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Tetrahydroquinoline Derivatives as Potent and Selective Factor XIa Inhibitors

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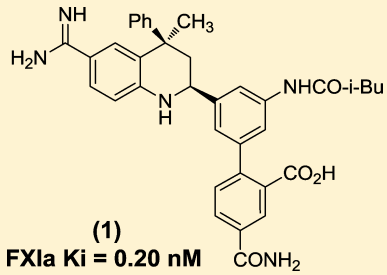
Supporting Information

ABSTRACT: Antithrombotic agents that are inhibitors of factor XIa (FXIa) have the potential to demonstrate robust efficacy with a low bleeding risk profile. Herein, we describe a series of tetrahydroquinoline (THQ) derivatives as FXIa inhibitors. Compound **1** was identified as a potent and selective tool compound for proof of concept studies. It exhibited excellent antithrombotic efficacy in rabbit thrombosis models and did not prolong bleeding times. This demonstrates proof of concept for the FXIa mechanism in animal models with a reversible, small molecule inhibitor.



(1)
FXIa Ki = 0.20 nM

INTRODUCTION

The process of unwanted or uncontrolled thrombosis is causative for many life-threatening conditions, with arterial thrombosis being the leading cause of morbidity and mortality.[1] The most commonly used oral anticoagulant warfarin[2] has a narrow therapeutic window. Warfarin exposure is affected by diet and cytochrome P450 enzyme polymorphisms leading to multiple drug−drug interactions. Coagulation monitoring and dose titration are required to maintain warfarin therapy in a proper therapeutic range. Tremendous progress has been made in developing new antithrombotic agents.[3−5] The recently approved novel oral anticoagulants dabigatran,[3f] rivaroxaban,[4] apixaban,[5] and edoxaban[3e] have addressed many of the issues associated with warfarin. With these new anticoagulants, we have entered a new era in the treatment and prevention of unwanted thrombosis.

Blood coagulation is the coordinated activation of plasma proteases, their cofactors, and platelets. The end product is the protease thrombin, which cleaves fibrinogen to generate a fibrin clot. The cascade has been classically divided into the intrinsic, extrinsic, and common pathways.[6] In the extrinsic pathway, vessel injury initiates the process by converting factor VII (FVII) to factor VIIa (FVIIa). Tissue factor-FVIIa (TF-FVIIa) complex catalyzes the formation of factor Xa (FXa), which in turn cleaves prothrombin to generate thrombin. In the intrinsic pathway, factor XIIa (FXIIa), formed by contact activation, catalyzes the formation of FXIa, which leads to the sequential activation of factor IX (FIX) and factor X (FX). Thrombin can also activate factor XI (FXI) to FXIa by feedback activation.[6b−d] The key to a successful anticoagulant is achieving an appropriate therapeutic balance between anticoagulation and bleeding. One hypothesis is that targeting proteases upstream from the common pathway provides a reduction in thrombin sufficient to impede occlusive thrombosis, yet allows enough thrombin generation to support hemostasis.[7] Since FXIa is located upstream in the intrinsic pathway,[8] we envision that by inhibiting FXIa, we can disrupt the intrinsic coagulation pathway without affecting either the extrinsic or the common pathways.

Genetic evidence indicates that FXI is not required for normal hemostasis in humans.[9] Mice that are homozygous for a targeted disruption of the FXI locus undergo normal development and have a normal life span, and no evidence for spontaneous or provoked bleeding has been noted.[10] Furthermore, FXI deficient mice are protected from thrombosis in a number of experimental models.[10b,11] In contrast, targeted disruption of other coagulation proteases in mice, except factor XII (FXII), is associated with perinatal death due to bleeding or bleeding disorders similar to the human phenotype.[12] Many recent studies have indicated that elevated FXI levels are associated with venous thrombosis, myocardial infarction, increased odds ratio for cerebrovascular events, and coronary artery disease.[13] Reduced incidence of ischemic stroke in subjects with severe FXI deficiency has also been observed.[14] Together, this evidence implies that FXIa may be an ideal target for pharmaceutical intervention for the treatment and prevention of thromboembolic diseases with minimal therapy-associated increase in bleeding risk.[7]

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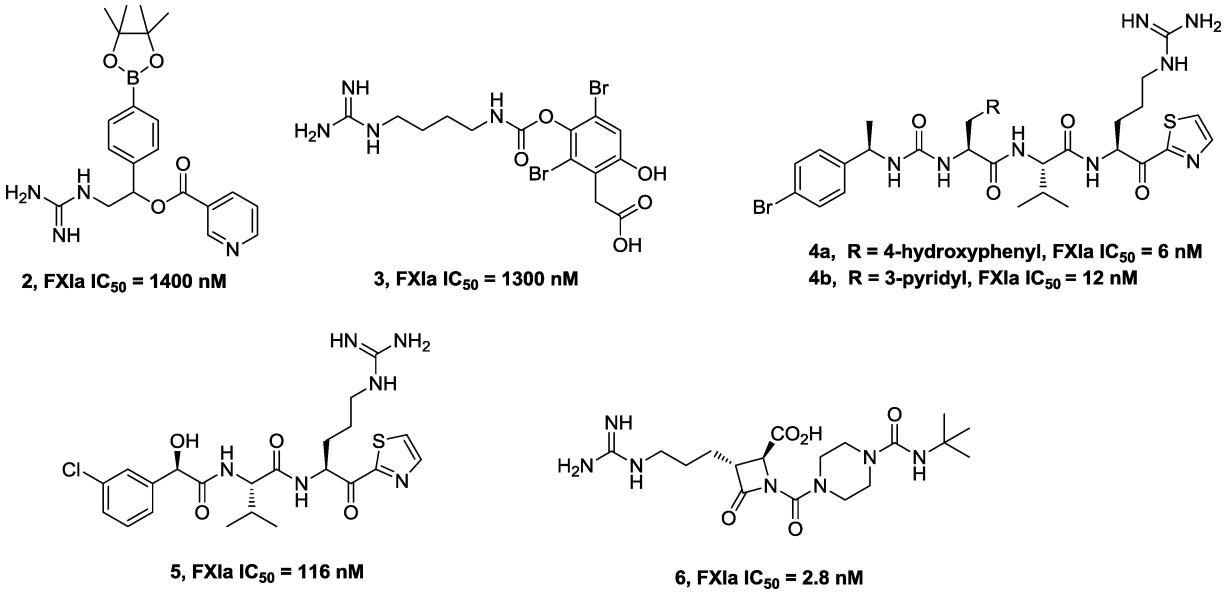


Figure 1. Small molecule FXIa inhibitors.

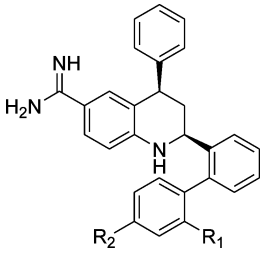
Small molecule inhibitors of FXIa have been reported (Figure 1). Racemic boronate **2** is a weak inhibitor of FXIa (IC_{50} = 1400 nM) with 8- and 30-fold selectivity over thrombin and FXa, respectively.[15a] Clavatadine A (**3**), a marine natural product, was found to have a XIa IC_{50} of 1300 nM.[15b] A series of potent, irreversible ketoarginine-based peptidomimetics has also been reported.[15c,d] Compound **4a** has a FXIa IC_{50} of 6 nM and aPTT EC_{2x} of 2.4 μM and shows good selectivity over FVIIa, FXa, and thrombin. Pyridyl analogue **4b** (FXIa IC_{50} = 12 nM) was evaluated in a rat mesenteric bleeding model and at 4-fold the efficacious dose (1 mg/kg, continuous iv infusion) did not alter bleeding time.[15d] Modifications to reduce the peptidic character and molecular weight of these inhibitors led to **5** with reduced affinity (FXIa IC_{50} = 116 nM).

