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7-Fluoroindazoles as Potent and Selective Inhibitors of Factor Xa†

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We have developed a novel series of potent and selective factor Xa inhibitors that employ a key 7-fluoroindazolyl moiety. The 7-fluoro group on the indazole scaffold replaces the carbonyl group of an amide that is found in previously reported factor Xa inhibitors. The structure of a factor Xa cocrystal containing 7-fluoroindazole **51a** showed the 7-fluoro atom hydrogen-bonding with the N–H of Gly216 (2.9 Å) in the peptide backbone. Thus, the 7-fluoroindazolyl moiety not only occupied the same space as the carbonyl group of an amide found in prior factor Xa inhibitors but also maintained a hydrogen bond interaction with the protein's β-sheet domain. The structure–activity relationship for this series was consistent with this finding, as the factor Xa inhibitory potencies were about 60-fold greater ($\Delta\Delta G \approx 2.4$ kcal/mol) for the 7-fluoroindazoles **25a** and **25c** versus the corresponding indazoles **25b** and **25d**. Highly convergent synthesis of these factor Xa inhibitors is also described.

Introduction

Thromboembolic diseases remain a leading cause of morbidity and mortality in developed countries, such as the U.S.[1–3] Anticoagulants provide effective treatment for venous or arterial thromboembolism, e.g., prevention of postoperative deep venous thrombosis (DVT[a])and pulmonary embolism (PE), prevention of stroke during atrial fibrillation, and treatment of acute coronary syndrome (ACS). Use of the current oral anticoagulant, warfarin, is plagued by its slow vitamin K-dependent antagonism, by drug−drug interactions, and by drug−food interactions, which results in the need for careful patient monitoring.[4,5] Since fast-acting heparin and direct thrombin inhibitors currently are only available for parenteral administration,[4,6] the development of new oral anticoagulants is still an unmet medical need.

Factor Xa (EC 3.4.21.6) is a unique serine protease in the blood coagulation cascade in that it is poised at a common junction where it is activated by both the intrinsic (contact activation) and extrinsic (tissue factor) pathways. In contrast to the multifunctional role that thrombin plays in the cascade, factor Xa only converts prothrombin to thrombin but does not affect the existing level of circulating thrombin. It has been proposed that factor Xa inhibitors may exhibit a reduced bleeding risk and offer a superior safety/efficacy profile with respect to thrombin inhibitors.[7–10] Therefore, in recent years factor Xa has emerged as an attractive target for the development of new anticoagulants.[11–17]

Compound **1** (DPC423)[18] and **2** (razaxaban)[19] were reported to be highly selective, potent, and orally bioavailable small-molecule factor Xa inhibitors. In addition, compound **2** showed good oral efficacy in treatment of venous thromboembolism after elective knee arthroplasty in a phase II clinical study.[20] However, since compound **2** and its analogues contain amide bonds, there was a concern that the amides would be hydrolyzed under in vivo conditions to release potentially mutagenic biarylamines (Figure 1).[21] Indeed, as some of these biarylamines have been found to be mutagenic,[22] much of the lead optimization efforts have been directed toward modifications of the carboxamide into a bicyclic core to reduce the susceptibility of in vivo hydrolysis.[21–25] While these designs have made the molecules less susceptible to hydrolysis, they did not completely eliminate the possibility of in vivo hydrolytic cleavage.[23] Recently, an effort to eliminate this potential liability, by replacing the biarylamines with nonaromatic P4 residues, was reported.[26] However, an unambiguous way to eliminate such a risk is to remove the carboxamide core entirely (Figure 2). In our thrombin inhibitor program, we have successfully replaced the carbonyl group of the pyrazinone core in known thrombin inhibitors with a fluorobenzene moiety. This straightforward change not only retained inhibitory potency but also improved metabolic stability.[27–30] Similar success has also been reported in factor VIIa inhibitor programs via replacement of the pyrazinone core with arenes.[31] In both cases, X-ray crystallographic studies showed that these novel fluorobenzene inhibitors occupied the active sites in the same orientation and maintained the key hydrogen-bonding interactions of the pyrazinone carbonyl groups with Gly216 of the protein's β-sheet domain. In this article, we report results from our studies involving the application of the same principle to the design of

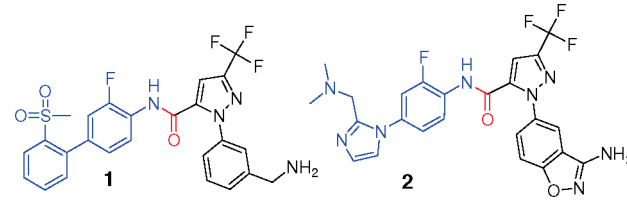

Figure 1. Compounds **1** and **2** share a pyrazolyl carboxamide core.

† The coordinates of **51a** in the human factor Xa active have been deposited (PDB code 2RA0).

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[a]Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; ACS, acute coronary syndrome; EC, enzyme commission number; aPTT, activated partial thromboplastin time; HLM, human liver microsomal.

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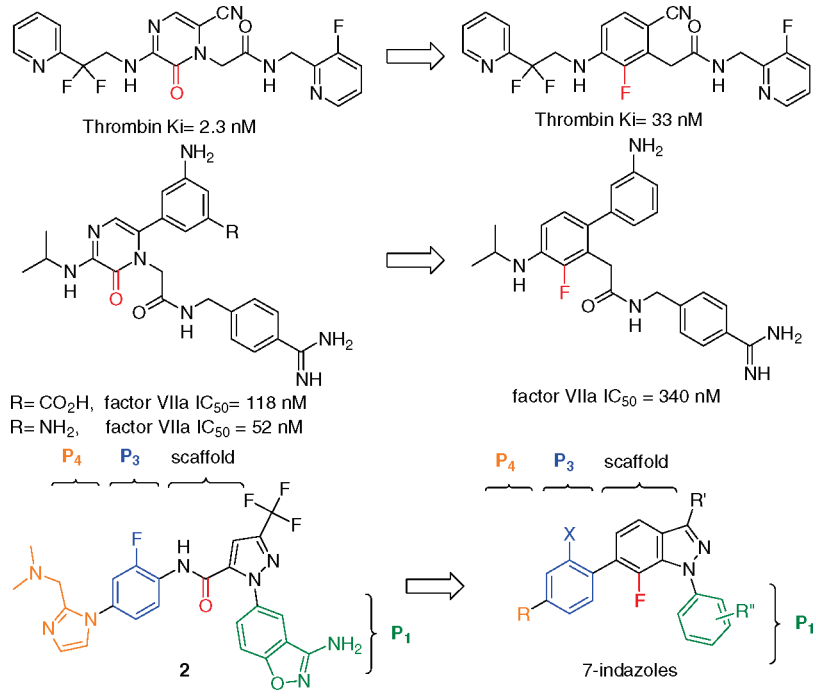


Figure 2. Fluorobenzenes replace carbonyl-based cores in serine protease inhibitors.

a novel series of factor Xa inhibitors, which possess a 7-fluoroindazole unit in place of the pyrazolylcarboxamide unit.

Chemistry

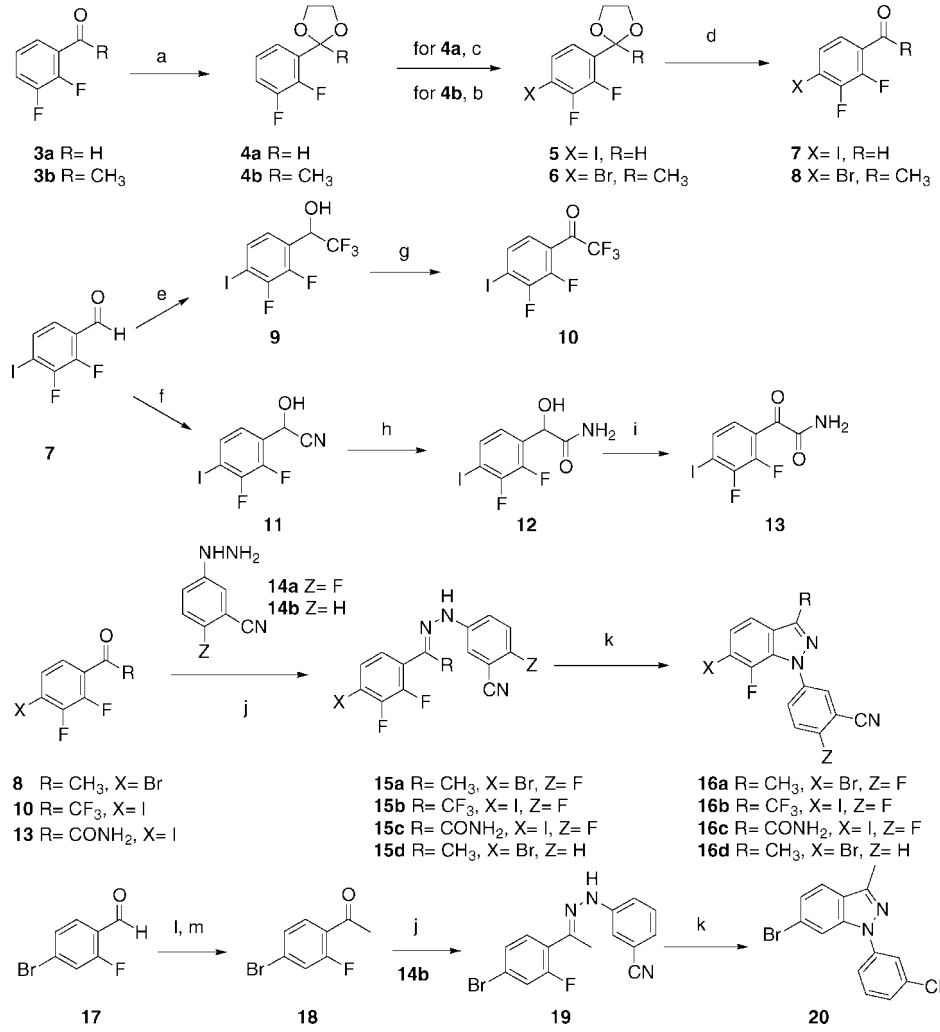
The 7-fluoroindazole scaffolds **16a**−**d** were synthesized as shown in Scheme 1. Commercially available difluorobenzaldehyde **3a** was protected with ethylene glycol to form dioxolane **4a**. Difluorobenzene **4a** was treated with lithium 2,2,6,6-tetramethylpiperidide at −78 °C and quenched with iodine to yield difluorobenzene **5**.[32] The protecting group on the carbonyl group of **5** was removed under acidic conditions to yield difluoroiodobenzaldehyde **7**. Bromodifluoroacetophenone **8** was prepared in a similar fashion from the commercially available acetophenone **3b**. Benzaldehyde **7** was reacted with trimethyl(trifluoromethyl)silane and followed by oxidation with the Dess−Martin periodinane to yield trifluoroacetophenone **10**. In the case of ketocarboxamide **13**, benzaldehyde **7** was reacted with trimethylsilyl cyanide to yield the cyanohydrin **11**. The cyanohydrin **11** was hydrolyzed to the corresponding β-hydroxycarboxamide **12** using strongly acidic conditions and then oxidized to the desired ketoacetamide **13**. The carbonyl moieties **8**, **10**, and **13** were condensed with arylhydrazine **14a**[33] to afford arylhydrazones **15a**−**c**. Acetophenone **8** was also reacted with arylhydrazine **14b** to yield arylhydrazone **15d**. The arylhydrazones **15a**−**d** were cyclized under basic conditions to yield the 7-fluoroindazoles **16a**−**d**.[34] The corresponding nonfluorinated indazole analogue **20** was prepared in four steps in a similar fashion. Aldehyde **17** was treated with methylmagnesium bromide, followed by the oxidation of the secondary alcohol to ketone **18**. Acetophenone **18** was reacted with arylhydrazine **14b** to form arylhydrazone **19**, which was then cyclized under basic conditions to yield indazole **20**.

The syntheses of the factor Xa inhibitors **25a**−**d** in Table 1 are described in Schemes 2 and 3. Anilines **21** and **22** were coupled to ω-bromoalkylcarboxylic acid chlorides, and the amides obtained were cyclized under basic conditions to afford lactams **23a**−**c**. Bromolactam **23c** was converted to boronate **23d** using the Miyaura borylation protocol.[35] Indazoles **16d** and **20** were coupled with the boronates **23a**,**b** using Suzuki−Miyaura reaction conditions to yield **24a**−**d**. Nitriles **24a**−**d** were reduced with Raney Ni under a pressurized hydrogen atmosphere to yield benzylamines **25a**−**d**.

The factor Xa inhibitors **29a**−**c** in Table 2 were prepared as outlined in Scheme 4. Boronates **26** were generated from indazoles **16a** using the Miyaura boronylation protocol[35] and coupled to lactam **23c** using Suzuki−Miyaura conditions to yield indazole **28a**. Indazoles **16b**−**c** were coupled to boronate **23d** using similar conditions to yield intermediates **28b**−**c**. Treatment of the intermediates **28a**−**c** with acetohydroxamic acid under basic conditions yielded aminobenzoxazoles **29a**−**c**.

