4135; found, 747.4110 $[M + H]^+$.

Methyl *N*-[(1*R*)-2-[(2*S*)-2-{5-[4-(4-{2-[(2*S*)-1-[(2*R*)-2-(Dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-phenyl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl]carbamate (54a). To a mixture of amine **44** (10 g, 40 mmol), *N*-Cbz-L-proline (11.9 g, 47.7 mmol), and HATU (15.9 g, 41.8 mmol) in DMF (155 mL) was added DIEA (14.0 mL, 80.2 mmol) dropwise. The reaction mixture was stirred at rt for 1 h. The volatile component was removed in vacuo, and the residue was dissolved in EtOAc and washed with H_2O (3×). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a white solid. The solid was first recrystallized from EtOAc and then from MeOH to afford ketoamide **45b** as white needles (11.5 g, 65%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42−8.18 (m, 1H), 8.03−7.83 (m, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.44−7.21 (m, 5H), 5.16−4.93 (m, 2H), 4.65−4.41 (m, 2H), 4.40−4.22 (m, 1H), 3.60−3.43 (m, 1H), 3.43−3.33 (m, 1H), 2.26−2.02 (m, 1H), 1.98−1.74 (m, 3H). LC/MS (ESI) m/z calcd for $C_{21}H_{22}N_2O_4Br$, 445.08; found, 444.82 $[M + H]^+$.

A mixture of ketoamide **45b** (11.5 g, 25.8 mmol) and NH_4OAc (9.95 g, 129 mmol) in xylenes was heated at 140 °C in a sealed vessel for 3 h. The reaction mixture was allowed to cool to rt, and the volatile component was removed in vacuo. The residue was partitioned between EtOAc and H_2O, and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with a solution of sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in

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vacuo. The residue was purified by flash chromatography (silica gel; 50% EtOAc/hexanes) to afford imidazole **46c** as a light yellow foam (8.7 g, 79%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.38−11.76 (m, 1H), 7.80−7.64 (m, 2H), 7.64−7.44 (m, 3H), 7.44−7.34 (m, 2H), 7.34−7.22 (m, 1H), 7.22−7.11 (m, 1H), 7.06−6.83 (m, 1H), 5.21−5.00 (m, 2H), 5.00−4.88 (m, 1H), 3.69−3.54 (m, 1H), 3.54−3.36 (m, 1H), 2.37−2.13 (m, 1H), 2.09−1.94 (m, 2H), 1.95−1.75 (m, 1H). LC/MS (ESI) m/z calcd for $C_{21}H_{21}N_3O_2Br$, 426.08; found, 426.06 $[M + H]^+$.

To a mixture of imidazole **46c** (8.52 g, 20.0 mmol), boronate **47** (see supplemental section of ref 3a for preparation; 8.82 g, 20.0 mmol), and $NaHCO_3$ (5.58 g, 66.4 mmol) in 1,2-dimethoxyethane (170 mL) and H_2O (53 mL) was added $Pd(Ph_3P)_4$ (0.83 g, 0.72 mmol). The reaction mixture was heated at 80 °C for 15 h. The volatile component was removed in vacuo, the residue was taken up in 20% MeOH/$CHCl_3$ and washed with H_2O, and the aqueous phase was re-extracted with 20% MeOH/$CHCl_3$. The combined organic phase was washed with a sat. aq. $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Silica gel mesh was prepared from the residue and subjected to flash chromatography (silica gel; 50−100% EtOAc/hexanes) to afford coupled product **51a** as a tan solid (7.04 g, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.49−11.49 (m, 2H), 7.99−7.79 (m, 3H), 7.79−7.64 (m, 4H), 7.64−7.45 (m, 2H), 7.44−7.23 (m, 3H), 7.21−7.07 (m, 2H), 7.07−6.90 (m, 1H), 5.19−4.68 (m, 4H), 3.72−3.60 (m, 1H), 3.60−3.50 (m, 1H), 3.50−3.41 (m, 1H), 3.41−3.33 (m, 1H), 2.41−2.12 (m, 2H), 2.12−1.95 (m, 3H), 1.95−1.73 (m, 3H), 1.41 (br s, 4H), 1.17 (br s, 5H). LC/MS (ESI) m/z calcd for $C_{39}H_{43}N_6O_4$, 659.33; found, 659.32 $[M + H]^+$.