We have previously reported compound **6** as a potent irreversible FXIa inhibitor (Figure 1) that shows efficacy in rat and rabbit thrombosis models with minimal bleeding time prolongation.[16] Herein we report the discovery of a series of tetrahydroquinoline (THQ) derivatives as reversible FXIa inhibitors and the identification of compound **1** as a tool compound for proof of concept studies.[17]

RESULTS AND DISCUSSION

Compound **7** (Table 1) was identified through screening of our compound collection of serine protease inhibitors. It was originally prepared as part of our FVIIa program[18] but found to have a FXIa K_i of 25 nM with about 4-fold selectivity over FVIIa and 40-fold selectivity over FXa. Removal of the amide at the R_2 position reduced FXIa affinity by 4-fold but increased selectivity versus FVIIa (**8**). Truncating the amide to a carboxylic acid group resulted in **9**, which showed a 3-fold improvement in FXIa affinity. The carboxylic acid group at R_1 was shown to be more crucial for FXIa activity than the carboxylic group at R_2, since removing the R_1 carboxylic group decreased FXIa activity by >280-fold (**10**), whereas only a 13-fold loss was observed when the R_2 carboxylic acid group was removed (**8**). Single-digit nanomolar FXIa affinity was achieved with compound **9** which has 30-fold and 100-fold selectivity over FVIIa and FXa, respectively.

Table 1. Tetrahydroquinoline SAR[a]



			K_i (nM)		
compd	R_1	R_2	FXIa	FVIIa	FXa
7	CO_2H	CONH-*i*-Bu	25	95	1100
8	CO_2H	H	110	2200	1940
9	CO_2H	CO_2H	8.5	290	970
10	H	CO_2H	2400	NT	NT

[a]All compounds shown are racemic.

One major issue with the 1,2-phenylene THQ compounds was atropisomerism; the rotation of the biaryl moiety is restricted by its two ortho substituents. This complicated the synthesis and purification of these compounds. Therefore, we decided to explore the 1,3-phenylene analogues in order to eliminate the atropisomers. The 1,3-phenylene compounds in general have equal or better FXIa inhibitory potency compared with the 1,2-phenylene compounds. However, this series of compounds is less selective relative to FXa and FVIIa (Table 2). Diacid analogue **12** has a FXIa K_i of 3.9 nM but only 20- and 30-fold selectivity over FVIIa and FXa, respectively.

A problem encountered with the 1,3-phenylene series was instability due to aromatization of the THQ ring. The aromatized compounds were 50- to 80-fold less active compared with the corresponding THQs. One of our strategies to solve this stability issue was to introduce substitution at the C-4 position on the THQ ring. This approach successfully blocked aromatization; however, the newly introduced alkyl group reduced FXIa affinity. FXIa affinity decreased as the size of the alkyl group increased, 15-fold for methyl (**13**), 200-fold

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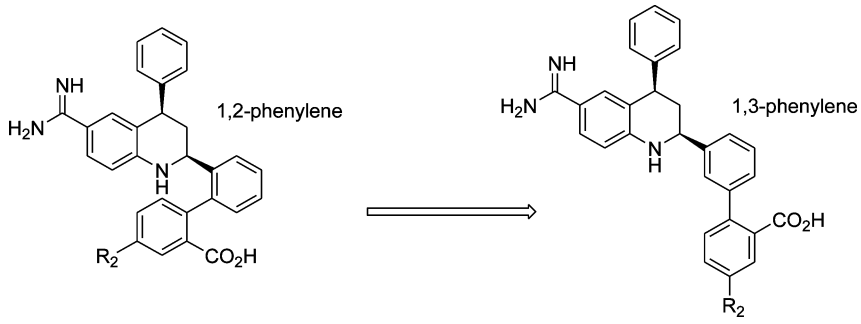
Table 2. Comparison of 1,2- and 1,3-Phenylene[a]

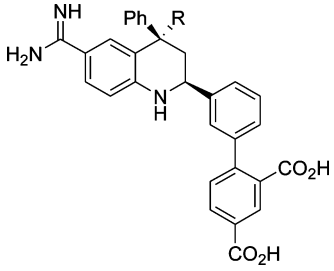


compd	R_2	K_i (nM) FXIa	FVIIa	FXa
7 (1,2)	CONH-*i*-Bu	25	95	1100
11 (1,3)	CONH-*i*-Bu	23	25	24
9 (1,2)	CO_2H	8.5	290	970
12 (1,3)	CO_2H	3.9	89	130

[a]All compounds shown are racemic.

for ethyl (**14**), and 500-fold for *n*-propyl (**15**) as shown in Table 3.

Table 3. SAR of THQ Stabilization by C4-Substitution[a]



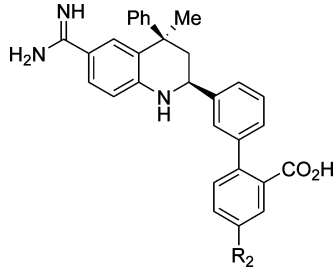
compd	R	FXIa K_i (nM)
12	H	3.9
13	Me	61
14	Et	830
15	*n*-Pr	1960

[a]All compounds shown are racemic.

Extensive SAR changes were explored at the R_2 position of the C4-methyl substituted THQ (Table 4). Methylurea (**17**) and methylsulfonamide (**18**) analogues resulted in compounds with slightly improved FXIa inhibitory activity. Cyano (**19**), amino (**20**), and methyl ester (**21**) substitutions produced compounds with potency similar to that of the carboxylic acid (**13**). Primary amide (**16**) restored single-digit nanomolar affinity for FXIa. Alkylation of the amide nitrogen resulted in >100-fold decrease in FXIa activity (**24**, **25**, **27**).

From the SAR studies described above, compound **16** was the most potent compound identified with a FXIa K_i of 1.5 nM. The trans isomer (**28**, Figure 2) of **16** was a minor product isolated from the reaction to form the THQ scaffold and was found to have 17-fold less inhibitory activity for FXIa when compared to **16**. The two cis enantiomers of **16** were separated by chiral HPLC. The dextrorotary enantiomer (+)-**16** was found to be >800-fold more potent than the levorotary enantiomer (−)-**16** (Figure 2). The dextrorotary enantiomer (+)-**16** has a FXIa K_i of 0.39 nM with >1000-fold selectivity over FXa and 200-fold over FVIIa.

Table 4. Biaryl Acid SAR[a]



compd	R_2	K_i (nM) FXIa	FVIIa	FXa
16	$CONH_2$	1.5	280	3000
17	NHCONHMe	15	451	1140
18	$NHSO_2Me$	37	237	>15000
19	CN	48	867	2060
13	CO_2H	61	2600	9300
20	NH_2	64	275	3980
21	CO_2Me	79	442	606
22	H	110	3060	6700
23	NHCOMe	110	705	5810
24	CONHMe	154	1960	4100
25	CONH-*i*-Pr	207	1770	1310
26	CH_2NMe_2	466	610	>15000
27	CONH-*t*-Bu	540	1290	6400

[a]All compounds shown are racemic.