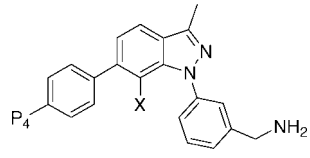
The syntheses of the biaryl P3−P4 moieties found in the factor Xa inhibitors **51a**−**l** in Table 3 are shown in Schemes 5 and 6. The preparations of P3−P4 biaryls **49b** and **49d**−**g** are outlined in Scheme 5. The pyrazole analogue **49b** was prepared by protection of commercially available pyrazole **36** with SEM-Cl, followed by Suzuki coupling with 4-bromo-3-fluorobenzeneboronic acid **30** and reductive amination with dimethylamine. Commercially available 2-pyridinecarboxaldehyde (**31**) was treated with *n*-butyllithium in the presence of *N*,*N*,*N*′-trimethylethylenediamine and quenched with iodine to form the 3-iodopyridine **32** as described in the literature.[36] Suzuki coupling of 4-bromo-3-fluorobenzeneboronic acid **30** with iodopyridine **32** followed by reductive amination with dimethylamine afforded the biaryl **49f**. Similarly, biaryls **49d**, **49e**, and **49g** were prepared from bromopyridines **35** and **34** and iodopyridine **33**,[36] respectively. The syntheses of P3−P4 biaryls **49a**, **49c**, and **49h**−**l** are described in Scheme 6. Reductive amination of commercially available 2-imidazolecarboxaldehyde with dimethylamine yielded imidazole **43**.[19] Ullmann coupling of imidazole **43** and 1-bromo-2-fluoro-4-iodobenzene **38** afforded biaryl **49a**. Suzuki coupling between iodobenzene **38** and boronic acid **45** followed by reductive amination of the product with dimethylamine yielded biphenyldimethylamine **49c**. Compound **49h** was prepared from Buchwald−Hartwig amination between 4-(methylamino)pyridine **44** and iodobenzene **38**. Compound **49i** was prepared from Buchwald−Hartwig

Scheme 1. Synthesis of 7-Fluoroindazole and the Corresponding Indazole Scaffolds[a]



[a] Reagents and conditions: (a) ethylene glycol, PhH, PPTS, reflux; (b) 2,2,6,6-tetramethylpiperidine, *n*-BuLi, THF, −78 °C, then Br_2; (c) 2,2,6,6-tetramethylpiperidine, *n*-BuLi, THF, −78 °C, then I_2; (d) 2 M HCl, THF, reflux; (e) $TMSCF_3$, catalytic TBAF, THF, 0 °C to room temp, then aqueous HCl; (f) TMSCN, catalytic TBAF, THF, 0 °C to room temp, then aqueous HCl; (g) Dess−Martin; (h) concentrated HCl, $HCl_{(g)}$, 1,4-dioxane; (i) MnO_2, CH_3CN; (j) EtOH, TSA; (k) K_2CO_3, DMF, 100 °C, 2 h; (l) CH_3MgBr, THF; (m) CrO_3, CH_2Cl_2.

Table 1. Importance of 7-Fluoro Substitution on Factor Xa Potency

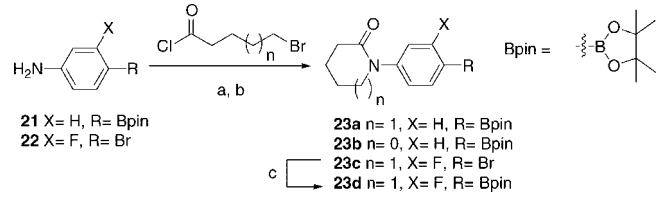


Compound	P4	X	fXa K_i (nM)[a]	Thrombin K_i (nM)[b]	Trypsin K_i (nM)[b]
25a		F	223	>15200	702
25b		H	>14400	>15200	>10000
25c		F	124	>15200	1899
25d		H	6850	>15200	>10000

[a] K_i values are averaged from two determinations ($n = 2$). [b] K_i values of ≤10000 nM are averaged from two determinations ($n = 2$).

amination between bromobenzene **39** and *N,N*-dimethylethylenediamine, followed by another Buchwald−Hartwig amination between the product aniline **41** with iodobenzene **38**. The pyridyl analogue **49j** was prepared in a similar fashion using 3-bromopyridine **40** as starting material. Compound **49k** and **49l** were prepared via the coupling of 4-chloropyridine **46** with *N,N*-dimethylaminoalkyldiamines, followed by Buchwald−Hartwig amination between the product aniline **47** and **48** with iodobenzene **38**.

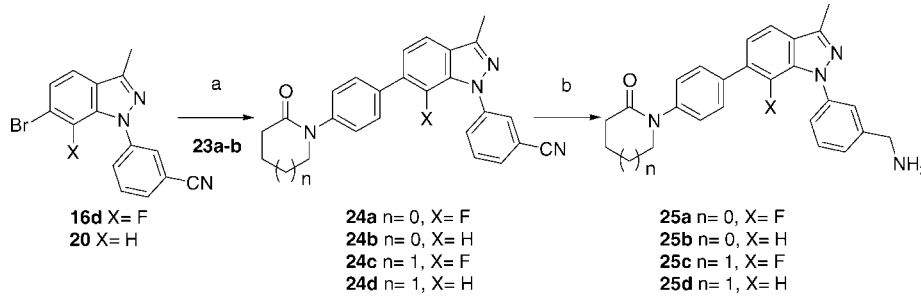
Scheme 2. Synthesis of P3−P4 Lactams **23**[a]



[a] Reagents and conditions: (a) TEA, CH_2Cl_2; (b) NaH, DMF; (c) bis(pinacolato)diboron, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, KOAc, 1,4-dioxane, 90 °C.

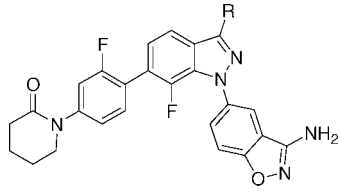
The final assembly of factor Xa inhibitors **51a−l** in Table 3 is outlined in Scheme 7. The biaryl P4 moieties **49a−l** were coupled to boronate **27** under Suzuki−Miyaura conditions to form intermediates **50a−l**. Compound **50a** and **50c−l** were treated with acetohydroxamic acid under basic conditions to yield aminobenzisoxazoles **51a** and **51c−l**, respectively.[19] In

Scheme 3. Synthesis of Compounds **25a**−**d**[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, EtOH, $PhCH_3$, 100 °C; (b) Raney Ni, H_2 (50 psi), EtOH.

Table 2. Effect of C-3 Substitution of the Indazole on Factor Xa Potency



compd	R	fXa K_i (nM)[a]	thrombin K_i (nM)[b]	trypsin K_i (nM)[b]
29a	CH_3	26	>15200	>10000
29b	CF_3	22.9	>15200	>10000
29c	$CONH_2$	6.4	5486	>10000

[a] K_i values are averaged from multiple determinations ($n \geq 2$), and the standard deviations are <5% of the mean. [b] K_i values are obtained from single determination ($n = 1$).

the case of pyrazole **50b**, the SEM protecting group was first removed with TFA before the conversion to aminobenzisoxazole **51b**.

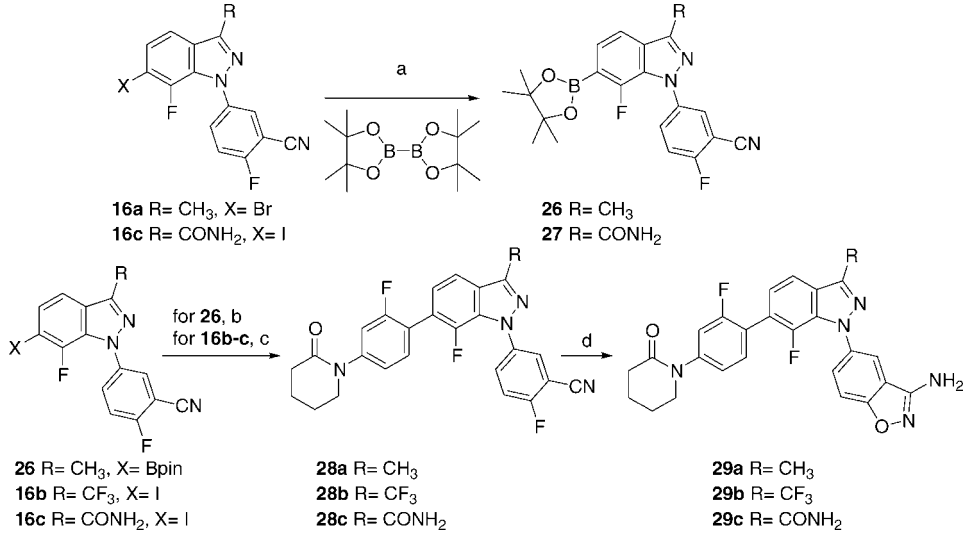
Results and Discussion

Fluorinated compounds have become increasingly important in pharmaceutical research, whether used to improve metabolic stability, modulate physiochemical properties, or guide protein–ligand interactions.[37] While a number of reports have been published on interactions between proteins and fluorinated ligands over the past decade,[37,38] the extent of fluorine participation in hydrogen-bonding interactions remains an ongoing debate.[38–40] Until recently, it was believed that $C(sp^3)-F$ is a better hydrogen bond acceptor than $C(sp^2)-F$.[38,41] Not surprisingly, the few reported examples of hydrogen bonding of fluorinated compounds in protein–ligand complexes were mostly of the $C(sp^3)-F$ type.[40,42] While many favorable interactions of aromatic fluorine in protein–ligand complexes have been described, no systematic study has been carried out to understand more fully the nature of these interactions. Böhm et al. have reported a systematic comparison between a pair of aryl molecules that differ by one fluorine atom and their respective thrombin inhibitory potency.[37] In this case, the fluorinated analogue was a moderately good thrombin inhibitor ($K_i = 260$ nM) but only 6-fold ($\Delta\Delta G \approx 1$ kcal/mol) more potent than the corresponding nonfluorinated compound ($K_i = 1600$ nM). The distance between the fluorine and the amide nitrogen of Gly216 of thrombin was 3.47 Å. They concluded that the evidence pointed toward a very weak hydrogen bond or a favorable dipolar interaction. Replacements of the carbonyl groups of pyrazinones with fluorobenzenes in inhibitors of thrombin or factor VIIa have also been recently published.[28,30,31] The fluorine atom in each of these active fluorinated inhibitors certainly provided favorable interactions in the protein–ligand complex. The X-ray crystallographic data of these protein–ligand complexes revealed that the distance between the aromatic fluorine to the amide nitrogen in Gly216 of the serine protease varied from 3.4 to 3.2 Å and that the fluorinated ligand adopted a similar orientation in the protein–ligand complex as did the carbonyl counterpart. However, in both cases no systematic study was carried out to determine the nature of the interaction between the aromatic fluorine and the N–H of Gly216. Therefore, early in our program a pair of the 7-fluoroindazoles **25a** and **25c** and the corresponding indazole analogues **25b** and **25d** were prepared to assess the role of the 7-fluoro atom in the scaffold, and the assay results are summarized in Table 1. The factor Xa inhibitory activities of 7-fluoroindazoles **25a** (fXa $K_i = 223$ nM) and **25c** (fXa $K_i = 124$ nM) are about 60 times more potent ($\Delta\Delta G \approx 2.4$ kcal/mol) than the corresponding indazoles **25b** (fXa $K_i > 14400$ nM) and **25d** (fXa $K_i = 6850$ nM). The comparison of these two pairs of analogues demonstrated the importance of the fluorine at the 7-position on binding affinity to factor Xa. The differences in the inhibitory potencies of the fluorinated and nonfluorinated compounds are also much higher than reported (60-fold versus 6-fold). The binding energy difference derived ($\Delta\Delta G \approx 2.4$ kcal/ mol) from comparison of the inhibitory potencies of these two pairs of analogues is in line with a plausible hydrogen bond of the carbon-bound fluorine.[38,41]

Although 7-fluoroindazoles **25a**,**c** were active against factor Xa, the potency was not optimal and the selectivity versus trypsin was only about 4-fold and 10-fold, respectively. Table 2 shows that the factor Xa potency was increased by about 5-fold and the selectivity against trypsin and thrombin was greatly improved when the P1 benzylamine was changed to an aminobenzisoxazole, along with the addition of a fluorine at the 2-position of P3 as in compound **29a** (fXa $K_i = 26$ nM). This improvement in potency and selectivity resulted from the larger size of the aminobenzisoxazole P1, which complemented more favorably with the larger S1 pocket found in factor Xa as opposed to other serine proteases.[19] While the replacement of the methyl group at the C-3 position of the indazole with a trifluoromethyl group in **29b** (fXa $K_i = 22.9$ nM) did not improve the factor Xa potency further, the potency of **29c** (fXa $K_i = 6.4$ nM) was increased by about 4-fold when the C-3 substitutent was changed to an amide group capable of hydrogen-bonding to Glu146, which was confirmed later by X-ray crystallography.

The factor Xa inhibitory activity of **29c** (fXa $K_i = 6.4$ nM) differs from compound **2** (fXa $K_i = 1.6$, 0.19 nM reported)[19] about 4-fold while also demonstrating good selectivity against trypsin and thrombin. However, the in vitro anticoagulant activity of **29c** proved disappointing, as shown by the plasma concentration required to increase aPTT by 2-fold (2-fold $aPTT_{EC50}$) value (Table 3). Because the 7-fluoroindazole

Scheme 4. Synthesis of Compounds **29a**−**c**[a]



[a] Reagents and conditions: (a) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 1,4-dioxane, KOAc, 90 °C; (b) **23c**, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, DMF, 95 °C; (c) **23d**, $Pd(PPh_3)_4$, aqueous Na_2CO_3, EtOH, $PhCH_3$, 80 °C; (d) AcNHOH, K_2CO_3, DMF, H_2O.

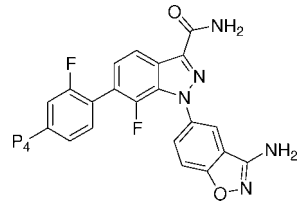
scaffold, consisting of an aminobenzisoxazole moiety as P1, primary carboxamide at the C-3 position of the indazole, and the 2-fluorophenyl moiety as P3 showed good potency and selectivity, we redirected our efforts to find a suitable P4 group (Table 3). The initial choice was to install a dimethylaminomethylimidazole P4 moiety as found in compound **2**. Surprisingly, the factor Xa potency of **51a** (fXa K_i = 15.9 nM), a close analogue of compound **2**, was lower than **29c** (fXa K_i = 6.4 nM). However, the 2-fold $aPTT_{EC50}$ for **51a** was 4-fold lower than **29c**. In a human liver microsomal (HLM) stability assay, **29c** showed good stability; therefore, the poor stability of **51a** and **2** may be due to the dimethylaminoimidazole group at P4, which both compounds share. We prepared dimethylaminomethylpyrazole **51b** and were surprised to find that the rearrangement of the nitrogen atoms had improved the factor Xa K_i by more than 10-fold to 1.4 nM while also improving the 2-fold $aPTT_{EC50}$ of **51b** (10.1 μM), similar to that observed with compound **2** (13.5 μM). Despite these improvements, the issues of poor permeability (Caco-2 P_{app} = 1.10 × 10^{-6} cm/s) and fair microsomal stability (54% parent compound remaining after 10 min) precluded the advancement of **51b**.