A mixture of **51a** (6.94 g, 10.5 mmol), 20% $Pd(OH)_2$ (1.388 g), and K_2CO_3 (6.94 g, 50.2 mmol) in MeOH (100 mL) was exposed to hydrogen gas at 60 psi in a Parr bottle for 3 h. The reaction mixture was filtered over Celite, and the filtrate was concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with H_2O, and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford impure **51b** as an off-white foam (5.08 g), which was used in the next step without further purification. LC/MS (ESI) m/z calcd for $C_{31}H_{37}N_6O_2$, 525.30; found, 525.30 $[M + H]^+$.

To a solution of pyrrolidine **51b** (0.40 g, 0.76 mmol), (*R*)-2-((methoxycarbonyl)amino)-2-phenylacetic acid (0.198 g, 0.946 mmol), and DIEA (0.27 mL, 1.5 mmol) in DMF (5.5 mL) was added HATU (0.294 g, 0.773 mmol). The mixture was stirred at rt for 1 h. Most of the volatile component was removed in vacuo, and the residue was partitioned between an aqueous medium (10 mL H_2O and 1 mL of sat. aq. $NaHCO_3$ solution) and organic medium (20 mL of EtOAc, 2 mL of CH_2Cl_2, and 2 mL of MeOH). The organic medium was washed with brine and evaporated in vacuo. The residue was dissolved in MeOH and submitted to reverse-phase HPLC purification (MeOH/H_2O/TFA), and the dominant peak was repurified under the same conditions to remove closely eluting peaks. The final HPLC elute was treated with excess 2.0 N NH_3/MeOH, and the volatile component was removed in vacuo. The residue was partitioned between an aqueous medium (10 mL of H_2O and 1 mL of sat. aq. $NaHCO_3$ solution) and an organic medium (20 mL of EtOAc and 1 mL of MeOH), and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **52** as a white foam (146.2 mg, 26.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23−1.77 (m, 2H), 8.03−6.94 (m, 16H), 5.56−5.40 (m, 1.26H), 5.14−5.07 (m, 0.74H), 4.89−4.76 (m, 1H), 3.91 (m, 0.7H), 3.62−3.52 (m, 4.6H), 3.39 (m, 1H), 3.15 (m, 0.7H), 2.29−1.85 (m, 8H), 3.60 (app br s, 3.6H), 1.18/1.17(two overlapping app s, 5.4H). LC (method B): t_R = 3.03 min. LC/MS (ESI) m/z calcd for $C_{41}H_{46}N_7O_5$, 716.36; found, 716.39 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{41}H_{46}N_7O_5$, 716.3555; found, 716.3536 $[M + H]^+$.

Pyrrolidine **53** (free base, light yellow solid) was synthesized from **52** according to the procedure described for the preparation of **14a** with the exception that an increased concentration of TFA in CH_2Cl_2 (i.e., 25%) was used. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.50−11.53 (m, 2H), 8.12−7.77 (m, 3.64H), 7.77−7.59 (m, 4.65H), 7.59−7.25 (m, 5.29H), 7.24−6.76 (m, 1.42H), 5.61−5.29 (m, 1.24H), 5.20−4.95 (m, 0.76H), 4.17 (t, J = 7.2 Hz, 0.88H), 4.00−3.78 (m, 0.66H), 3.67−3.46 (m, 3.46H), 3.25−3.06 (m, 1.43H), 3.06−2.92 (m, 1.34H), 2.92−2.73 (m, 1.23H), 2.46−2.12 (m, 0.57H), 2.12−1.96 (m, 3.39H), 1.96−1.82 (m, 2.07H), 1.82−1.60 (m, 1.94H). Note that the 1H signal is believed to have overlapped with that of water peak around 3.3 ppm. LC/MS (ESI) m/z calcd for $C_{36}H_{38}N_7O_3$, 616.30; found, 616.34 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{36}H_{38}N_7O_3$, 616.3031; found, 616.3018 $[M + H]^+$.