An X-ray crystal structure of (+)-**16** bound in the FXIa active site was obtained to understand the binding mode of this series of compounds (2.3 Å, Figure 3). The benzamidine group was bound tightly in the S1 pocket by a typical salt bridge to Asp189 (2.9 and 3.0 Å) and also can form an H-bond to the backbone carbonyl of Gly218 (2.9 Å). The NH of the THQ forms an H-bond with the side chain OH of Ser195 (3.3 Å). A stacking interaction was observed between His57 and the inner phenyl ring. The carboxylic group forms H-bonds with His57 (2.8 Å) and the oxyanion hole which comprises Gly193 and Ser195. The amide nitrogen formed two H-bonds with the backbone carbonyls of Leu41 (3.0 Å) and His40 (3.1 Å). The amide carbonyl can interact either with Arg39 directly (3.1 Å)

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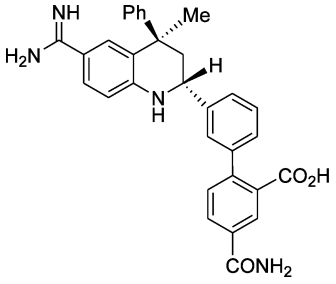
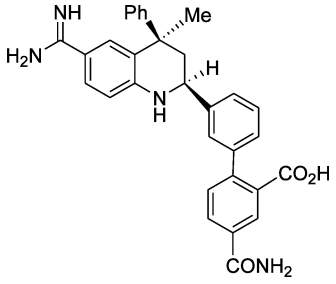


Trans
(±)-28
FXIa K_i = 26 nM
FVIIa K_i = 16300 nM
FXa K_i = 8350 nM



Cis
(±)-16
FXIa K_i = 1.5 nM
FVIIa K_i = 280 nM
FXa K_i = 3000 nM

(+)-16
FXIa K_i = 0.39 nM
FVIIa K_i = 86 nM
FXa K_i = 2330 nM

(-)-16
FXIa K_i = 335 nM
FVIIa K_i > 15000 nM
FXa K_i > 15000 nM

Figure 2. Comparison of stereoisomers.

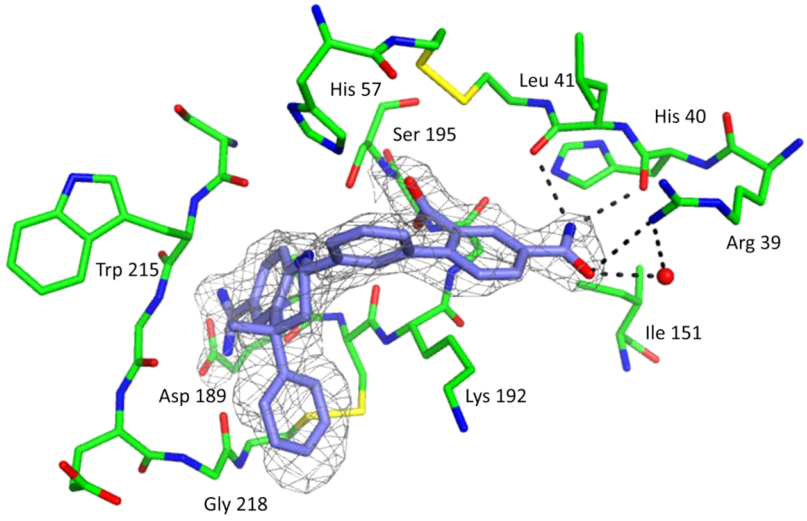


Figure 3. X-ray crystal structure of compound **16** complexed to FXIa. The initial $2F_o - F_c$ electron density contoured at 1 rmsd is shown with the final model. The protein is shown with green carbon atoms, and **16** is shown with purple carbon atoms. Nitrogen atoms are shown in blue, oxygen atoms in red, and sulfur atoms in yellow. The red spheres represent crystallographic water molecules. Hydrogen bonds are represented by black dashes. Figure was prepared with PyMol (Schrödinger).

or through a water molecule (2.7 and 2.8 Å). These interactions obtained on introduction of the primary amide resulted in enhanced FXIa affinity. This is a unique interaction that has not been previously observed in FXa or FVIIa X-ray structures.

To further improve selectivity over FVIIa, we decided to probe the interactions in the S2 pocket, since FXIa has a larger S2 pocket than FVIIa. We first obtained an X-ray crystal structure of compound **29** (2.2 Å, FXIa K_i = 7.6 nM and FVIIa K_i = 41 nM) in the FVIIa active site to confirm the binding mode in FVIIa. The amino group was found to be pointing toward the S2 pocket (Figure 4). As expected, the rest of the molecule interacts similarly as that observed in the FXIa structure of (+)-**16**.

As shown in Table 5, a series of amides were prepared using the amino group as a linker for substitutions. Acylation of the amino group maintained and in some cases further improved the FXIa potency. In general, selectivity relative to FVIIa increased as the size of the alkyl group increased while the selectivity over FXa decreased. Compound **35** showed the best profile in terms of potency and selectivity in this series. The two enantiomers of **35** were separated by chiral HPLC. The dextrorotatory enantiomer **1** has a FXIa K_i of 0.20 nM, and the levorotary enantiomer **36** was much less potent with a XIa K_i of 230 nM. Compound **1** has >1000-fold selectivity for FXIa versus most of the enzymes tested except for plasma kallikrein (23-fold) and activated protein C (365-fold). Compared with (+)-**16**, the selectivity for FVIIa was improved from 220-fold to >1000-fold (Table 6). An X-ray crystal structure of the **1**−XIa complex was obtained (2.8 Å, Figure 5). Its binding mode is very similar to that of (+)-**16** and shows the same interactions in the P1, P2′, and oxyanion hole regions. The only difference is that the carbonyl of the isobutylamide in **1** forms an additional H-bond with the hydroxyl of Tyr58b (2.8 Å), extending the isobutyl moiety deeper into the P2 pocket.

Compound **1** exhibits excellent in vitro anticoagulant activity in the activated partial thromboplasmin time (aPTT) assay with an EC_{2x} of 2.2 μM. Consistent with inhibition of the intrinsic coagulation system, no activity in the prothrombin time (PT) assay was observed (IC_{2x} > 20 μM). Compound **1** is competitive with small molecule FXIa substrates and shows reversible inhibition kinetics. It shows mixed type inhibition using FIX as a substrate, where FIX activation was monitored by using a novel sensitive assay.[19] Similar potency and selectivity were observed with human and rabbit enzymes

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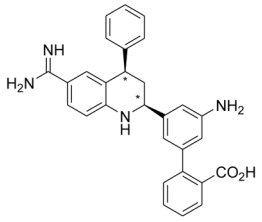


29
FXIa Ki = 7.6 nM
FVIIa Ki = 41 nM
FXa Ki = 57 nM

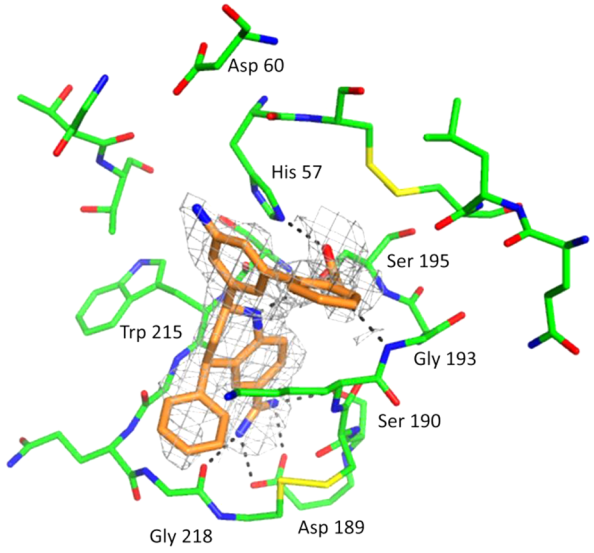
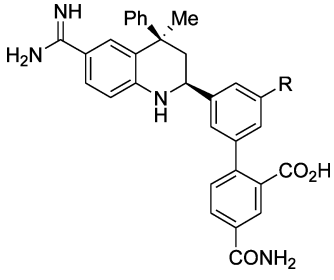


Figure 4. X-ray crystal structure of compound **29** complexed to FVIIa. The initial $2F_o - F_c$ electron density contoured at 1 rmsd is shown with the final model. The protein is shown with green carbon atoms, and **29** is shown with orange carbon atoms. Nitrogen atoms are shown in blue, oxygen atoms in red, and sulfur atoms in yellow. Hydrogen bonds are represented by black dashes. Figure was prepared with PyMol (Schrödinger).