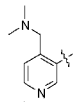
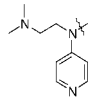
An X-ray crystal structure of **51a** in the human factor Xa active site (PDB code 2RA0) was obtained to a resolution of 2.3 Å (Figure 3). The overall binding mode is similar to what was reported for **1**[18] and **2**.[19] As anticipated, the fluorine at the 7-position of the indazole forms a hydrogen bond with the N–H of Gly216 (2.90 Å). This is close to the distance observed between the 5-carboxamide carbonyl in compound **2** and Gly216 (3.04 Å).[19] The aminobenzisoxazole was also bound in S1 as predicted, and the amino group formed a hydrogen bond with the carboxylic acid of Asp189 (2.77 and 2.96 Å) and the carbonyl group of the Ala190 (3.37Å). The N–H of the amide at the C-3 position of the indazole interacted with the carbonyl group Glu146 (2.56 Å). The fluorine at the 2-position of the P3 is within hydrogen bond distance to the hydroxy group of Try99 (3.28 Å). The distance between the N-3 nitrogen of the imidazole P4 group and Glu97 was reduced to 2.58 Å compared to 3.66 Å in compound **2**. Overall, these interactions showed that the 7-fluoroindazole **51a** bound into the active site in a highly complementary fashion. The combination of the X-ray crystallographic structure and the structure–activity relationship data for these 7-fluoroindazoles demonstrates, for the first time unequivocally, hydrogen bonding between a $C(sp^2)$−F and N–H in a peptide backbone.

We then investigated different dimethylaminoaryl moieties (**51c**−**g**) as P4 substituents and found that the presence and the position of the pyridyl ring nitrogen atom were also crucial to the factor Xa activities, as well as to the in vitro anticoagulation parameters. The nitrogens at the 6- or 5-positions in **51d** (fXa K_i = 2255 nM) and **51e** (fXa K_i = 147 nM) were not well tolerated. Their factor Xa inhibitory potencies were poorer than the corresponding phenyl analogue **51c** (fXa K_i = 8.1 nM). However, the nitrogens at the 4- or 3-position of the pyridyl system in **51f** (fXa K_i = 3.0 nM) and **51 g** (fXa K_i = 4.4 nM) afforded better factor Xa potency than the corresponding phenyl group **51c**. In addition, 3-pyridyl analogue **51g** showed a significantly better in vitro anticoagulation parameter (2-fold $aPTT_{EC50}$ = 4.4 μM) when compared to the other two analogues **51c** (2-fold $aPTT_{EC50}$ = 47 μM) and **51f** (2-fold $aPTT_{EC50}$ = 55.1 μM). While the microsomal stabilities of phenyl **51c** and 3-pyridyl **51g** analogues were greatly improved over 4-pyridyl analogue **51f**, the permeability of **51f** was found to be higher than the phenyl analogue **51c** and much higher than the 3-pyridyl analogue **51g**.

In an attempt to optimize the microsomal stability and the in vitro 2-fold $aPTT_{EC50}$, we replaced the P4 group with the *N*-alkylaminopyridine moiety found in **51h**−**l**. Compound **51h** (fXa K_i = 4.1 nM) showed that the dimethylaminomethyl groups in these analogues are not essential to the factor Xa activities and the in vitro anticoagulation parameter when compared to **51k** (fXa K_i = 4.9 nM) and **51l** (fXa K_i = 5.2 nM). However the permeability was improved by about 4-fold with the presence of the dimethylamino "tail" as in **51l** (Caco-2 P_{app} = 5.5 × 10^{-6} cm/s), when it is compared to that of the methylamine **51h** (Caco-2 P_{app} = 1.4 × 10^{-6} cm/s). The length of the dimethylamino chain in **51k** (fXa K_i = 4.9 nM) and **51l** (fXa K_i = 5.2 nM) did not affect the factor Xa activity. However, extension of the pendent dimethylamino group improved in vitro anticoagulation parameters about 2-fold in **511** compared to **51k**. The importance of the presence and location of the nitrogen atom on the pyridine ring was demonstrated once again in

Table 3. Effect of P4 Substitutents on Factor Xa Potency, in Vitro Anticoagulant Activity in Human Plasma, HLM Stability, and Permeability



Compound	P4	fXa K_i (nM)[a]	Thrombin K_i (nM)[b]	Trypsin K_i (nM)[b]	2x aPTT $_{EC50}$ (μM)	HLM Stability[c]	Caco2 (Papp x10^{-6} cm/s)
51a		15.9	>15200	>10000	23	5.4	2.03
51b		1.4	>15200	>10000	10.1	54.0	1.10
51c		8.1	8700	>10000	47	83.0	3.76
51d		2255	>15200	>10000	-		-
51e		147	>15200	>10000	-		-
51f		3.0	9623	>10000	55.1	7.0	6.69
51g		4.4	7594	>10000	4.4	86.0	1.04
51h		4.1	2456	6638	11.1	79.0	1.40
51i		690	>15200	>10000	-		-
51j		231	>15200	>10000	-		-
51k		4.9	>15200	>10000	7.6	52.0	-
51l		5.2	>15200	>10000	3.1	87.0	5.50
29c		6.4	5486	>10000	92	68.6	3.04
2		1.6 (0.19)[d]	3100 (600)[d]	>10000	13.5 (6.1)[d]	9.1	1.97(5.56)[d]

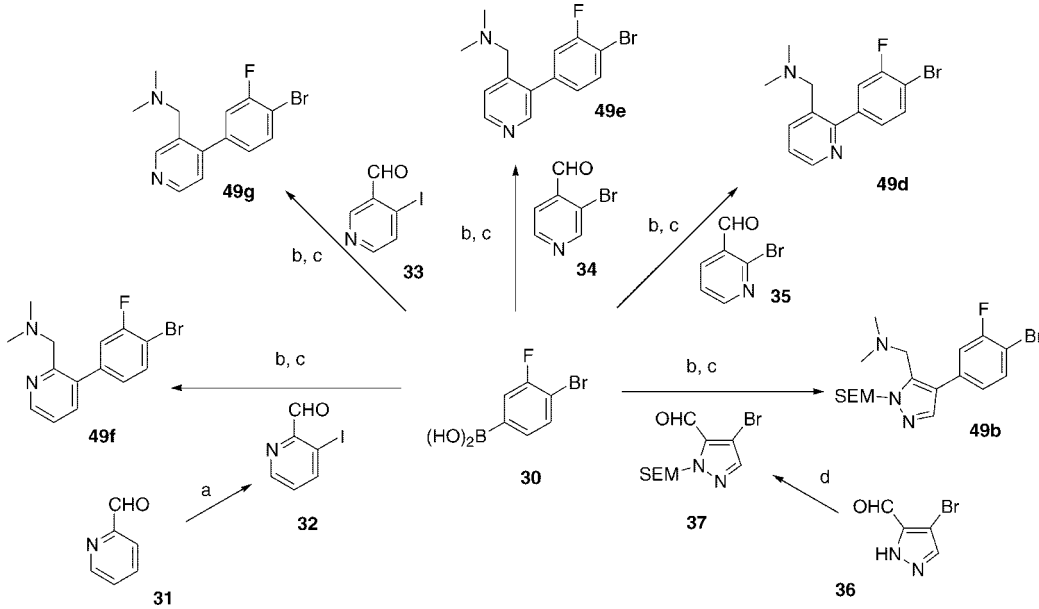
[a] K_i values are averaged from multiple determinations ($n \geq 3$), and the standard deviations are <14% of the mean. [b] K_i values of <10000 nM are averaged from two determinations ($n = 2$). [c] Human liver microsomal stability: percentage of compound remaining after 10 min in the assay. [d] Data in parentheses were reported in ref 19.

51h−**k**. The presence of the nitrogen atom accounted for a 3-fold increase in the factor Xa activities as shown in **51i** (fXa $K_i = 690$ nM) and **51j** (fXa $K_i = 231$ nM). The movement of the nitrogen atom from the 3-position to the 4-position in **51k** (fXa $K_i = 4.9$ nM) enhanced the factor Xa activity by 46-fold. We also found that the potency, anticoagulation parameters, and permeability of **51l** were similar to those of compound **2** and with improvements in microsomal stability.

Conclusion

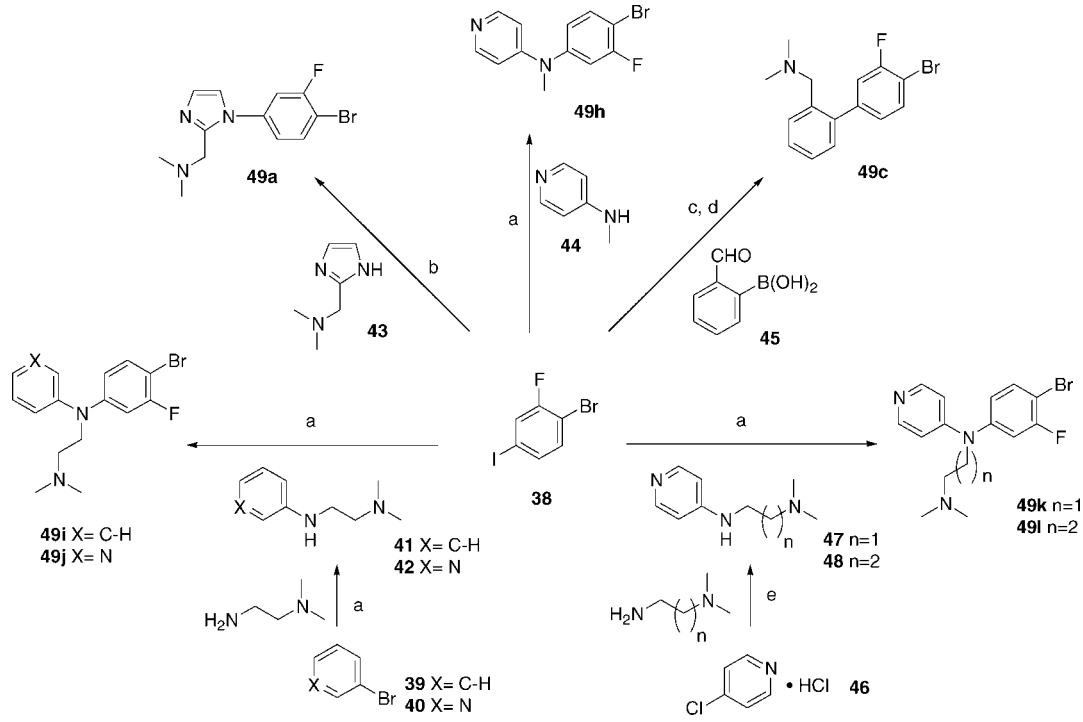
Novel factor Xa inhibitors that use a 7-fluoroindazole as a carbonyl group replacement were developed. Comparison of the

Scheme 5. Synthesis of P4 Biaryls **49b** and **49d**−**g**[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, *N*,*N*,*N*′-trimethylethylenediamine, −42 °C; (ii) iodine; (b) $PdCl_2(PPh_3)_2$, DME, 2 M Na_2CO_3, 90 °C; (c) $(CH_3)_2NH$, $NaBH(OAc)_3$, DMF; (d) SEM-Cl, NaH, DMF.

Scheme 6. Synthesis of P4 Biaryls **49a**, **49c**, and **49h**−**l**[a]



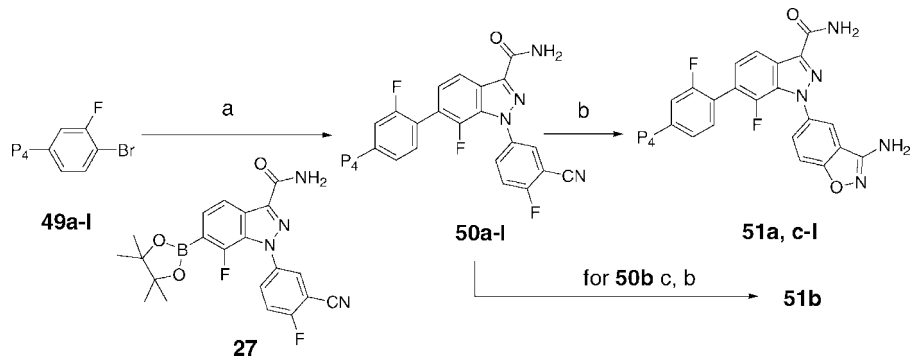
[a] Reagents and conditions: (a) $Pd_2(dba)_3$, XANTPHOS, *t*-BuONa, 1,4-dioxane, 140 °C; (b) CuI, Cs_2CO_3, DMF, 125 °C; (c) $Pd(PPh_3)_4$, aqueous Na_2CO_3, EtOH/$PhCH_3$, reflux; (d) $(CH_3)_2NH$, $NaBH(OAc)_3$, DMF; (e) 1-pentanol, 140 °C.

structure–activity relationship of 7-fluoroindazoles with their corresponding nonfluorinated indazoles unequivocally demonstrated that the interaction of the 7-fluoro group in the series ($\Delta\Delta G \approx 2.4$ kcal/ mol) with factor Xa was beyond a simple van der Waals complex while X-ray crystallography also confirmed the interaction between the 7-fluoro group and the N–H of Gly216 of factor Xa (2.9 Å). The binding orientation of the 7-fluoroindazole was similar to the carboxamides that it replaced. Our data also support the notion of fluorobenzene as a good hydrogen bond acceptor. Several 7-fluoroindazoles, such as **51g** and **51l**, were found to be very potent, highly selective inhibitors of factor Xa.

Experimental Section

Chemistry. Reagents and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography was performed using Fisher Chemical silica gel sorbent (230–400 mesh, grade 60). Preparative thin-layer chromatography was performed on Analtech silica gel GF plates (1000 μm or 2000 μm, 20 cm × 20 cm). ^{1}H NMR spectra were recorded on a Bruker B-ACS-120 (400 MHz) spectrophotometer at room

Scheme 7. Syntheses of Compounds **51a−l** [a]



[a] Reagents and conditions: (a) Pd(dppf)Cl_2·CH_2Cl_2, K_2CO_3, DMF, 95 °C; (b) AcNHOH, K_2CO_3, DMF, H_2O; (c) TFA, CH_2Cl_2, EtOH.