Title compound **54a** (TFA salt, off-white foam) was prepared from pyrrolidine **53** and (*R*)-2-(dimethylamino)-2-phenylacetic acid·HCl according to the procedure described for the preparation of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (br s, 1H), 8.18−7.07 (series of s and m, 21H), 5.77 (m, 0.15H), 5.56−5.42 (m, 1.98H), 5.23 (m, 1.87H), 4.04 (m, 0.81H), 3.95 (m, 0.84H), 3.87−3.81 (m, 0.24H), 3.77−3.73(m, 0.11H), 3.57/3.55 (2 overlapping s, 3H), 3.24−3.14 (m, 0.75H), 3.10−3.30 (m, 1.1H), 3.03−2.71 (very br m, ∼3.15H), ∼2.6−2.34 (br signal overlapped with that of solvent, ∼3H), 2.31−2.18 (m, 2H), 2.14−1.78 (series of overlapping m, 6H). LC (method K): t_R = 1.85 min. LC/MS (ESI) m/z calcd for $C_{46}H_{49}N_8O_4$, 777.39; found, 777.32 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{46}H_{49}N_8O_4$, 777.3877; found, 777.3847 $[M + H]^+$.

Methyl *N*-[(1*R*)-2-Oxo-1-phenyl-2-[(2*S*)-2-{5-[4-(4-{2-[(2*S*)-1-(2-phenylacetyl) pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]ethyl]carbamate (54b). Title compound **54b** (TFA salt, off-white foam) was prepared from pyrrolidine **53** and phenylacetic acid according to the procedure described for the preparation of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.49 (very br s, 2H), 8.17−8.09 (m, 2H), 7.99−7.82 (m, 8H), 7.76−7.72 (m, 1H), 7.42−7.05 (m, 10H), 5.74 (5.74 (m, 0.08H), 5.55−5.51 (m, 0.82H), 5.40 (m, 0.18H), 5.20 (m, 1.92H), 3.96−3.87 (m, 1.75H), 3.80−3.61 (m, 3.0H), 3.54−3.46 (m, 3.5H), 3.21−3.15 (m, 0.75H), 2.44−1.86 (collections of m, 8H). LC (method H): t_R = 1.66 min. LC/MS (ESI) m/z calcd for $C_{44}H_{44}N_7O_4$,734.34; found 734.39 $[M + H]^+$. HRMS (ESI) m/z calcd for $C_{44}H_{44}N_7O_4$, 734.3445; found, 734.3433 $[M + H]^+$.

Ames Mutagenicity Assay. The Ames assay was conducted in *Salmonella typhimurium* (TA 100 strain) according to the following protocol: a DMSO solution of test compound (1, 3.2, 10, 32, 100, 320, and 1000 μg/well, n = 3) and bacteria (with or without rat S9 liver fractions) are mixed into top agar containing trace amounts of histidine, poured into a 100 mm dish, and incubated for 48 h at 37 °C along with positive (n = 3) and solvent (n = 6)-control groups. 2-Aminoanthracene and sodium azide were used as positive controls for the studies with and without metabolic activation, respectively. The total number of revertant bacteria colonies per dish per treatment condition is compared with that of the solvent control dish, and a 2-fold or greater increase in the mean revertant colonies is judged as a positive response.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

DIAD, diisopropyl azodicarboxylate; DIEA, *N*,*N*-diisopropylethylamine; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·HCl; EEDQ, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; EtOAc, ethyl acetate; HATU, 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; HOAT, 1-hydroxy-7-azabenzotriazole;

HOBT, 1-hydroxybenzotriazole; MeOH, methanol; sat. aq., saturated aqueous; rt, room temperature.

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(15) There is an error in the replicon activity of the phenylacetyl cap analogue of **21** (i.e., (2*S*)-1-(2-phenylacetyl)-*N*-[4-(5-{4-[(2*S*)-1-(2-phenylacetyl)pyrrolidine-2-amido]phenyl}-1,3-oxazol-2-yl)phenyl]pyrrolidine-2-carboxamide) reported previously in ref 14a because of a sample contamination issue. The revised EC_{50} value of this analogue toward GT-1b replicon is 429 nM.

(16) Preparation of compound **31b** from 3-aminobenzoic acid according to the procedure described for its regioisomer, **31a**, resulted in a final product containing a significant amount of an unidentified impurity, which could not be removed readily. The alternate route provided a sample of **31b** in 90% HPLC purity.

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