Table 5. Probing the S2 Pocket To Improve FVIIa Selectivity



compd	R	FXIa (nM)	FVIIa (nM)	FXa (nM)	aPTT (μM)
(±)-**16**	H	1.5	280	3000	8.6
(±)-**30**	NH_2	0.64	56	2250	1.2
(±)-**31**	NHCOMe	1.0	230	1810	2.1
(±)-**32**	NHCOEt	0.69	450	1480	3.4
(±)-**33**	NHCO-*n*-Pr	0.30	520	641	4.1
(±)-**34**	NHCO-*c*-Pr	0.72	474	880	4.5
(±)-**35**	NHCO-*i*-Bu	0.59	1010	784	6.1
(−)-**36**	NHCO-*i*-Bu	230	>10900	5670	not tested
(+)-**1**	NHCO-*i*-Bu	0.20	630	340	2.2

(Table 7). Compound **1** was studied in the rabbit AV shunt thrombosis model[20] by iv administration at five doses given by loading dose plus continuous infusion. A dose-dependent antithrombotic effect was observed with an ID_{50} of 0.95 mg kg^{-1} h^{-1} (Figure 6). Bleeding time was not increased compared to vehicle treated animals.[21] The ex vivo aPTT was prolonged (the expected pharmacodynamic effect of a FXIa inhibitor) but not the PT (indicative of selectivity over FVIIa, FXa, and FIIa).

Table 6. Human Enzyme Selectivity Profile for Compound 1

	human enzyme K_i (nM) for **1**
FXIa	0.20
plasma kallikrein	4.6
activated protein C	73
FXa	340
FVIIa	630
trypsin	740
plasmin	910
tPA	1700
urokinase	2100
thrombin	12600
chymotrypsin	14000
FIXa	>20000

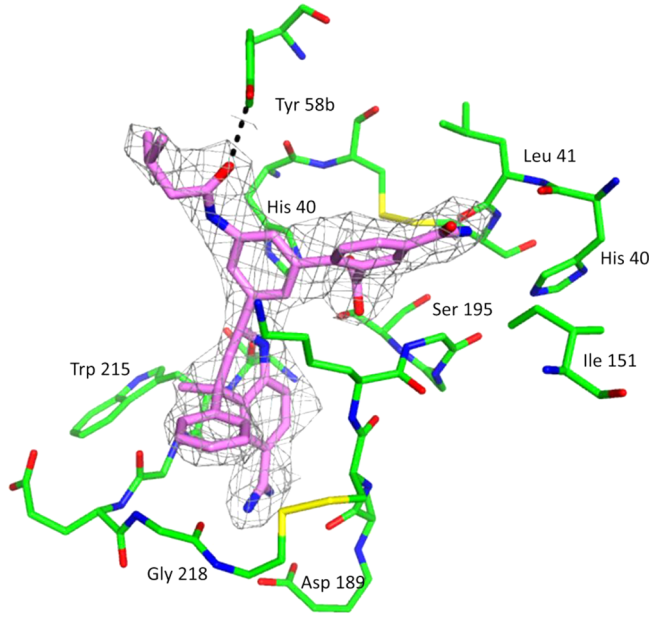


Figure 5. X-ray crystal structure of compound **1** complexed to FXIa. The initial $2F_o - F_c$ electron density contoured at 1 rmsd is shown with the final model. The protein is shown with green carbon, and **1** is shown with pink carbon atoms. Nitrogen atoms are shown in blue, oxygen atoms in red, and sulfur atoms in yellow. Hydrogen bonds are represented by black dashes. Figure was prepared with PyMol (Schrödinger).

Table 7. Comparison of Human and Rabbit in Vitro Potency of Compound 1

enzyme	human K_i (nM)	rabbit K_i (nM)
FXIa	0.20	0.42
thrombin	12600	7900
FXa	343	3200
FVIIa	629	200[a]
plasma kallikrein	4.6	4.6
aPTT EC_{2x}	2200	2400

[a]Experiment at 37 °C.

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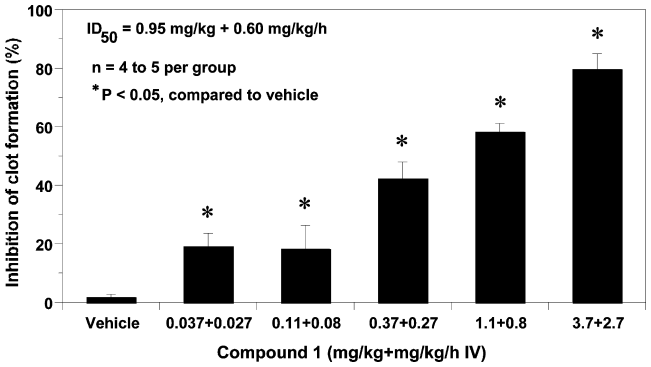


Figure 6. Antithrombotic activity of compound **1** in the rabbit A-V shunt model. Compound **1** was given as a single bolus followed by continuous iv infusion at five doses. Thrombi formed were removed from the shunt and weighed. The % inhibition values are relative to control animals that did not receive **1**.

A fuller description of the pharmacology will be published separately.[21]

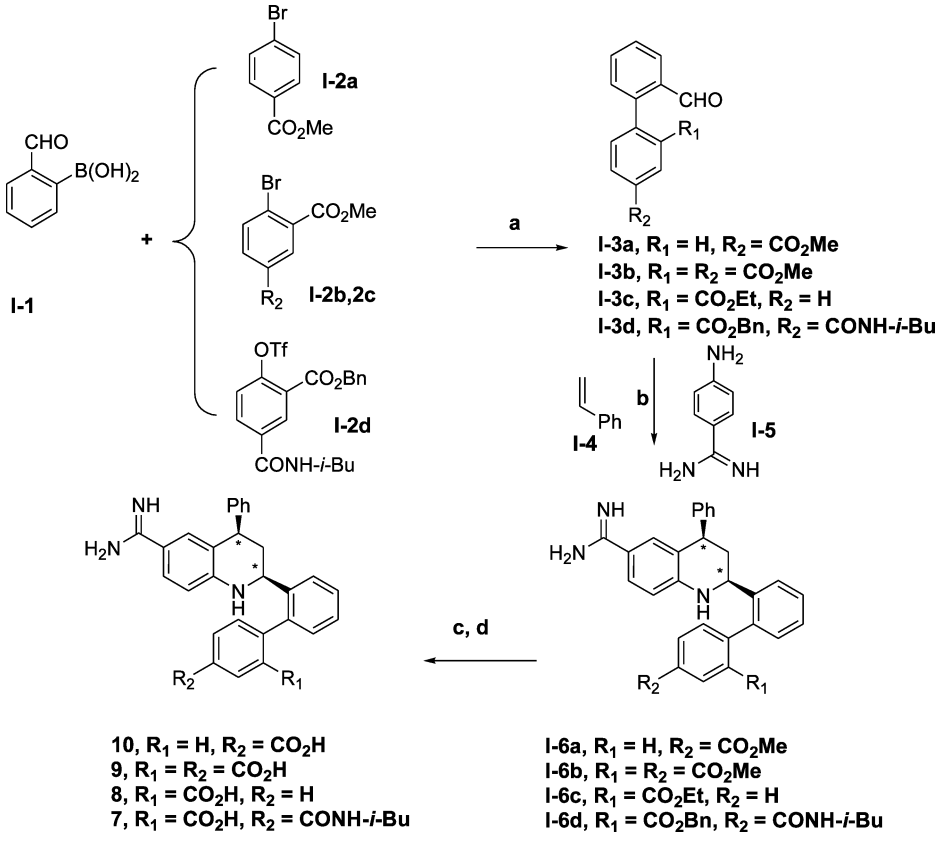
CHEMISTRY

The syntheses of ortho-substituted biaryl compounds are shown in Scheme 1. Boronic acid **I-1** was coupled either with bromide **I-2a–c** or triflate **I-2d**[22] to give biarylaldehyde **I-3**. Reaction of a mixture of aldehyde **I-3**, styrene **I-4**, and aniline **I-5** with indium triflate in acetonitrile afforded *cis*-THQ **I-6** (racemate) as the major product.[18a] Hydrolysis or hydrogenation of **I-6** produced the final compounds (**7–10**).