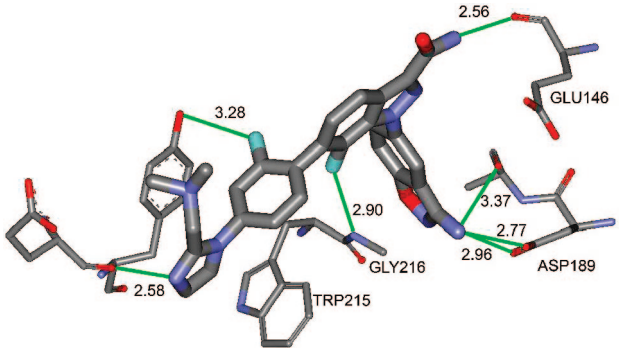


Figure 3. X-ray crystal structure of compound **51a** in the factor Xa active site (PDB code 2RA0).

temperature. Chemical shifts are given in ppm (δ), coupling constants (J) are in hertz (Hz), and signals are designed as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br s) broad singlet, (dd) doublet of doublet, (dt) doublet of triplet, (dq) doublet of quartet, (tm) triplet of multiplet, (ddd) doublet of doublet of doublet, (ddt) doublet of doublet of triplet, (dddd) doublet of doublet of double of doublet. LC−MS was performed on a system consisting of an electrospray source on a Finnigan LCQ ion trap mass spectrometer, a SEDEX 75C evaporative light scattering detector, a Shimadzu LC-10ADvp binary gradient pumping system, a Gilson 215 configured as an autosampler, and a Princeton Chromatography HTS HPLC column (5 μm, 50 mm × 3.0 mm). Accurate mass measurements were performed using either of two methods: (1) One method is a Micromass (Manchester, U.K.) Autospec E OA-TOF high-resolution magnetic sector mass spectrometer tuned to a resolution of >5000 using the 5% valley definition. The ions were produced in a fast atom bombardment (FAB) ion source at an accelerating voltage of 8kV. Linear voltage scans at 33 Da/s were collected to include the protonated sample ion and two polyethylene glycol (PEG) or PEG monomethyl ether ions, which were used as internal reference standards. The molecular mass was calculated using a linear extrapolation method. Reported mass values are averages over 100 s. (2) Positive ion electrospray (ESI) high-resolution mass spectrometry was carried out with a Micromass Q-Tof API US hybrid quadrupole/time-of-flight mass spectrometer. The mass spectrometer was externally calibrated using cesium iodide. PEG 400 was added to the samples as internal calibrant. The purities of the key target compounds were determined on a Varian HPLC system equipped with two Varian PrepStar delivery pumps (model 218) and a Varian UV–vis detector (model 345). The HPLC method used was as follows: column, Princeton-SPHER-100 phenyl, 4.6 mm × 150 mm, 5 μm; column temperature, ambient; flow rate, 1.0 mL/min; gradient, 20% acetonitrile (0.01% TFA and 0.2% formic acid) in water (0.01% TFA and 0.2% formic acid) to 80% acetonitrile (0.01% TFA and 0.2% formic acid) in water (0.01% TFA and 0.2% formic acid) in 30 min. All of the final compounds had 98% or greater purity.

2-(2,3-Difluorophenyl)[1,3]dioxolane (4a). A mixture of 2,3-difluorobenzaldehyde (10 g, 70.4 mmol), ethylene glycol (5.1 mL, 91.5 mmol), and pyridinium *p*-toluenesulfonate (1.77 g, 7 mmol) in benzene (60 mL) was refluxed overnight using a Dean–Stark apparatus. The mixture was allowed to cool to room temperature, and cold water was added to the mixture. The two layers were separated, and the aqueous layer was thrice extracted with hexanes. The organic layers were combined and washed with brine. The solution was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield a colorless oil (12.9 g, 99%) as the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (tdd, J = 1.5, 7.6, 5.9 Hz, 1H), 7.17 (dddd, J = 9.3, 8.2, 7.5, 1.8 Hz, 1H), 7.09 (ddt, J = 4.8, 1.5, 8.2 Hz, 1H), 6.09 (s, 1H), 4.21–4.11 (m, 2H), 4.10–4.04 (m, 2H).

2-(2,3-Difluoro-4-iodophenyl)[1,3]dioxolane (5). To a solution of 2,2,6,6-tetramethylpiperidine (16.6 mL, 98.5 mmol) in anhydrous THF (100 mL) under argon at –78 °C was added *n*-butyllithium (33.3 mL, 83.4 mmol, 2.5 M in hexanes) dropwise at a rate maintaining the internal temperature below –60 °C. After the mixture was held at –78 °C for 15 min, a solution of 2-(2,3-difluorophenyl)[1,3]dioxolane (**4a**) (14.1 g, 75.8 mmol) in anhydrous THF (50 mL) was added dropwise to the mixture to maintain the internal temperature below –65 °C. After being held at –78 °C for 15 min, the lithiated difluorobenzene solution was then transferred to a solution of iodine (28.9 g, 113.7 mmol) in anhydrous THF (80 mL) at –78 °C using a cannula. The resulting mixture was stirred at –78 °C for 1 h and then allowed to warm to room temperature slowly. The mixture was quenched with water and then poured into a solution of sodium thiosulfate (100 mL, 30% w/v). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield a pale-orange liquid. This was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (ddd, J = 8.3, 5.3, 1.9 Hz, 1H), 7.03 (ddd, J = 8.1, 6.4, 1.7 Hz, 1H), 6.00 (s, 1H), 4.12–3.97 (m,4H).

2,3-Difluoro-4-iodobenzaldehyde (7). A mixture of **5** obtained above in THF (60 mL) and 3.6 N hydrochloric acid (60 mL) was heated to reflux for 18 h. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. Yellow precipitate formed in the remaining aqueous solution. The precipitate was then filtered, rinsed with cold water, and dried under vacuum. The dried solid was then triturated with hexanes (100 mL) for 15 min, filtered, and dried under vacuum to yield 14.7 g (80% over two steps) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (d, J = 0.5 Hz, 1H), 7.69 (dddd, J = 0.6, 1.8, 5.0, 9.0 Hz, 1H), 7.42 (ddd, J = 1.7, 6.1, 8.4 Hz, 1H).

2-(2,3-Difluorophenyl)-2-methyl[1,3]dioxolane (4b). 2′,3′-Difluoroacetophenone was converted to the title compound using a similar procedure as described in the preparation of compound **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (ddt, J = 7.99, 6.40, 1.71 Hz, 1H), 7.01 (m, 1H), 6.93 (tdd, J = 8.12, 4.86, 1.56 Hz, 1H), 3.99 (dt, J = 4.12, 5.96 Hz, 2H), 3.75 (dt, J = 4.12, 6.29 Hz, 2H), 1.66 (d, J = 0.94 Hz, 3H).

2-(4-Bromo-2,3-difluorophenyl)-2-methyl[1,3]dioxolane (6). Compound **4b** was converted into the title compound using a similar procedure as described in the preparation of compound **5** except that neat bromine was used instead of solution of iodine in THF. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.19 (ddd, J = 8.65, 6.92, 1.96 Hz, 1H), 4.10 (m, 2H), 3.85 (m, 2H), 1.75 (d, J = 0.93 Hz, 3H).

1-(2,3-Difluoro-4-bromophenyl)ethanone (8). Compound **6** was then converted into the title compound using a similar procedure as described in the preparation of compound **7**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (ddd, J = 8.73, 6.78, 2.01 Hz, 1H), 7.40 (ddd, J = 8.69, 5.69, 1.85 Hz, 1H), 2.64 (d, J = 4.95 Hz, 3H).

1-(2,3-Difluoro-4-iodophenyl)-2,2,2-trifluoroethanol (9). To a solution of aldehyde **7** (16.1 g, 60 mmol) in THF (60 mL) under argon at 0 °C was added trimethyl(trifluoromethyl)silane (10.6 mL, 72 mmol) slowly, followed by a catalytic amount of tetrabutylammonium fluoride hydrate (150 mg, 0.6 mmol). The resulting mixture was allowed to warm to room temperature. After the mixture was stirred at room temperature for an additional 1 h, dilute hydrochloric acid (30 mL, 3 M) was added to the mixture. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined, washed with saturated sodium bicarbonate solution, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield the title compound. This was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (ddd, J = 8.35, 5.37, 1.99 Hz, 1H), 7.18 (tm, J = 7.12 Hz, 1H), 5.40 (q, J = 6.26 Hz, 1H), 3.11 (s, 1H).

1-(2,3-Difluoro-4-iodophenyl)-2,2,2-trifluoroacetone (10). To a solution of alcohol **9** (21 g, 60 mmol) in dichloromethane (140 mL) at 0 °C was added Dess−Martin periodinane (25.7 g, 61 mmol) in small portions. After the addition, the mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was then poured into a solution of potassium carbonate (10% w/v) and sodium hydroxide (10% w/v). The pH of the mixture was adjusted to about pH 8 using a saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 17.1 g (85% over two steps) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (ddd, J = 8.58, 5.12, 1.90 Hz, 1H), 7.42 (tm, J = 7.84 Hz, 1H).

(2,3-Difluoro-4-iodophenyl)hydroxyacetonitrile (11). Trimethylsilyl cyanide (3 mL, 22.3 mmol) was added slowly to a solution of benzaldehyde **7** (5 g, 18.7 mmol) in anhydrous THF (30 mL) at 0 °C. After the addition was completed, a catalytic amount of tetrabutylammonium fluoride hydrate (50 mg, 0.2 mmol) was added to the mixture. The mixture was allowed to warm to room temperature over a period of 2 h and concentrated under reduced pressure to yield an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (ddd, J = 2.06, 5.33, 8.44 Hz, 1H), 7.22 (ddd, J = 1.84, 6.41, 8.30 Hz, 1H), 5.72 (s, 1H), 0.28 (s, 9H).

The oil was dissolved in THF (15 mL) to which was added diluted hydrochloric acid (3 N, 3 mL). After being heated to 65 °C for 1 h, the mixture was allowed to cool to room temperature and diluted with 10 mL of water. The two layers were separated, and the aqueous layer was extracted with ethyl acetate thrice. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 5.76 g (quantative over two steps) of the title compound as a yellowish brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (ddd, J = 2.04, 5.31, 8.35 Hz, 1H), 7.23 (ddd, J = 1.75, 6.43, 8.39 Hz, 1H), 5.81 (s, 1H), 3.03 (br s, 1H).

2-(2,3-Difluoro-4-iodophenyl)-2-hydroxyacetamide (12). To a solution of acetonitrile **11** (5.12 g, 17.4 mmol) in anhydrous 1,4-dioxane (35 mL) at 0 °C was added cold concentrated HCl (3.5 mL), and anhydrous hydrogen chloride gas was then bubbled into the mixture at 0 °C for 30 min. The mixture was then allowed to stand without stirring and warm to room temperature overnight. (Caution: pressure developed as the solution was warming up.) The orange solution was then poured into ice. Sodium hydroxide solution (5 N, cooled in ice–water) was added slowly to the mixture at 0 °C until the pH of the solution was 8. The pink solution was then thrice extracted with ethyl acetate. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 1.95 g (36%) of pink solid as the title product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (ddd, J = 1.61, 5.76, 8.29 Hz, 1H), 7.52 (br s, 1H), 7.42 (br s, 1H), 7.07 (ddd, J = 1.38, 6.63, 8.29 Hz, 1H), 6.42 (d, J = 5.15 Hz, 1H), 5.11 (d, J = 5.12 Hz, 1H).

2-(2,3-Difluoro-4-iodophenyl)-2-oxoacetamide (13). To a solution of acetamide **12** (5.15 g, 16.4 mmol) in 300 mL of anhydrous acetonitrile was added activated manganese(IV) oxide (20 g, 230 mmol) in one portion. The reaction was monitored with TLC and stirred at room temperature for 1 h. The mixture was then filtered through a pad of Celite. The pale-yellow filtrate was concentrated under reduced pressure to yield 3.43 g (67%) of pale-yellow solid as the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, J = 1.86, 5.10, 8.44 Hz, 1H), 7.50 (ddd, J = 1.80, 6.02, 8.43, 1H), 6.84 (br s, 1H), 5.75 (br s, 1H).

2-[(3-Cyano-4-fluorophenyl)hydrazono]-2-(2,3-difluoro-4-iodophenyl)acetamide (15c). A mixture of acetamide **13** (3.43 g, 11.1 mmol), 2-fluoro-5-hydrazinobenzonitrile[19] (**14a**) (1.67 g, 11.1 mmol), and *p*-toluenesulfonic acid monohydrate (110 mg, 0.55 mmol) in 100 mL of anhydrous ethanol was refluxed for 4 h. Yellow precipitate was formed, and the mixture was allowed to cool to room temperature. The orange suspension was then cooled to 0 °C in an ice–water bath. The mixture was filtered, and the pale-yellow solid was rinsed with cold ethanol. The filtrate was concentrated under reduced pressure, and the residue was triturated with cold ethanol. The mixture was filtered and the yellow solid obtained was combined with the first crop of solid to give 3.63 g (74%) of pale-yellow solid as the desired product. The NMR indicated the yellow solid is a mixture of cis/trans isomers in a ratio of 1:2. The trans isomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 7.92 (br s, 1H), 7.72–7.62 (m, 4H), 7.44 (t, J = 9.07 Hz, 1H), 7.25 (ddd, J = 1.52, 6.82, 8.34 Hz, 1H). The cis and trans isomers: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s), 9.98 (s), 8.11 (dd, J = 2.87, 5.55 Hz), 8.02 (br s), 7.92 (br s), 7.77–7.58 (m), 7.44 (t, J = 9.10 Hz), 7.40 (t, J = 9.10 Hz), 7.31 (br s), 7.25 (ddd, J = 1.59, 7.07, 8.42 Hz), 6.95 (ddd, J = 1.56, 6.09, 8.14 Hz).

1-(3-Cyano-4-fluorophenyl)-7-fluoro-6-iodo-1*H*-indazole-3-carboxylic Acid Amide (16c). A mixture of hydrazone **15c** (3.63 g, 8.2 mmol) and potassium carbonate (1.3 g, 9.4 mmol) in 60 mL of anhydrous DMF was heated to 100 °C for 2 h. The mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was triturated with dichloromethane overnight and filtered to yield 2.92 g of light-brown solid. The red filtrate was concentrated under reduced pressure. The residue was then triturated with cold ethyl acetate for 1 h and filtered to yield another 0.37 g of pale-yellow solid. The solid was combined to give 3.28 g (95%) of pale-yellow solid as the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (dt, J = 5.62, 2.67 Hz, 1H), 8.22 (ddt, J = 4.70, 9.04, 2.87 Hz, 1H), 8.09 (br s, 1H), 7.90 (d, J = 8.45 Hz, 1H), 7.81 (t, J = 9.01 Hz, 1H), 7.72 (dd, J = 5.00, 8.50 Hz, 1H), 7.70 (br s, 1H).

5-(6-Bromo-7-fluoro-3-methylindazol-1-yl)-2-fluorobenzonitrile (16a). Compound **8** was converted into hydrazone **15a** using a similar procedure as described in the preparation of compound **15c**. Compound **15a** was then converted into the title compound using a similar procedure as described in the preparation compound **16c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (td, J = 5.44, 2.75, 2.75 Hz, 1H), 7.83 (m, 1H), 7.38–7.33 (m, 3H), 2.62 (s, 3H).