The meta-substituted compounds described in Tables 2–5 were prepared in a similar manner using meta-substituted boronic acids as the starting material. Compounds where R_2 is $CONH_2$ were prepared using the procedures described in Scheme 2. 2-Bromo-5-iodobenzoic acid **II-1** was reacted with benzyl bromide in $KHCO_3$/DMF to give the benzyl ester **II-2**. The iodo was converted to the cyano group (**II-3**) by reaction with $Zn(CN)_2$ in $Pd(PPh_3)_4$/DMF at 80 °C. Oxidation with hydrogen peroxide in K_2CO_3/DMSO afforded the amide **II-4**. Suzuki coupling of **II-4** with boronic acid **II-5** or 3-formylphenylboronic acid **II-6** in K_3PO_4/ $Pd(PPh_3)_4$/DMF at 100 °C produced biaryl compound **II-7** or **II-8**, respectively. Reduction of the carboxylic group in **II-7** followed by oxidation with the Dess–Martin reagent gave aldehyde **II-9**. Reaction of aldehyde **II-9** with aniline **II-10** and the appropriate alkene (**II-11a**) in $In(OTf)_3/CH_3CN$ afforded tetrahydroquinoline **II-12**. Compound **II-12** was reduced to the corresponding aniline (**II-13**). **II-13** was coupled with an appropriate acyl chloride, then deprotected under hydrogenation conditions to afford compounds **31–35**. For compound **1**, the two enantiomers were separated by chiral HPLC after acylation. The dextrorotatory enantiomer was deprotected under hydrogenation conditions to afford **1**. Compound **16** was prepared using intermediate **II-8** via the similar procedures described.

Meta-substituted compounds **17**, **18**, **20**, and **23** were prepared as described in Scheme 3. Bromide **III-1** was coupled with 3-formylphenylboronic acid **II-6** via Suzuki coupling to

Scheme 1. Synthesis of the Ortho-Substituted Biaryl THQ Compounds[a]



[a]Reagents: (a) $Pd(PPh_3)_4$, $PhCH_3$/EtOH, reflux, 65–90%; (b) $In(OTf)_3$, CH_3CN, 70 °C; (c) LiOH, THF/H_2O, reflux; (d) Pd/C, H_2, 20–40% for the last three steps combined.

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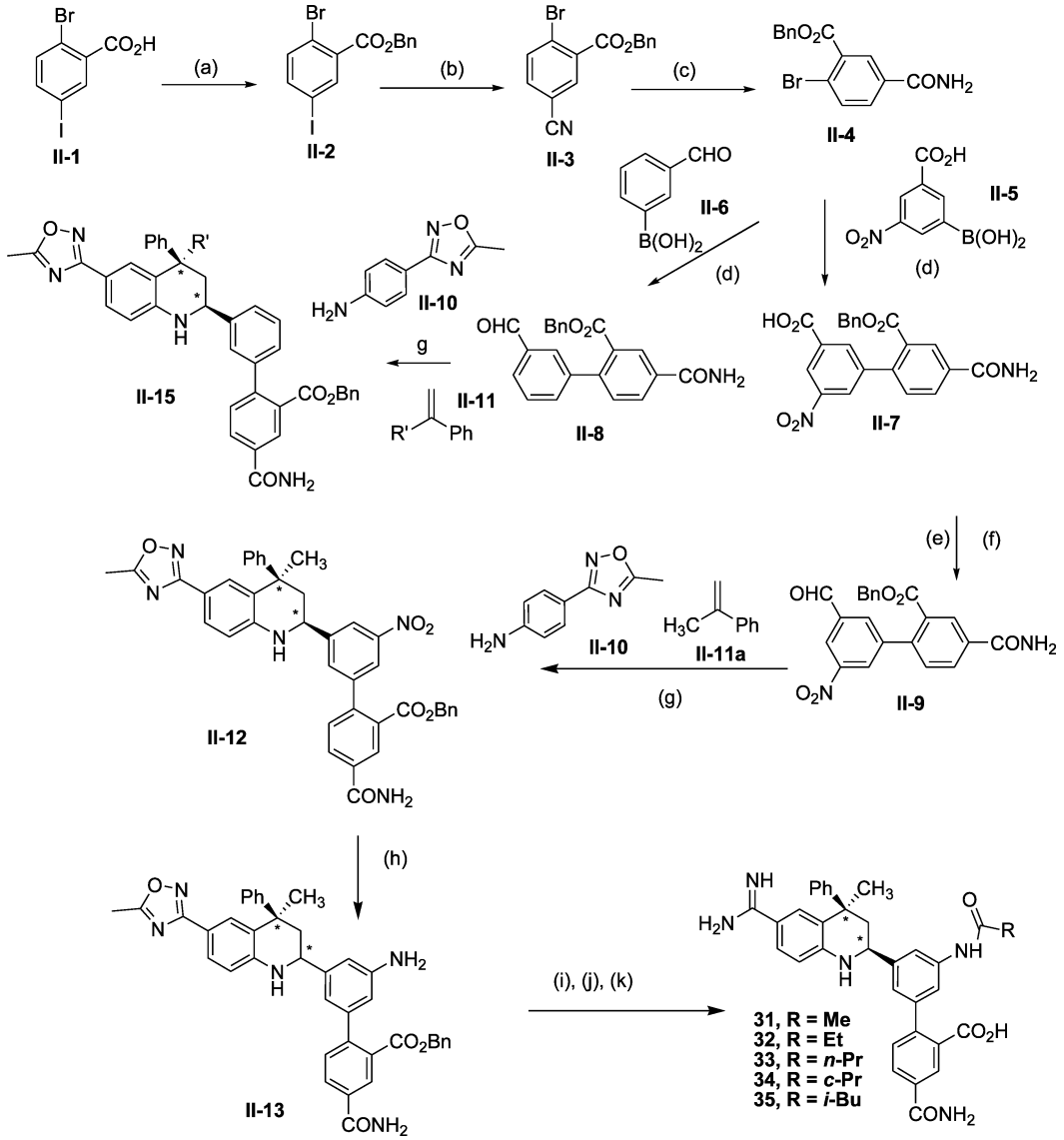
Scheme 2. Synthesis of the Meta-Substituted Biaryl THQ Compounds[a]



[a]Reagents: (a) $KHCO_3$, $PhCH_2Br$, DMF, rt, 100%; (b)Zn $(CN)_2$, $Pd(PPh_3)_4$, DMF, 90 °C, 74%; (c) K_2CO_3, 30% H_2O_2, DMSO, rt, 75%; (d) $Pd(PPh_3)_4$, K_3PO_4, DMF, 100 °C, 93%; (e) (1) isobutyl chloroformate, Et_3N, THF, (2) $NaBH_4/H_2O$, 36%; (f) Dess–Martin, EtOAc, 72%; (g) $In(OTf)_3$, Et_3N, CH_2Cl_2, 70 °C, 61%; (h) Fe, EtOH/HOAc/H_2O, 80 °C, 91%; (i) RCOCl, CH_3CN, 64–90%; (j) Raney Ni/H_2; (k) 10% Pd/C/H_2, 13–90% for steps j and k combined.

give biaryl **III-2**. **III-2** was then reacted with alkene **II-11a** and aniline **II-10** using the conditions described above to afford THQ **III-4**. The nitro group of **III-4** was reduced to aniline **III-5**, which was reacted with acetyl chloride, isobutyl carbamate, or methanesulfonyl chloride to give the desired products after deprotection. Compound **26** was prepared as described in Scheme 4. Benzoic acid **IV-1** was protected with benzyl bromide. Reductive amination with dimethylamine and sodium cyanoborohydride in MeOH gave the dimethylbenzylamine (**IV-2**). The benzyl ester was exchanged to the methyl ester during this step. The phenol was then reacted with pyridine and triflic anhydride to give **IV-3**. Suzuki coupling of **IV-3** with 3-formylphenylboronic acid **II-2** afforded biaryl **IV-4**, which was converted to compound **26** following the procedures described above.

CONCLUSION

A series of potent, selective, and reversible FXIa inhibitors incorporating a tetrahydroquinoline scaffold was explored, and a suitable tool compound (**1**) was identified for in vivo evaluation. Compound **1** has an outstanding in vitro profile with an FXIa K_i of 0.20 nM and >1000-fold selectivity over related serine proteases except plasma kallikrein and activated protein C. It exhibited excellent antithrombotic efficacy in rabbit thrombosis models and did not prolong bleeding times.[21] To our knowledge, this is the first report demonstrating proof of concept for the FXIa mechanism in animal models with a reversible, small molecule inhibitor.

EXPERIMENTAL SECTION

All reactions were run under an atmosphere of dry nitrogen or argon unless otherwise noted. Solvents and reagents were obtained from commercial vendors in the appropriate grade and used without further

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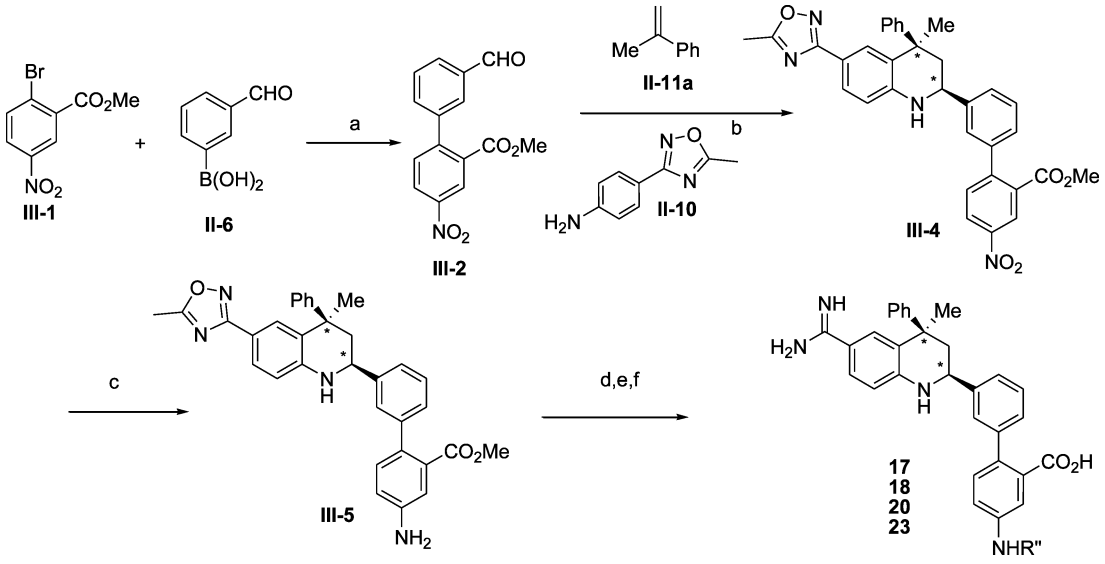
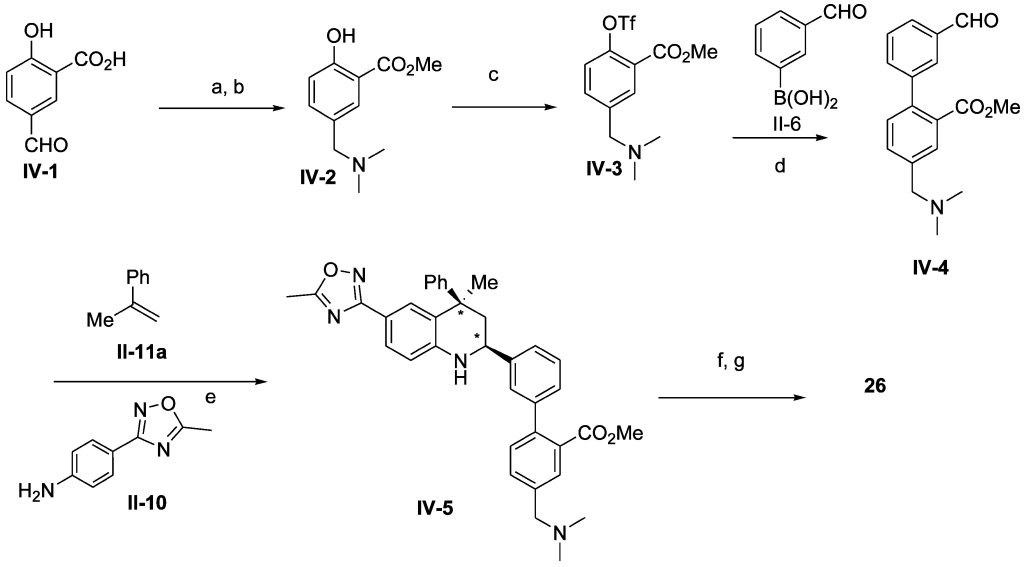
Scheme 3. Synthesis of the Meta-Substituted Biaryl THQ Compounds[a]



[a]Reagents: (a) $Pd(PPh_3)_4$, K_3PO_4, $PhCH_3$/EtOH, reflux, 85%; (b) $In(OTf)_3$, Et_3N, CH_2Cl_2, 70 °C, 61%; (c) NaSH, THF/dioxane, 92%; (d) RNCO or RCOCl or $MeSO_2Cl$, Et_3N/CH_2Cl_2, 40−90%; (e) LiOH, THF/H_2O, reflux, 90−100%; (f) Raney Ni/H_2, 8−26%.

Scheme 4. Synthesis of the Meta-Substituted Biaryl THQ Compounds[a]



[a]Reagents: (a) $NaHCO_3$/BnBr/DMF; (b) $NHMe_2/NaCNBH_3$/MeOH; (c) pyridine/triflate anhydride/CH_2Cl_2; 22% for steps a, b, and c combined; (d) $Pd(PPh_3)_4$, toluene/EtOH, reflux, 86%; (e) $In(OTf)_3$, Et_3N, CH_2Cl_2, 70 °C; (f) LiOH, THF/H_2O, reflux, 77% for steps e and f combined; (g)10% $Pd/C/H_2$, 38%.

purification unless otherwise indicated. NMR spectra (^1H, ^{13}C, ^{19}F) were obtained on VXR or Unity 300 MHz instruments (Varian Instruments, Palo Alto, CA) with chemical shifts in ppm downfield from TMS as an internal reference standard. ^1H assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q),quintet (quin), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ 08888, and were within 0.4% of the theoretical values. Mass spectra were measured with a HP 5988A mass spectrometer with particle beam interface using NH_3 for chemical ionization or a Finnigan MAT 8230 mass spectrometer with NH_3-DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 ionization. Flash chromatography was performed using EM Science silica gel 60 (230−400 mesh). Preparative thin layer chromatography was done on EM Science 60 plates F_{254} (2 mm, 20 cm × 20 cm). HPLC purification was performed on a Jasco 900 series instrument or a Rainin Dynamax SD200 using a C18 reverse phase column with acetonitrile/H_2O (containing 0.05% TFA) as a mobile phase. All compounds were found to be >95% pure by HPLC analysis unless otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected.