2-Fluoro-5-(7-fluoro-6-iodo-3-trifluoromethylindazol-1-yl)benzonitrile (16b). Compound **10** was converted into hydrazone **15b** using a similar procedure as described in the preparation of compound **15c**. Compound **15b** was then converted into the title compound using a similar procedure as described in the preparation of compound **16c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (td, J = 2.94, 8.36 Hz, 1H), 7.88 (m, 1H), 7.69 (dd, J = 8.61, 4.90 Hz, 1H), 7.48 (dq, J = 8.60, 0.93 Hz, 1H), 7.42 (t, J = 8.40, 1H).

3-(6-Bromo-7-fluoro-3-methylindazol-1-yl)benzonitrile (16d). Compound **8** was converted into hydrazone **15d** using 3-hydrazinobenzonitrile (**14b**) and a similar procedure as described in the preparation of compound **15c**. Compound **15d** was then converted into the title compound using a similar procedure as described in the preparation of compound **16c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 1H), 7.84 (dm, J = 7.90 Hz, 1H), 7.65 (td, J = 1.39, 7.72, Hz, 1H), 7.60 (t, J = 7.84 Hz, 1H), 7.39–7.35 (m, 2H), 2.62 (s, 3H).

1-(4-Bromo-2-fluorophenyl)ethanone (18). Methylmagnesium bromide (3.0 M) in ether (2.1 mL, 6.3 mmol) was added dropwise to a solution of 4-bromo-2-fluorobenzaldehyde (**17**) (1.1 g, 5.4 mmol) in anhydrous THF (20 mL) at –78 °C. The mixture was allowed to warm to room temperature and then stirred for 1.5 h. Additional methylmagnesium bromide (0.3 mL, 0.9 mmol, 3.0 M in ether) was added. After being stirred at room temperature for 18 h, the mixture was quenched with ammonium chloride solution. The layers were separated, and the aqueous layer was twice extracted with ethyl acetate. The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to yield an oil. The oil was dissolved in dichloromethane (50 mL), and pyridinium dichromate (3.2 g, 8.4 mmol) was added. After being stirred at room temperature for 3 d, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluted with ethyl acetate/hexanes, 0:1 to 1:9, v/v) to yield 1.1 g (91% over two steps) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, J = 8.13 Hz, 1H), 7.36 (m, 2H), 2.62 (d, J = 5.04 Hz, 3H).

3-(6-Bromo-3-methylindazol-1-yl)benzonitrile (20). Compound **18** was converted into hydrazone **19** using 3-hydrazinobenzonitrile (**14b**) and a similar procedure as described in the preparation of compound **15c**. Compound **19** was then converted into the title compound using a similar procedure as described in the preparation of compound **16c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.93 (dm, J = 7.76 Hz, 1H), 7.85 (d, J = 1.00 Hz, 1H), 7.67–7.55 (m, 3H), 7.35 (dd, J = 8.50, 1.46 Hz, 1H), 2.61 (s, 3H).

1-[4-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]piperidin-2-one (23a). 5-Bromovaleryl chloride (0.65 mL, 4.85 mmol) was added slowly to a mixture of 4-aminophenylboronic acid pinacol ester (1.0 g, 4.6 mmol) and triethylamine (0.75 mL, 5.4 mmol) in dichloromethane (30 mL). After the mixture was stirred at room temperature for 15 min, water was added to the mixture. The two layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution and brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in 40 mL of anhydrous DMF and cooled to 0 °C, and sodium hydride (0.23 g, 5.75 mmol, 60% dispersion in mineral oil) was added in small portions. After being stirred at room temperature for 18 h, the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with 10% aqueous citric acid solution. The aqueous layer was extracted with dichloromethane three times. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The yellow solid was triturated with ether/hexanes (1:1, v/v). After filtration and drying under vacuum, 0.77 g (52% over two steps) of off-white solid was obtained as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dm, J = 8.41 Hz, 2H), 7.27 (m, J = 8.41 Hz, 2H), 3.64 (m, 2H), 2.56 (m, 2H), 1.94 (m, 4H), 1.33 (s, 12H).

1-[4-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]pyrrolidin-2-one (23b). Compound **21** was converted into boronic acid ester **23b** using 4-bromobutyryl chloride and a similar procedure as described in the preparation of compound **23a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.65 Hz, 2H), 7.64 (d, J = 8.67 Hz, 2H), 3.88 (t, J = 7.04 Hz, 2H), 2.62 (t, J = 8.08 Hz, 2H), 2.16 (m, 2H), 1.34 (s, 12H).

1-(4-Bromo-3-fluorophenyl)piperidin-2-one (23c). 4-Bromo-3-fluoroaniline (**22**) was converted into lactam **23c** using 4-bromovaleryl chloride and a similar procedure as described in the preparation of compound **23a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.42, 7.82 Hz, 1H), 7.11 (dd, J = 9.64, 2.38 Hz, 1H), 6.98 (ddd, J = 8.58, 2.36, 0.96 Hz, 1H), 3.63 (t, J = 5.91 Hz, 2H), 2.56 (t, J = 6.32 Hz, 2H), 1.94 (m, 4H).

1-[3-Fluoro-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]piperidin-2-one (23d). A mixture of lactam **23c** (50 mg, 0.184 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, (20 mg, 0.024 mmol), bis(pinacolato)diboron (70 mg, 0.276 mmol), and potassium acetate (54 mg, 0.550 mmol) under argon in 4 mL of anhydrous 1,4-dioxane was heated to 90 °C for 18 h. Upon cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified using preparative TLC plates (silica gel, 20 cm × 20 cm, 1000 μm, ethyl acetate/hexanes, 1:1 v/v) to give 35.2 mg (60%) of off-white solid as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.99, 6.83 Hz, 1H), 7.08 (dd, J = 8.03, 1.88 Hz, 1H), 7.00 (dd, J = 10.49, 1.82 Hz, 1H), 3.63 (t, J = 5.88 Hz, 2H), 2.55 (t, J = 6.32 Hz, 2H), 2.03–1.82 (m, 4H), 1.34 (s, 12H).

3-{3-Methyl-6-[4-(2-oxopiperidin-1-yl)phenyl]indazol-1-yl}benzonitrile (24d). A mixture of boronic acid ester **23a** (58 mg, 0.192 mmol), indazole **20** (50 mg, 0.160 mmol), tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.016 mmol), sodium carbonate solution (0.64 mL, 1.28 mmol), and 3 mL of ethanol/toluene (1:2, v/v) was heated to 100 °C for 18 h. Upon cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice. The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using sequential preparative TLC (silica gel, 20 cm × 20 cm, 1000 μm, ethyl acetate/hexanes, 7:3 v/v, and then ethyl acetate/dichloromethane, 3:7 v/v) to give the title compound (48 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 8.01 (dm, J = 8.03 Hz, 1H), 7.82 (s, 1H), 7.78 (d, J = 8.32 Hz, 1H), 7.66–7.64 (m, 3H), 7.58 (dm, J = 7.70 Hz, 1H), 7.47 (dd, J = 8.15, 0.84 Hz, 1H), 7.38 (d, J = 8.40 Hz, 2H), 3.71 (t, J = 5.55 Hz, 2H), 2.67 (s, 3H), 2.60 (t, J = 6.24 Hz, 2H), 1.98 (m, 4H).

1-{4-[1-(3-Aminomethylphenyl)-3-methyl-1*H*-indazol-6-yl]phenyl}piperidin-2-one (25d). A mixture of benzonitrile **24d** (47.8 mg, 0.118 mmol) and Raney nickel (~0.5 g) in 15 mL of ethanol was hydrogenated in a Parr apparatus at 50 psi and room temperature for 18 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluted with 7 N ammonia in methanol/dichloromethane, 0:1 v/v to 5:95 v/v) to yield 20 mg (39%) of white solid as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.76–7.74 (m, 2H), 7.63 (d, J = 8.59 Hz, 2H), 7.60 (ddd, J = 2.65, 2.06, 1.07 Hz, 1H), 7.46 (t, J = 7.77 Hz, 1H), 7.42 (dd, J = 8.34, 1.35 Hz, 1H), 7.35 (br d, J = 7.51 Hz, 1H), 7.32 (d, J = 8.57 Hz, 2H), 3.96 (s, 2H), 3.66 (t, J = 5.72 Hz, 2H), 2.66 (s, 3H), 2.58 (t, J = 6.24 Hz, 2H), 1.95 (m, 4H). HRMS (FAB+) m/z calcd for $C_{26}H_{25}N_4O$ $[M - H]^+$, 409.2028; found, 409.2034.

Compounds **25a**−**c** were prepared using the same procedures as for the synthesis of compound **25d** using appropriate starting materials.

1-{4-[1-(3-Aminomethylphenyl)-7-fluoro-3-methyl-1*H*-indazol-6-yl]phenyl}pyrrolidin-2-one (25a). ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$) δ 7.66 (d, J = 8.75 Hz, 2H), 7.57–7.54 (m, 2H), 7.52–7.48 (m, 2H), 7.46–7.40 (m, 2H), 7.30 (br d, J = 6.90 Hz, 1H), 7.21 (dd, J = 8.20, 5.98 Hz, 1H), 3.90–3.87 (m, 4H), 2.63–2.59 (m, 5H), 2.17 (m, 2H). HRMS (FAB+) m/z calcd for $C_{25}H_{22}N_4OF$ $[M - H]^+$, 413.1778; found, 413.1773.

1-{4-[1-(3-Aminomethylphenyl)-3-methyl-1*H*-indazol-6-yl]phenyl}pyrrolidin-2-one (25b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.78 (d, J = 8.34 Hz, 1H), 7.75–7.70 (m, 3H), 7.67 (d, J = 8.80 Hz, 2H), 7.63 (br d, J = 8.32 Hz, 1H), 7.51 (t, J = 7.78 Hz, 1H), 7.46 (dd, J = 1.33, 8.35 Hz, 1H), 7.33 (br d, J = 7.57 Hz, 1H), 4.00 (s, 2H), 3.94 (t, J = 7.03 Hz, 2H), 2.70 (s, 3H),

2.67 (t, $J = 8.11$ Hz, 2H), 2.22 (quintet, $J = 7.59$ Hz, 2H). HRMS (FAB+) *m/z* calcd for $C_{25}H_{23}N_4O$ $[M - H]^+$, 395.1872; found, 395.1879.

1-{4-[1-(3-Aminomethylphenyl)-7-fluoro-3-methyl-1*H*-indazol-6-yl]phenyl}piperidin-2-one (25c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.59 (m, 3H), 7.50–7.48 (m, 2H), 7.42 (t, $J = 7.70$ Hz, 1H), 7.36–7.32 (m, 3H), 7.22 (dd, $J = 8.24$, 5.92 Hz, 1H), 3.98 (br s, 1H), 3.68 (t, $J = 5.38$ Hz, 2H), 2.61 (s, 3H), 2.57 (t, $J = 6.18$ Hz, 2H), 1.96 (m, 4H). HRMS (ESI+) *m/z* calcd for $C_{26}H_{26}N_4OF$ $[M + H]^+$, 429.2091; found, 429.2085.

2-Fluoro-5-[7-fluoro-3-methyl-6-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)indazol-1-yl]benzonitrile (26). A mixture of bromoindazole **16a** (398 mg, 1.14 mmol), Pd(dppf)$Cl_2 \cdot CH_2Cl_2$, (94 mg, 0.114 mmol), bis(pinacolato)diboron (436 mg, 1.72 mmol), and potassium acetate (337 mg, 3.43 mmol) under argon in 35 mL of anhydrous 1,4-dioxane was heated to 90 °C for 18 h. Upon cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluted with dichloromethane) to yield 433 mg (95%) of white solid as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.83 (m, 2H), 7.53 (dd, $J = 8.04$, 4.09 Hz, 1H), 7.48 (dd, $J = 8.02$, 0.65 Hz, 1H), 7.31 (t, $J = 8.58$ Hz, 1H), 2.63 (s, 3H), 1.39 (s, 12H).

1-(3-Cyano-4-fluorophenyl)-7-fluoro-6-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-1*H*-indazole-3-carboxylic Acid Amide (27). A mixture of 1-(3-cyano-4-fluorophenyl)-7-fluoro-6-iodo-1*H*-indazole-3-carboxylic acid amide **16c** (105 mg, 0.24 mmol), Pd(dppf)Cl_2 (20 mg, 0.024 mmol), bis(pinacolato)diboron (90 mg, 0.35 mmol), potassium acetate (70 mg, 0.71 mmol) under argon in 5 mL of anhydrous 1,4-dioxane was heated at 110 °C for 2 d. After cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was then purified using silica gel flash chromatography (ethyl acetate/dichloromethane, 1:1 v/v) to yield 92 mg (88%) of light-yellow solid as the title product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (dt, $J = 5.59$, 2.49 Hz, 1H), 8.21 (ddt, $J = 4.70$, 9.06, 2.70 Hz, 1H), 8.10 (d, $J = 8.16$ Hz, 1H), 8.07 (br s, 1H), 7.81 (t, $J = 9.01$ Hz, 1H), 7.69 (br s, 1H), 7.54 (dd, $J = 4.33$, 8.15 Hz, 1H), 1.32 (s, 12H).

2-Fluoro-5-{7-fluoro-6-[2-fluoro-4-(2-oxo-piperidin-1-yl)phenyl]-3-methylindazol-1-yl}benzonitrile (28a). A mixture of indazole boronate **26** (433 mg, 1.26 mmol), lactam **23c** (378 mg, 1.38 mmol), Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (103 mg, 0.126 mmol), and potassium carbonate (698 mg, 5.1 mmol) in 30 mL of anhydrous DMF was heated to 95 °C for 18 h. Upon cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (eluted with ethyl acetate/hexanes, 7:3 v/v) to yield 382 mg (66%) of white solid as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (td, $J = 2.75$, 5.57 Hz, 1H), 7.85 (dd, $J = 8.56$, 4.24 Hz, 1H), 7.55 (d, $J = 8.22$ Hz, 1H), 7.43 (t, $J = 8.28$ Hz, 1H), 7.31 (t, $J = 8.61$ Hz, 1H), 7.26–7.16 (m, 4H), 3.70 (t, $J = 5.41$ Hz, 2H), 2.64 (s, 3H), 2.59 (t, $J = 6.27$ Hz, 2H), 1.97 (m, 4H).