X-ray Crystal Structure Data Collection and Structure Refinement (See Supporting Information Table 1). Data for factor VIIa and factor XIa crystals in complex with inhibitors were collected at the Advanced Photon Source (APS) beamline 17-BM or in the laboratory. Raw data were processed with the program HKL2000.[23] The atomic coordinates of human factor VIIa (PDB code 1DAN) or factor XIa were used as a search model. Original refinement was carried out with CNX (Accelrys), and inhibitor restraint

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dictionaries were built with QUANTA (Accelrys), which was also used for modeling. Later the structures were rerefined using BUSTER/TNT[24] (GlobalPhasing, Ltd.), MakeTNT or GRADE (GlobalPhasing, Ltd.) for inhibitor restraint dictionaries, and COOT[25] for modeling. Coordinates for the enzyme/inhibitor structures, data collection and refinement statistics, and the X-ray diffraction data have been deposited with the Protein Data Bank (PDB). The PDB deposition number for compounds **1**, (+)-**16**, and **29** are 4NA7, 4NA8, and 4NA9, respectively.

Enzyme Affinity Assays. The affinity of compounds for various enzymes was determined using purified enzymes and synthetic substrates from commercial sources. Assays were conducted at room temperature (~25 °C) or at 37 °C in temperature controllable, 96-well microtiter plate spectrophotometers (Molecular Devices, Spectramax) with simultaneous measurement of enzyme activities in control and inhibitor-containing solutions. Assays were initiated by adding enzyme to buffered solutions containing synthetic substrate in the presence or absence of inhibitor. Hydrolysis of the substrate resulted in the release of pNA (*p*-nitroaniline), which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. The rate of absorbance change is proportional to enzyme activity. A decrease in the rate of absorbance in the presence of inhibitor is indicative of enzyme inhibition. Assays were conducted under conditions of excess substrate and inhibitor over enzyme. The Michaelis−Menten constant, K_m, for substrate hydrolysis was determined by nonlinear fitting of the reaction velocity data from multiple substrate concentrations to the Michaelis−Menten equation,

$$v = \frac{V_{max}S}{K_m + S}$$

where v is the observed velocity of the reaction, V_{max} is the maximal velocity, S is the concentration of substrate, and K_m is the Michaelis−Menten constant for the substrate.

Values of K_i were determined by allowing the enzyme to react with the substrate in the presence of the inhibitor. Reactions were allowed to go for periods of 10−120 min, and the velocities were measured when a linear steady state rate was observed. The following relationships were used to calculate K_i values using nonlinear fitting routines

$$\frac{v_s}{v_o} = A + \frac{B - A}{1 + \left(\frac{IC_{50}}{I}\right)^n}$$

and

$$K_i = \frac{IC_{50}}{1 + \frac{S}{K_m}}$$

for a competitive inhibitor, where v_o is the velocity of the control in the absence of inhibitor, v_s is the velocity in the presence of inhibitor, I is the concentration of inhibitor, A is the minimum activity remaining (usually locked at zero), B is the maximum activity remaining (usually locked at 1.0), n is the Hill coefficient, a measure of the number and cooperativity of potential inhibitor binding sites, IC_{50} is the concentration of inhibitor that produces 50% inhibition, K_i is the dissociation constant of the enzyme−inhibitor complex, S is the concentration of substrate, and K_m is the Michaelis−Menten constant for the substrate.

K_i values were determined in this manner at a fixed substrate concentration. The IC_{50} values were obtained over 4−11 inhibitor concentrations assayed in duplicate with a standard error of <20%. For several of the enzymes negligible inhibition was observed at the highest inhibitor concentration tested. In these cases the value assigned as a lower limit for K_i is the value that would be obtained with 50% inhibition at the highest inhibitor concentration assuming competitive inhibition.

By use of established protein purification procedures,[26] FX and prothrombin were isolated from citrated plasma obtained from healthy New Zealand white rabbits. Purified FXa was obtained after activation with Russell's viper venom followed by affinity chromatography. Purified thrombin was obtained after prothrombin activation with rabbit prothrombinase complex (rabbit FXa/human FVa/phospholipids) followed by affinity chromatography. The resulting proteins were >95% pure as judged by sodium dodecyl sulfate−polyacrylamide gel electrophoresis. Aliquots of each enzyme were stored at −70 °C and were rapidly thawed in a 37 °C water bath just prior to use. Rabbit FVIIa activity was determined via the use of a coupled enzyme assay.[18c] Activated rabbit plasma kallikrein was generated following a procedure described for human plasma kallikrein.[27] The factor IX activation methods are described in ref 19.

In Vitro Coagulation Assays (aPTT). Standard clotting assays were performed in a temperature-controlled automated coagulation device (Sysmex CA-6000, Dade-Behring). Blood was obtained from healthy volunteers by venipuncture and anticoagulated with $^1/_{10}$ volume of 0.11 M buffered sodium citrate (Vacutainer, Becton Dickinson). Plasma was obtained after centrifugation at 2000*g* for 10 min and kept on ice prior to use. An initial stock solution of the inhibitor at 10 mM was prepared in DMSO. Subsequent dilutions were done in plasma. Clotting time was determined on control plasma and on plasma containing different concentrations of inhibitor. Determinations at each plasma concentration were done in duplicate. The clotting time at each concentration was compared with the control clotting time for each pooled plasma. The activated partial thromboplastin time (aPTT) was performed using Alexin (Sigma) according to the reagent instructions. Plasma (50 μL) was warmed to 37 °C for 1 min before adding aPTT reagent (50 μL). At 3 min later calcium chloride (50 μL) was added.

Benzyl 2′-Formyl-4-(isobutylcarbamoyl)biphenyl-2-carboxylate (I-3d). Benzyl 5-(isobutylcarbamoyl)-2-(trifluoromethylsulfonyloxy)benzoate[22] (2.1 g, 4.6 mmol), 2-formylphenylboronic acid (1.0 g, 6.8 mmol), K_3PO_4 (1.5 g, 6.8 mmol), and $Pd[PPh_3]_4$ (0.53 g, 10%) were added together in 30 mL of DMF. The mixture was degassed and heated at 100 °C under N_2 for 2 h. The reaction mixture was cooled and poured into water. It was extracted with EtOAc. The combined organic solution was washed with brine and dried over $MgSO_4$. It was concentrated and purified by chromatography (silica gel, 10% EtOAc in CH_2Cl_2) to give 1.75 g of the biarylaldehyde **I-3d** (91%). MS: 416.4 $(M + 1)^+$. ^1H NMR ($CDCl_3$) δ 9.72 (s, 1H), 8.38 (s, 1H), 8.00 (dd, 1H), 7.84 (dd, 1H), 7.53−7.24 (m, 6H), 7.14 (d, 1H), 7.06 (m, 2H), 6.29 (m, 1H), 5.01 (s, 2H), 3.32 (m, 2H), 1.94 (m, 1H), 0.98 (d, 6 H).