2-Fluoro-5-{7-fluoro-6-[2-fluoro-4-(2-oxopiperidin-1-yl)phenyl]-3-trifluoromethylindazol-1-yl}benzonitrile (28b). A mixture of iodoindazole **16b** (15 mg, 0.033 mmol), lactam boronate **23d** (16 mg, 0.050 mmol), tetrakis(triphenylphosphine)palladium(0) (2 mg, 0.002 mmol), aqueous sodium carbonate solution (0.1 mL, 0.2 mmol, 2 M), and 0.7 mL of ethanol/toluene (1:6, v/v) was heated to 80 °C for 20 h. Upon cooling to room temperature, the mixture was diluted with ethyl acetate. The mixture was purified using preparative TLC (silica gel, 20 cm × 20 cm, 250 μm, ethyl acetate/dichloromethane, 1:9 v/v) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (td, $J = 2.65$, 5.17, Hz, 1H), 7.91 (m, 1H), 7.77 (dd, $J = 8.42$, 0.80 Hz, 1H), 7.45–7.37 (m, 3H), 7.24–7.18 (m, 2H), 3.72 (t, $J = 5.52$ Hz, 2H), 2.60 (t, $J = 6.35$ Hz, 2H), 1.99 (m, 4H).

1-{4-[1-(3-Aminobenzo[*d*]isoxazol-5-yl)-7-fluoro-3-methyl-1*H*-indazol-6-yl]-3-fluorophenyl}piperidin-2-one (29a). A mixture of lactam indazole **28a** (381 mg, 0.83 mmol), acetohydroxamic acid (186 mg, 2.48 mmol), and potassium carbonate (686 mg, 4.96 mmol) in 14 mL of DMF and 2.0 mL of water was stirred at room temperature for 3 d. The reaction was then quenched with water. The off-white precipitate was filtered and washed with ethyl acetate. The solid was then purified by silica gel flash chromatography (eluted with ethyl acetate/hexanes, 7:3 v/v) to yield 298 mg (76%) of white solid as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (ddd, $J = 8.90$, 3.01, 2.30 Hz, 1H), 7.73 (m, 1H), 7.56 (d, $J = 8.23$ Hz, 1H), 7.51 (d, $J = 8.87$ Hz, 1H), 7.44 (t, $J = 8.25$ Hz, 1H), 7.21–7.14 (m, 3H), 4.40 (br s, 2H), 3.69 (t, $J = 5.35$ Hz, 2H), 2.68 (s, 3H), 2.60 (t, $J = 6.20$ Hz, 2H), 1.97 (m, 4H). HRMS (FAB+) *m/z* calcd for $C_{26}H_{22}N_5O_2F_2$ $[M + H]^+$, 474.1742; found, 474.1752.

1-{4-[1-(3-Aminobenzo[*d*]isoxazol-5-yl)-7-fluoro-3-trifluoromethyl-1*H*-indazol-6-yl]-3-fluorophenyl}piperidin-2-one (29b). Compound **28b** was converted into the title compound using the procedure as described in the preparation of compound **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, $J = 2.20$ Hz, 1H), 7.81–7.75 (m, 2H), 7.54 (d, $J = 8.88$ Hz, 1H), 7.40 (t, $J = 8.30$ Hz, 1H), 7.35 (dd, $J = 8.37$, 5.62 Hz, 1H), 7.20–7.15 (m, 2H), 4.56 (br s, 1H), 3.69 (t, $J = 5.53$ Hz, 2H), 2.59 (t, $J = 6.35$ Hz, 2H), 1.96 (m, 4H). HRMS (FAB+) *m/z* calcd for $C_{26}H_{19}N_5O_2F_5$ $[M + H]^+$, 528.1459; found, 528.1465.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-7-fluoro-6-[2-fluoro-4-(2-oxo-piperidin-1-yl)phenyl]-1*H*-indazole-3-carboxamide (29c). Compound **16c** was converted into compound **28c** using the procedure as described in the preparation of compound **28b**. Compound **28b** was then converted into the title compound using the procedure as described in the preparation of compound **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, $J = 8.4$ Hz, 1H), 7.84–7.78 (m, 2H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.43 (t, $J = 8.3$ Hz, 1H), 7.34 (dd, $J = 5.8$, 8.4 Hz, 1H), 7.21–7.14 (m, 2H), 6.96 (br s, 1H), 5.55 (br s, 1H), 4.49 (br s, 2H), 3.69 (t, $J = 5.4$ Hz, 2H), 2.59 (t, $J = 6.3$ Hz, 2H), 1.97 (m, 4H). HRMS (FAB+) *m/z* calcd for $C_{26}H_{20}N_6O_3F_2$ $[M]^+$, 502.1565; found, 502.1562.

3-Iodo-2-pyridinecarboxaldehyde (32)..[36] To a solution of *N,N,N′*-trimethylethylenediamine (1.63 mL, 12.6 mmol) in anhydrous THF (30 mL) under argon at –78 °C was added 1.65 M *n*-butyllithium in hexanes (7 mL, 21 mmol). After the mixture was held for 15 min, 2-pyridinecarboxaldehyde (1 mL, 10.5 mmol) was added to the solution. After the mixture was stirred at –78 °C for an additional 15 min, another aliquot of 1.65 M *n*-butyllithium in hexanes (12.7 mL, 21 mmol) was added to the mixture. After being stirred at –78 °C for another 1 h and at –42 °C (dry ice/acetonitrile bath) for 4 h, the solution was transferred to a solution of iodine (5.6 g, 22 mmol) in anhydrous THF (30 mL) using a cannula. The mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was quenched with brine, and the two layers were separated. The aqueous layers was extracted with ether twice. The organic layers were combined, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, ethyl acetate/dichloromethane, 15:85 v/v) to give 314 mg (13%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.76 (dd, $J = 4.46$, 1.33 Hz, 1H), 8.32 (dm, $J = 8.02$ Hz, 1H), 7.19 (dd, $J = 8.02$, 4.49 Hz, 1H).

4-Iodo-3-pyridinecarboxaldehyde (33)..[36] 3-Pyridinecarboxaldehyde was converted into compound **33** using the procedure as described in the preparation of compound **32**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.86 (s, 1H), 8.31 (d, $J = 5.25$ Hz, 1H), 7.90 (d, $J = 5.26$ Hz, 1H).

4-Bromo-2-(2-trimethylsilanylethoxymethyl)-2*H*-pyrazole-3-carboxaldehyde (37). To a suspension of sodium hydride (150 mg, 3.6 mmol, 60% dispersion in mineral oil) in anhydrous DMF (30 mL) was added a solution of 4-bromo-1*H*-pyrazole-5-carboxaldehyde (**36**) (500 mg, 2.9 mmol) in DMF (5 mL) and then (chloromethyl)methyldiethoxysilane (0.66 mL, 3.6 mmol). After being stirred at room temperature for 18 h, the mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice. The organic layers were combined, washed

with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, ×3, ethyl acetate/dichloromethane, 15:85 v/v) to give 331 mg (39%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.59 (s, 1H), 5.76 (s, 2H), 3.61–3.53 (m, 2H), 0.94–0.83 (m, 2H), −0.05 (s, 9H).

***N,N*-Dimethyl-*N′*-phenylethane-1,2-diamine (41).** A mixture of bromobenzene (0.26 mL, 2.5 mmol), *N,N*-dimethylethylenediamine (0.3 mL, 2.75 mmol), $Pd_2(dba)_3$ (114 mg, 0.125 mmol), sodium *tert*-butoxide (504 mg, 5.25 mmol), and XANTPHOS (174 mg, 0.3 mmol) under argon in 1,4-dioxane was heated to 140 °C in a Biotage Initiator microwave synthesizer for 30 min. Upon cooling, the mixture was diluted with ethyl acetate and filtered, and the filtrate was concentrated under reduced pressure. The reside was purified using silica gel flash chromatography (eluted with methanol/dichloromethane, 5:95 v/v) followed by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, ethyl acetate) to give 150 mg (37%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.15 (m, 2H), 6.72–6.67 (m, 1H), 6.65–6.62 (m, 2H), 4.25 (br s, 1H), 3.17–3.13 (m, 2H), 2.58–2.54 (m, 2H), 2.26 (s, 6H).

***N,N*-Dimethyl-*N′*-pyridin-3-ylethane-1,2-diamine (42).** 3-Bromopyridine was converted into compound **42** using the procedure as described in the preparation of compound **41**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.8 Hz, 1H), 7.95 (dd, *J* = 1.3, 4.7 Hz, 1H), 7.08 (ddd, *J* = 0.4, 4.7, 8.3 Hz, 1H), 6.88 (ddd, *J* = 1.3, 2.9, 8.3 Hz, 1H), 4.39 (br s, 1H), 3.19–3.11 (br m, 2H), 2.60–2.56 (m, 2H), 2.26 (s, 6H).

***N,N*-Dimethyl-*N′*-pyridin-4-ylethane-1,2-diamine (47).** A mixture of 4-chloropyridine hydrochloride (150 mg, 1.0 mmol) and *N,N*-dimethylethylenediamine (0.33 mL, 3 mmol) in anhydrous 1-pentanol (1 mL) under argon was heated to 140 °C for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, methanol/dichloromethane, 1:9 v/v, followed by 10% 7 N ammonia in methanol/dichloromethane, 1:9 v/v) to give 152 mg (92%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.17 (m, 2H), 6.46–6.43 (m, 2H), 4.86 (br s, 1H), 3.19–3.13 (m, 2H), 2.58–2.53 (m, 2H), 2.26 (s, 6H).

***N,N*-Dimethyl-*N′*-pyridin-4-ylpropane-1,3-diamine (48).** 4-Chloropyridine hydrochloride and *N,N*-dimethyl-1,3-propanediamine were coupled into compound **48** using the procedure as described in the preparation of compound **47**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.14 (m, 2H), 6.43–6.39 (m, 2H), 5.42 (br s, 1H), 3.25–3.20 (m, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 2.25 (s, 6H), 1.78 (quintet, *J* = 6.4 Hz, 2H).

[1-(4-Bromo-3-fluorophenyl)-1*H*-imidazol-2-ylmethyl]dimethylamine (49a). A mixture of imidazole **43**[19] (300 mg, 2.4 mmol), 1-bromo-2-fluoro-4-iodobenzene (720 mg, 2.4 mmol), cesium carbonate (1.56 g, 4.8 mmol), and copper(I) iodide (91 mg, 0.48 mmol) in 15 mL of anhydrous DMF was heated to 125 °C for 18 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was triturated with ethyl acetate and methanol and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography (eluted with methanol/ethyl acetate, 0:1 v/v to 1:9 v/v) to yield 236 mg (33%) of pale-yellow solid as the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 9.48, 2.35 Hz, 1H), 7.61 (dd, *J* = 8.49, 7.51 Hz, 1H), 7.27 (ddd, *J* = 8.55, 2.39, 0.99 Hz, 1H), 7.06 (dd, *J* = 2.92, 1.23 Hz, 2H), 3.34 (s, 2H), 2.24 (s, 6H).

[4-(4-Bromo-3-fluorophenyl)-2-(2-trimethylsilanylethoxymethyl)-2*H*-pyrazol-3-ylmethyl]dimethylamine (49b). A mixture of pyrazole **37** (480 mg, 1.57 mmol), 4-bromo-3-fluorobenzeneboronic acid (413 mg, 1.88 mmol), $PdCl_2(PPh_3)_2$ (110 mg, 0.16 mmol), and aqueous sodium carbonate solution (6.3 mL, 13.6 mmol, 2 M) in 50 mL of 1,2-dimethoxyethane was heated to 90 °C for 18 h. Upon cooling, the mixture was partitioned between brine and ethyl acetate, and the aqueous layer was extracted thrice with ethyl acetate. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, ethyl acetate/hexanes, 1:9 v/v) to give 285 mg (45%) of 4-(4-bromo-3-fluorophenyl)-2-(2-trimethylsilanylethoxymethyl)-2*H*-pyrazole-3-carboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.69 (s, 1H), 7.64 (dd, *J* = 8.14, 7.20 Hz, 1H), 7.24 (dd, *J* = 9.15, 1.99 Hz, 1H), 7.13 (dd, *J* = 7.93, 1.72 Hz, 1H), 5.85 (s, 2H), 3.64 (m, 2H), 0.94 (m, 2H), −0.03 (s, 9H).

A mixture of 4-(4-bromo-3-fluorophenyl)-2-(2-trimethylsilanylethoxymethyl)-2*H*-pyrazole-3-carboxaldehyde (285 mg, 0.71 mmol), dimethylamine (1.8 mL, 3.6 mmol, 2 M in THF), and 4 Å molecular sieves in 30 mL of anhydrous DMF was stirred at room temperature for 18 h. Sodium triacetoxyborohydride (230 mg, 1.1 mmol) was added to the mixture and stirred for additional 3 d. The mixture was concentrated under reduced pressure and partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane twice. The organic layers were combined, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, ethyl acetate/hexanes, 1:1 v/v) to give 152 mg (92%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.54 (dd, *J* = 7.62, 7.49 Hz, 1H), 7.32 (dd, *J* = 9.96, 1.87 Hz, 1H), 7.13 (dd, *J* = 8.25, 1.86 Hz, 1H), 5.65 (s, 2H), 3.62–3.58 (m, 4H), 2.19 (s, 6H), 0.91 (m, 2H), −0.03 (s, 9H).

(4′-Bromo-3′-fluorobiphenyl-2-ylmethyl)dimethylamine (49c). A mixture of 2-formylphenylboronic acid (500 mg, 3.3 mmol), 1-bromo-2-fluoro-4-iodobenzene (1.1 g, 3.7 mmol), aqueous sodium carbonate solution (27 mL, 14 mmol, 2M), tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.17 mmol) in ethanol/toluene (12 mL, 1:1 v/v) was heated to 100 °C for 16 h. The mixture was allowed to cool and then partitioned between ethyl acetate and water. The aqueous layer was then extracted twice with ethyl acetate. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified using silica gel flash chromatography (eluted with ethyl acetate/hexanes, 0:1 v/v to 1:9 v/v) to give 733 mg (79%) of 4′-bromo-3′-fluorobiphenyl-2-carboxaldehyde as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.04 (dd, *J* = 1.24, 7.78 Hz, 1H), 7.70–7.64 (m, 2H), 7.56 (t, *J* = 7.57, 1H), 7.42 (dd, *J* = 0.69, 7.67 Hz, 1H), 7.19 (dd, *J* = 2.01, 9.02 Hz, 1H), 7.06 (dd, *J* = 1.98, 8.15 Hz, 1H).

To a mixture of 4′-bromo-3′-fluorobiphenyl-2-carboxaldehyde (100 mg, 0.36 mmol) and 2.0 M dimethylamine in tetrahydrofuran solution (0.36 mL, 0.72 mmol) in 10 mL of anhydrous DMF was added sodium triacetoxyborohydride (114 mg, 0.54 mmol) and stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to yield 113 mg (100%) of colorless residue as the title compound. The mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.95, 7.57 Hz, 1H), 7.58 (dd, *J* = 7.42, 1.00 Hz, 1H), 7.46 (ddd, *J* = 1.52, 7.44, 7.52 Hz, 1H), 7.43–7.39 (m, 2H), 7.32 (dd, *J* = 1.40, 7.49 Hz, 1H), 7.19 (dd, *J* = 1.84, 8.18 Hz, 1H), 3.38 (s, 2H), 2.27 (s, 6H).

[2-(4-Bromo-3-fluorophenyl)pyridin-3-ylmethyl]dimethylamine (49d). A mixture of 2-bromo-3-pyridinecarboxaldehyde (256 mg, 1.4 mmol), 4-bromo-3-fluorobenzeneboronic acid (100 mg, 0.46 mmol), $PdCl_2(PPh_3)_2$ (32 mg, 0.05 mmol), and aqueous sodium carbonate solution (2 mL, 3.7 mmol, 2 M) in 15 mL of 1,2-dimethoxyethane was heated to 90 °C for 4 h. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was then extracted with ethyl acetate twice. The organic layers were combined, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, ethyl acetate/hexanes, 1:4 v/v) to yield 72 mg (18%) of 2-(4-bromo-3-fluorophenyl)py-

ridine-3-carboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.88 (dd, J = 4.73, 1.79 Hz, 1H), 8.32 (dd, J = 7.88, 1.79 Hz, 1H), 7.71 (dd, J = 8.10, 6.98 Hz, 1H), 7.50 (ddd, J = 7.87, 4.74, 0.50 Hz, 1H), 7.45 (dd, J = 8.96, 1.99 Hz, 1H), 7.22 (dd, J = 8.17, 1.81 Hz, 1H).

To a mixture of 2-(4-bromo-3-fluorophenyl)pyridine-3-carboxaldehyde (72 mg, 0.26 mmol) and dimethylamine (0.26 mL, 0.51 mmol, 2 M in THF) in 10 mL of anhydrous DMF was added sodium triacetoxyborohydride (82 mg, 0.39 mmol). After being stirred at room temperature for 18 h, the mixture was concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to yield 78.3 mg (99%) of pale-yellow oil as the title compound. The mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 4.72, 1.69 Hz, 1H), 7.82 (dd, J = 7.78, 1.65 Hz, 1H), 7.66–7.54 (m, 1H), 7.37 (dd, J = 8.23, 1.79 Hz, 1H), 7.29 (dd, J = 7.77, 4.73 Hz, 1H), 3.34 (s, 2H), 2.20 (s, 6H).

[3-(4-Bromo-3-fluorophenyl)pyridin-4-ylmethyl]dimethylamine (49e). Commercially available 3-bromopyridine-4-carboxaldehyde (**34**) was converted into the title compound **49e** using the procedures as described in the preparation of compound **49d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 5.07 Hz, 1H), 8.45 (s, 1H), 7.62 (dd, J = 8.02, 7.33 Hz, 1H), 7.48 (d, J = 5.07 Hz, 1H), 7.25 (dd, J = 9.38, 1.94 Hz, 1H), 7.05 (dd, J = 8.18, 1.89 Hz, 1H), 3.30 (s, 2H), 2.18 (s, 6H).

[3-(4-Bromo-3-fluorophenyl)pyridin-2-ylmethyl]dimethylamine (49f). 3-Iodo-2-pyridinecarboxaldehyde (**32**) was converted into the title compound **49f** using the procedures as described in the preparation of compound **49d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, J = 4.78, 1.70 Hz, 1H), 7.59 (dd, J = 8.13, 7.28 Hz, 1H), 7.55 (dd, J = 7.73, 1.72 Hz, 1H), 7.39 (dd, J = 9.64, 1.98 Hz, 1H), 7.26 (dd, J = 7.70, 4.82 Hz, 1H), 7.13 (dd, J = 8.20, 1.53 Hz, 1H), 3.42 (s, 2H), 2.22 (s, 6H).

[4-(4-Bromo-3-fluorophenyl)pyridin-3-ylmethyl]dimethylamine (49g). 4-Iodo-3-pyridinecarboxaldehyde (**33**) was converted into the title compound **49g** using the procedures as described in the preparation of compound **49d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.56 (d, J = 5.06 Hz, 1H), 7.61 (dd, J = 8.15, 7.18 Hz, 1H), 7.43 (dd, J = 9.54, 1.97 Hz, 1H), 7.19 (d, J = 5.04 Hz, 1H), 7.15 (dd, J = 8.21, 1.58 Hz, 1H), 3.35 (s, 2H), 2.20 (s, 6H).

***N*-(4-Bromo-3-fluorophenyl)-*N*′,*N*′-dimethyl-*N*-phenylethane-1,2-diamine (49i).** A mixture of 1-bromo-2-fluoro-4-iodobenzene (301 mg, 1.0 mmol), *N,N*-dimethyl-*N*′-phenylethane-1,2-diamine (**41**) (150 mg, 0.91 mmol), $Pd_2(dba)_3$ (42 mg, 0.046 mmol), sodium *tert*-butoxide (184 mg, 1.92 mmol), and XANTPHOS (63 mg, 0.11 mmol) under argon in 1,4-dioxane was heated to 140 °C in a Biotage Initiator microwave synthesizer for 30 min. Upon cooling, the mixture was diluted with ethyl acetate and filtered and the filtrate was concentrated under reduced pressure. The reside was purified using preparative TLC plates (silica gel, 20 cm × 20 cm, 2000 μm, methanol/dichloromethane, 1:9 v/v) to give 243 mg (79%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2H), 7.26 (dd, J = 8.3, 8.6 Hz, 1H), 7.16–7.12 (m, 3H), 6.58 (dd, J = 2.8, 11.8 Hz, 1H), 6.49 (dd, J = 2.7, 8.8 Hz, 1H), 3.80–3.75 (m, 2H), 2.56–2.51 (m, 2H), 2.25 (s, 6H).

Compounds **49h**, **49j**, **49k**, and **49l** were prepared using the same procedure as for the preparation of compound **49i** using anilines **44**, **42**, **47**, and **48**, respectively.

(4-Bromo-3-fluorophenyl)methylpyridin-4-ylamine (49h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 2H), 7.57 (dd, J = 8.0, 8.4 Hz, 1H), 7.02 (dd, J = 2.5, 9.7 Hz, 1H), 6.93 (ddd, J = 0.9, 2.5, 8.6 Hz, 1H), 6.65 (m, 2H), 3.33 (s, 3H). Isolated in quantitative yield.

***N*-(4-Bromo-3-fluorophenyl)-*N*′,*N*′-dimethyl-*N*-pyridin-3-ylethane-1,2-diamine (49j).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 3.9 Hz, 1H), 7.44 (ddd, J = 1.2, 2.4, 8.2 Hz, 1H), 7.35 (t, J = 8.3 Hz, 1H), 7.26 (dd, J = 4.7, 8.3 Hz, 1H), 6.70 (dd, J = 2.7, 11.1 Hz, 1H), 6.59 (dd, J = 2.4, 8.8 Hz, 1H), 3.83–3.78 (m, 2H), 2.57–2.52 (m, 2H), 2.26 (s, 6H). Isolated in 49% yield.

***N*-(4-Bromo-3-fluorophenyl)-*N*′,*N*′-dimethyl-*N*-pyridin-4-ylethane-1,2-diamine (49k).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 6.4 Hz, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.11 (dd, J = 2.4, 9.3 Hz, 1H), 7.00 (dd, J = 1.8, 8.5 Hz, 1H), 6.67 (d, J = 6.5 Hz, 2H), 3.91–3.86 (m, 2H), 2.68–2.63 (m, 2H), 2.34 (s, 6H). Isolated in 45% yield.

***N*-(4-Bromo-3-fluorophenyl)-*N*′,*N*′-dimethyl-*N*-pyridin-4-ylpropane-1,3-diamine (49l).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 6.2 Hz, 2H), 7.58 (t, J = 8.1 Hz, 1H), 7.05 (dd, J = 2.4, 9.7 Hz, 1H), 6.94 (dd, J = 1.8, 8.6 Hz, 1H), 6.64 (d, J = 6.5 Hz, 2H), 3.79–3.74 (m, 2H), 2.32 (t, J = 6.8 Hz, 2H), 2.23 (s, 6H), 1.84–1.76 (m, 2H). Isolated in 39% yield.

1-(3-Cyano-4-fluorophenyl)-6-(2′-dimethylaminomethyl-3-fluorobiphenyl-4-yl)-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (50c). A mixture of 1-(3-cyano-4-fluorophenyl)-7-fluoro-6-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1*H*-indazole-3-carboxylic acid amide (**27**) (38 mg, 0.09 mmol), (4′-bromo-3′-fluorobiphenyl-2-ylmethyl)dimethylamine (**49c**) (27.6 mg, 0.09 mmol), dichlorobis(triphenylphosphine)palladium(II) (7 mg, 0.01 mmol), and aqueous sodium carbonate solution (0.36 mL, 0.72 mmol, 2.0 M) was stirred under argon in 2 mL of anhydrous DME. The mixture was heated to 90 °C for 18 h. Upon cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was then partitioned between water and ethyl acetate. The aqueous layer was then extracted with ethyl acetate twice. The organic layers were combined, washed with brine, and dried with anhydrous sodium sulfate. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, 7 N ammonia in methanol solution/ethyl acetate, 1:200 v/v) to give 27.2 mg (58%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.37 Hz, 1H), (dt, J = 5.31, 2.63 Hz, 1H), 7.94 (m, 1H), 7.68 (d, J = 12.01 Hz, 1H), 7.66 (dd, J = 1.43, 11.99 Hz, 1H), 7.54 (d, J = 7.26 Hz, 1H), 7.49–7.44 (m, 2H), 7.43–7.29 (m, 4H), 6.95 (s, 1H), 5.71 (s, 1H), 3.38 (s, 2H), 2.20 (s, 6H). Mass spectrum (LCMS, ESI+) *m/z* calcd for $C_{30}H_{22}F_3N_5O$ $\{M + H\}^+$ 526.2; found, 526.0.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-(2′-dimethylaminomethyl-3-fluorobiphenyl-4-yl)-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51c). A mixture of 1-(3-cyano-4-fluorophenyl)-6-(2′-dimethylaminomethyl-3-fluorobiphenyl-4-yl)-7-fluoro-1*H*-indazole-3-carboxylic acid amide (**50c**) (37.8 mg, 0.072 mmol), acetohydroxamic acid (16 mg, 0.22 mmol), and potassium carbonate (60 mg, 0.43 mmol) in 4.9 mL of DMF and 0.7 mL of water was stirred at room temperature overnight. The reaction was then quenched with water. The mixture was extracted with ethyl acetate thrice. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, 7 N ammonia in methanol/ethyl acetate/dichloromethane, 1:5:5 v/v/v) to yield 21.6 mg (56%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 8.42 Hz, 1H), 8.20 (t, J = 2.00 Hz, 1H), 8.05 (br s, 1H) 7.93 (dt, J = 8.87, 2.16 Hz, 1H), 7.65 (d, J = 8.76 Hz, 1H) 7.65 (br s, 1H), 7.59 (t, J = 7.90 Hz, 1H), 7.52 (dd, J = 1.44, 11.49 Hz, 1H), 7.48 (dd, J = 2.32, 13.89 Hz), 1H), 7.46 (d, J = 13.97 Hz, 1H), 7.41–7.31 (m, 4H), 6.57 (s, 2H) 3.32 (s, 2H), 2.09 (s, 6H). HRMS (FAB+) *m/z* calcd for $C_{30}H_{25}N_6O_2F_2$ $[M + H]^+$, 539.2007; found, 539.2000.

Compounds **50a** and **50d**−**l** were prepared using the same procedure as for the preparation of compound **50c** using the corresponding biarylbromide **49a** and **49d**−**l** and were converted to compounds **51a** and **51d**−**l** using the same procedure as for the preparation of compound **51c**. Compound **50b** was prepared using the same procedure as for the preparation of compound **50c** using biaryl bromide **49b**.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-[4-(2-dimethylaminomethylimidazol-1-yl)-2-fluorophenyl]-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51a). ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 8.40 Hz, 1H), 8.13 (t, J = 2.28 Hz, 1H), 7.91 (dt, J = 8.89,

2.32 Hz, 1H), 7.74 (dd, J = 2.00, 10.78 Hz, 1H), 7.69 (t, J = 8.06 Hz, 1H), 7.60 (d, J = 8.79 Hz, 1H), 7.57 (td, J = 6.44, 1.97 Hz, 1H), 7.44 (dd, J = 8.15, 5.46 Hz, 1H), 4.23 (s, 1H), 3.52 (s, 2H), 2.25 (s, 6H). HRMS (ESI+) m/z calcd for $C_{27}H_{23}N_8O_2F_2$ $[M + H]^+$, 529.1912; found, 529.1915.

1-(3-Cyano-4-fluorophenyl)-6-[4-(3-dimethylaminomethyl-1*H*-pyrazol-4-yl)-2-fluorophenyl]-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51b). To a mixture of amide **50b** (49.4 mg, 0.077 mmol) in dichloromethane (3 mL) and ethanol (0.1 mL) was added trifluoroacetic acid (1 mL, 13.5 mmol) slowly at 0 °C. After being stirred at 0 °C for 6 h, the mixture was kept in a freezer at –4 °C without stirring for 18 h. The mixture was stirred and then allowed to warm to room temperature for 0.5−1 h while the reaction was monitored by LC−MS. The mixture was then concentrated under reduced pressure. To the residue was added acetohydroxamic acid (23 mg, 0.31 mmol), potassium carbonate (85 mg, 0.61 mmol), 4.9 mL of DMF, and 0.7 mL of water. After being stirred at room temperature for 18 h, the reaction was then quenched with water. The mixture was thrice extracted with ethyl acetate. The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, 20 cm × 20 cm, 2000 μm, 7 N ammonia in methanol/ethyl acetate, 1:9 v/v) to yield 39.2 mg (97%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23–8.20 (m, 2H), 8.06 (s, 1H), 7.93 (m, J = 8.89 Hz, 1H), 7.68–7.66 (m, 3H), 7.59–7.53 (m, 2H), 7.44 (dd, J = 6.29, 8.00 Hz, 1H), 7.29 (br s, 1H), 6.69 (br s, 1H), 6.59 (s, 2H), 3.35 (s, 2H), 1.76 (s, 6H). HRMS (FAB+) m/z calcd for $C_{27}H_{23}N_8O_2F_2$ $[M + H]^+$, 529.1912; found, 529.1903.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-[4-(3-dimethylaminomethylpyridin-2-yl)-2-fluorophenyl]-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51d). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (dd, J = 1.6, 4.7 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.20 (t, J = 1.9 Hz, 1H), 8.06 (br s, 1H), 7.93 (dt, J = 8.75, 2.28 Hz, 1H), 7.89 (dd, J = 1.53, 7.78 Hz, 1H), 7.75 (dd, J = 10.55, 1.29 Hz, 1H), 7.66–7.61 (m, 4H), 7.47 (dd, J = 5.83, 8.23 Hz, 1H), 7.42 (dd, J = 4.71, 7.75 Hz, 1H), 6.57 (s, 2H), 3.40 (s, 2H), 2.13 (s, 6H). HRMS (FAB+) m/z calcd for $C_{29}H_{24}N_7O_2F_2$ $[M + H]^+$, 540.1960; found, 540.1952.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-[4-(4-dimethylaminomethylpyridin-3-yl)-2-fluorophenyl]-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51e). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 5.04 Hz, 1H), 8.49 (s, 1H), 8.22 (d, J = 8.38 Hz, 1H), 8.20 (t, J = 1.96 Hz, 1H), 8.06 (br s, 1H), 7.93 (dt, J = 8.86, 2.28 Hz, 1H), 7.66–7.62 (m, 3H), 7.54 (m, 2H), 7.47 (dd, J = 5.80, 8.23 Hz, 1H), 7.42 (dd, J = 1.56, 7.91 Hz, 1H), 6.57 (s, 2H), 3.40 (s, 2H), 2.11 (s, 6H). HRMS (ESI+) m/z calcd for $C_{29}H_{24}N_7O_2F_2$ $[M + H]^+$, 540.1960; found, 540.1959.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-[4-(3-dimethylaminomethylpyridin-4-yl)-2-fluorophenyl]-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51f). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (br s, 1H), 8.56 (d, J = 5.00 Hz, 1H), 8.24 (d, J = 8.39 Hz, 1H), 8.22 (m, 1H), 8.07 (s, 1H), 7.95 (dt, J = 8.92, 2.26 Hz), 7.72–7.66 (m, 4H), 7.53 (dd, J = 1.52, 7.95 Hz, 2H), 7.48 (dd, J = 5.81, 8.23 Hz, 1H), 7.41 (d, J = 5.03 Hz, 1H), 6.59 (br s, 2H), 3.39 (s, 2H), 2.13 (s, 6H). HRMS (FAB+) m/z calcd for $C_{29}H_{24}N_7O_2F_2$ $[M + H]^+$, 540.1960; found, 540.1954.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-[4-(2-dimethylaminomethylpyridin-3-yl)-2-fluorophenyl]-7-fluoro-1*H*-indazole-3-carboxylic Acid Amide (51g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (dt, J = 4.75, 1.58 Hz), 8.25–8.20 (m, 2H), 8.07 (br s, 1H), 7.95 (dt, J = 8.84, 1.71 Hz, 1H), 7.83 (dt J = 7.76, 1.54 Hz, 1H), 7.74 (m, J = 11.51 Hz, 1H), 7.69–7.64 (m, 3H), 7.56 (dt, J = 7.94, 1.47 Hz, 1H), 7.50–7.44 (m, 2H), 6.59 (br s, 2H), 3.44 (s, 2H), 2.17 (s, 6H). HRMS (FAB+) m/z calcd for $C_{29}H_{24}N_7O_2F_2$ $[M + H]^+$, 540.1960; found, 540.1955.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-7-fluoro-6-[2-fluoro-4-(methylpyridin-4-ylamino)phenyl]-1*H*-indazole-3-carboxamide (51h). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24–8.19 (m, 4H), 8.07 (br s, 1H), 7.94 (dt, J = 2.2, 8.9 Hz, 1H), 7.69–7.65 (m, 2H), 7.60 (t, J = 8.4 Hz, 1H), 7.44 (dd, J = 5.6, 8.0 Hz, 1H), 7.34 (dd, J = 2.1, 11.7 Hz, 1H), 7.26 (dd, J = 2.2, 8.3 Hz, 1H), 6.83–6.80 (m, 2H), 6.59 (br s, 2H), 3.36 (s, 3H). HRMS (FAB+) m/z calcd for $C_{27}H_{20}N_7O_2F_2$ $[M + H]^+$, 512.1647; found, 512.1662.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-{4-[(2-dimethylaminoethyl)phenylamino]-2-fluorophenyl}-7-fluoro-1*H*-indazole-3-carboxamide (51i). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (br s, 1H), 8.19 (br s, 1H), 8.17 (d, J =8.4 Hz, 1H), 8.03 (br s 1H), 7.91 (dt, J = 2.1, 8.8 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.64 (br s, 1H), 7.50–7.45 (m, 2H), 7.38–7.32 (m, 2H), 7.29 (d, J =7.8 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H), 6.81 (dd, J = 2.2, 13.3 Hz, 1H), 6.67 (dd, J = 2.3, 8.6 Hz, 1H), 6.58 (br s, 2H), 4.12–4.05 (m, 2H), 3.37–3.31 (m, 2H), 2.85 (br s, 3H), 2.84 (br s, 3H), 2.30 (s, 3H). HRMS (FAB+) m/z calcd for $C_{31}H_{28}N_7O_2F_2$ $[M + H]^+$, 568.2273; found, 568.2270.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-{4-[(2-dimethylaminoethyl)pyridin-3-ylamino]-2-fluorophenyl}-7-fluoro-1*H*-indazole-3-carboxamide (51j). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (br s, 1H), 8.55 (d, J =2.0 Hz, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.21 (br s, 1H), 8.06 (br s, 1H), 7.94–7.89 (m, 2H), 7.71 (dd, J = 5.2, 8.4 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.66 (br s, 1H), 7.56 (t, J = 8.5 Hz, 1H), 7.39 (dd, J = 6.0, 8.3 Hz, 1H), 7.23 (d, J = 12.8 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.58 (br s, 2H), 4.22–4.16 (m, 2H), 3.42–3.36 (m, 2H), 2.85 (br s, 3H), 2.84 (br s, 3H), 2.33 (s, 6H). HRMS (FAB+) m/z calcd for $C_{30}H_{27}N_8O_2F_2$ $[M + H]^+$, 569.2225; found, 569.2226.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-{4-[(2-dimethylaminoethyl)pyridin-4-ylamino]-2-fluorophenyl}-7-fluoro-1*H*-indazole-3-carboxamide (51k). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 6.9 Hz, 2H), 8.28 (d, J = 8.4 Hz, 1H), 8.11 (t, J =2.2 Hz, 1H), 7.89 (dt, J = 2.3, 8.9 Hz, 1H), 7.79 (t, J =8.1 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.49–7.38 (m, 3H), 7.09 (d, J = 5.9 Hz, 2H), 4.36–4.29 (m, 2H), 3.40–3.34 (m, 2H), 2.84 (br s, 6H), 2.70 (s, 6H). HRMS (ESI+) m/z calcd for $C_{30}H_{27}N_8O_2F_2$ $[M + H]^+$, 569.2225; found, 569.2225.

1-(3-Aminobenzo[*d*]isoxazol-5-yl)-6-{4-[(3-dimethylaminopropyl)pyridin-4-ylamino]-2-fluorophenyl}-7-fluoro-1*H*-indazole-3-carboxamide (51l). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 7.3 Hz, 2H), 8.11 (t, J =2.2 Hz, 1H), 7.89 (dt, J = 2.4, 8.9 Hz, 1H), 7.79 (t, J = 8.1 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.47 (dd, J = 2.2, 10.0 Hz, 1H), 7.44–7.38 (m, 2H), 7.09 (br s, 2H), 4.09–4.03 (m, 2H), 3.27–3.21 (m, 2H), 2.90 (s, 6H), 2.70 (s, 6H), 2.23–2.13 (m, 2H). HRMS (FAB+) m/z calcd for $C_{31}H_{29}N_8O_2F_2$ $[M + H]^+$, 583.2382; found, 583.2382.

Enzymology. All buffer salts were obtained from Sigma Chemical Company (St. Louis, MO) and were of the highest purity available. The enzyme−substrate S-2765 (Z-D-Arg-Gly-Arg-*p*-nitroanilide) was obtained from DiaPharma (West Chester, OH). *N*-Succinyl-Ala-Ala-Pro-Arg-*p*-nitroanilide (Bachem L-1720) was obtained from Bachem Bioscience (King of Prussia, PA). Human α-thrombin and human factor Xa were obtained from Enzyme Research Laboratories (South Bend, IN). Human trypsin was obtained from Calbiochem (La Jolla, CA).

Compounds were assessed for their inhibitory activity toward factor Xa, thrombin, and trypsin by kinetic analysis using *p*-nitroaniline chromogenic substrates monitored at 405 nm. The assay buffer employed was 50 mM HEPES, pH 7.5, 200 mM NaCl, and fresh 0.05% *n*-octyl β-D-glucopyranoside. DMSO was present at a final concentration of 4%, derived from the substrate and inhibitory compound stock solutions. In a 96-well low-binding polystyrene plate, 280 μL of substrate in assay buffer was preincubated at 37 °C for 15 min with 10 μL of test compound in DMSO to obtain final test compound concentrations that bracketed the K_i. Reactions were initiated by addition of 10 μL of protease, and increase in absorbance due to proteolytic cleavage of substrate was kinetically monitored at 37 °C and 405 nm with a Molecular Devices Spectramax 340 plate reader. Initial velocities were determined by analysis of the initial linear portion of the reactions. Plots of v_o/v_i vs inhibitor concentration, where v_o is the velocity without inhibitor and v_i is the inhibited velocity, were fit to a linear regression line, and IC_{50} was determined from the reciprocal of the slope. The dissociation constant (K_i) was calculated using the equation K_i =

$IC_{50}/(1 + S/K_m)$ where S is the substrate concentration.[43] K_m for the enzyme–substrate pair was determined from Hanes−Wolf plots using the same final buffer conditions as K_i determinations. Respective substrate, substrate concentration, K_m, and enzyme concentrations for human factor Xa were S-2765 (Z-D-Arg-Gly-Arg-*p*-nitroanilide), $S = 100\ \mu M$, $K_m = 260\ \mu M$, fXa = 0.5 nM. For human α-thrombin, they were L-1720 (succinyl-Ala-Ala-Pro-Arg-*p*-nitroanilide), $S = 100\ \mu M$, $K_m = 320\ \mu M$, thrombin = 1 nM. For human trypsin, they were S-2765, $S = 60\ \mu M$, $K_m = 61\ \mu M$, trypsin = 0.3 nM. Within-run assay coefficient of variation (CV) was generally <10%; between-run the CV was <20%.

In Vitro Coagulation Assays. The plasma concentrations of factor Xa inhibitors needed to produce a 2-fold prolongation of activated partial thromboplastin time (aPTT) were determined in human plasma. Fresh whole human blood was centrifuged to obtain plasma, and factor Xa inhibitors were added to yield concentrations from 0.001 to 100 μM. After a short stabilization period, the samples were placed in an ACL-100 microsampler coagulation analyzer (Instrument Laboratory, Milano, Italy) to determine clotting times in seconds.

Human Liver Microsomal (HLM) Stability Assay. Pooled human liver microsomes (1 mg/mL protein) were preincubated with the test compound at 37 °C for 3 min in the absence of NADPH as described below. The enzymatic reaction was initiated by addition of NADPH and then incubated under the same conditions. One aliquot (1 mL) of the incubation mixture was withdrawn at 0, 15, 30, and 60 min and combined immediately with 0.5 mL of ACN. After vortex-mixing, the sample was centrifuged at approximately 10000*g* for 5 min. The supernatant (0.7 mL) was transferred into a 1 mL vial and was analyzed for metabolites using an Agilent 1100 LC system equipped with a Zorbax SB-C18 column (150 mm × 2.1 mm i.d., 3.5 μm) interfaced with a Micromass Quattro Micro mass spectrometer that was operated with the electrospray ionization in positive ion mode.

Caco-2 Permeability Assay. Caco-2 monolayers were grown to confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar Transwell plates. The permeability assay buffer was Hank's balanced salt solution containing 10 mM HEPES and 15 mM glucose at a pH of 7.0 ± 0.2. Dosing solution concentrations were 10 μM in assay buffer. After 1 h, inserts were moved to receiver (basolateral) chambers that contained fresh assay buffer. Cells were dosed on the apical side (A to B) and incubated at 37 °C with 5% CO_2 and 90% relative humidity. Each determination was performed in duplicate. Permeability through a cell-free (blank) membrane was studied to determine nonspecific binding and free diffusion of the compound through the device. Lucifer yellow flux was also measured for each monolayer after being subjected to the test compounds to ensure no damage was inflicted to the cell monolayers during the flux period. All samples were assayed by LC−MS using electrospray ionization.

Crystallization, Data Collection, and Structure Determination and Refinement. The purified protein was buffer exchanged in 20 mM Tris at pH 8.0, 100 mM NaCl, and 5 mM benzamidine and concentrated to 15 mg/mL. The protein was later dialyzed overnight against compound **51a** in a 100:1 excess molar ratio. The crystals were formed by microseeding into a pre-equilibrated hanging drop containing a 1:1 ratio of protein to precipitation solution (20% PEG 3350, 10 mM $CaCl_2$, and 100 mM Tris-maleate, pH 5.5) at 295 K. The crystals were then transferred to a cryoprotectant solution containing 40% PEG 3350, 10 mM $CaCl_2$, and 100 mM Tris-maleate at pH 5.5 and flash-frozen by immersion in liquid nitrogen. X-ray diffraction data to a resolution of 2.3 Å were collected on a Bruker AXS Proteum 6000 detector. Diffraction data were indexed, integrated, and scaled using the Proteum processing program suite from Bruker AXS. The crystals belong to the $P2_12_12_1$ space group, with unit cell parameters $a = 48.87$ Å, $b = 74.98$ Å, and $c = 75.09$ Å. The structure was determined by molecular replacement with CNX[44] using the PDB coordinates 1EZQ[45] as the search model. All model building was done using the computer program O,[46] and refinement map calculations were carried out using CNX. The final structure was refined to an R_{factor} of 24.6 and R_{free} of 31.3.

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Supporting Information Available: HPLC analysis results for the target compounds **25a−d**, **29a−c**, and **51a−l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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