Dimethyl 2′-Formylbiphenyl-2,4-dicarboxylate (I-3b). Dimethyl 4-bromoisophthalate (0.53 g, 2.0 mmol), 2-formylphenylboronic acid (0.66 g, 4.4 mmol), K_3PO_4 (0.59 g, 2.8 mmol), and $Pd[PPh_3]_4$ (0.23 g, 10 mol %) were reacted using the same procedure described for **I-3d** to give 0.35 g of the biarylaldehyde **I-3b** (65%). ^1H NMR ($CDCl_3$) δ 10.01 (s, 1H), 8.59 (d, 1H), 8.24 (d, 1H), 7.93 (d, 1H), 7.84 (s, 1H), 7.60 (m, 3H), 7.40 (d, 1H), 3.99 (s, 3H), 3.71 (s, 3H).

Ethyl 2′-Formylbiphenyl-2-carboxylate (I-3c). This compound was prepared by the same method described for **I-3b** using ethyl 2-bromobenzoate and 2-formylphenylboronic acid. MS: 255.1 $(M + 1)^+$.

Ethyl 2′-Formylbiphenyl-4-carboxylate (I-3a). This compound was prepared by the same method described for **I-3b** using ethyl 4-bromobenzoate and 2-formylphenylboronic acid. MS: 255.1 $(M + 1)^+$.

2′-(6-Carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-isobutylcarbamoylbiphenyl-2-carboxylic Acid (7). 4-Aminobenzamidine mono-HCl salt (0.13 g, 0.77 mmol) was suspended in acetonitrile (30 mL). Benzyl 2′-formyl-4-(isopentylcarbamoyl)biphenyl-2-carboxylate (**I-3d**) (0.32 g, 0.77 mmol) and styrene (0.88 mL, 7.7 mmol) were added, followed by indium triflate (0.45 g, 0.77 mmol). The mixture was heated at 70 °C under N_2 for 12 h. The mixture was concentrated and dissolved in 30 mL of MeOH and 5 mL of acetic acid. Catalytic amount of 10% Pd/C was added, and the mixture was stirred under 1 atm of H_2 for 3 h. The reaction mixture was filtered through Celite, concentrated, and purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 100 mg of the desired product TFA salt as a mixture of atropisomers (20%). MS: 547.5 $(M + 1)^+$. Structure was confirmed by variable temperature ^1H NMR (DMSO-d_6, 60−140 °C).

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2′-(6-Carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2,4-dicarboxylic Acid (9). This compound was prepared using the same procedures described for compound **7**. MS: 492.3 $(M + 1)^+$.

2′-(6-Carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylic Acid (8). This compound was prepared using the same procedures described for compound **7**. MS: 448.5 $(M + 1)^+$.

2′-(6-Carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-4-carboxylic Acid (10). This compound was prepared using the same procedures described for compound **7**. MS: 448.4 $(M + 1)^+$. ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 2H), 8.18 (s, 2H), 8.04−8.02 (d, 2H), 7.74−7.72 (d, 1H), 7.54−7.22 (m, 11H), 6.84 (s, 1H), 6.73−6.70 (d, 1H), 4.61−4.57 (d, 1H), 4.35 (m, 1H), 4.05−3.99 (m, 1H), 2.16−2.01 (m, 2H).

3′-(6-Carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-isobutylcarbamoylbiphenyl-2-carboxylic Acid (11). This compound was prepared using benzyl 3′-formyl-4-(isopentylcarbamoyl)biphenyl-2-carboxylate (prepared by the same procedures described for **I-3d**) following the same procedure described for compound **7**. MS: 547.5 $(M + 1)^+$. Analytical HPLC purity, 91.4%. ^{1}H NMR (DMSO-d_6) δ 8.70 (m, 3H), 8.38 (s, 2H), 8.22 (s, 1H), 8.04 (d,1H), 7.53−7.26 (m, 6H), 4.78 (m, 1H), 4.35 (m, 1H), 3.12 (t, 2H), 2.22 (m, 1H), 2.08 (m, 1H), 1.86 (m, 1H), 0.90 (d, 6H).

3′-(6-Carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2,4-dicarboxylic Acid (12). This compound was prepared using dimethyl 3′-formylbiphenyl-2,4-dicarboxylate (prepared by the same procedures described for **I-3b**) following the same procedure described for compound **7**. MS: 492.3 $(M + 1)^+$. Analytical HPLC purity, 99.9%. ^{1}H NMR (CD_3OD) δ 8.43 (s, 1H), 8.20 (d, 1H), 7.53−7.26 (m, 11H), 7.01 (s, 1H), 6.76 (d, 1H), 4.78 (d, 1H), 4.35 (m, 1H), 2.37−2.10 (m, 2H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2,4-dicarboxylic Acid (13). This compound was prepared following the same procedure as described for **7**. MS: 506.3 $(M + 1)^+$. Analytical HPLC purity, 99.7%. ^{1}H NMR (CD_3OD) δ 8.39 (d, 1H), 8.15 (d, 1H), 7.48−7.22 (m, 9H), 7.18 (m, 1H), 7.06 (s, 1H), 6.76 (d, 1H), 4.75 (m, 1H), 2.20 (t, 1H), 1.98 (m, 1H), 1.81 (s, 3H).

3′-(6-Carbamimidoyl-4-ethyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2,4-dicarboxylic Acid (14). This compound was prepared following the same procedure as described for **7**. MS: 520.3 $(M + 1)^+$. Analytical HPLC purity, 95%. ^{1}H NMR (CD_3OD) δ 8.41 (s, 1H), 8.18 (d, 1H), 7.50−7.25 (m, 10H), 7.18 (m, 1H), 7.06 (s, 1H), 6.80 (d, 1H), 4.75 (m, 1H), 2.30−2.17 (m, 4H), 1.03 (t, 3H).

3′-(6-Carbamimidoyl-4-propylyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2,4-dicarboxylic Acid (15). This compound was prepared following the same procedure as described for **7**. MS: 534.3 $(M + 1)^+$. Analytical HPLC purity, 95%. ^{1}H NMR (CD_3OD) δ 8.50 (s, 1H), 8.17 (d, 1H), 7.48−7.22 (m, 10H), 7.18 (m, 1H), 7.08 (s, 1H), 6.81 (d, 1H), 4.77 (m, 1H), 2.21−2.08 (m, 4H), 1.14 (m, 2H), 1.10 (t, 3H).

Benzyl 2-Bromo-5-cyanobenzoate (II-3). 2-Bromo-5-iodobenzoic acid (6.5 g, 20 mmol) was dissolved in DMF (70 mL). Potassium bicarbonate (2.2 g, 22 mmol) was added, followed by benzyl bromide (2.8 mL, 22 mmol). The mixture was stirred at room temperature under N_2 for 12 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic solution was washed with brine and dried over $MgSO_4$. It was concentrated and dried to give 9.0 g (100%) of the benzyl ester. The benzyl ester (2.3 g, 7.7 mmol), $Zn(CN)_2$ (1.3 g, 12 mmol), and $Pd[PPh_3]_4$ 10 mol % were added together with 25 mL of DMF. The mixture was degassed and heated at 90 °C for 4 h. The cooled reaction mixture was diluted with 100 mL of NH_4OH/H_2O and extracted with EtOAc. The combined organic solution was washed with brine and dried over $MgSO_4$. It was concentrated and purified by chromatography (silica gel, 5% EtOAc in hexane) to give 1.8 g of the cyano derivative (74%). MS: 316.0, 317.9 $(M + 1)^+$.

Benzyl 2-Bromo-5-carbamoylbenzoate (II-4). Benzyl 2-bromo-5-cyanobenzoate (**II-3**) (1.4 g, 4.4 mmol) was dissolved in 15 mL of DMF. The reaction mixture was cooled at 0 °C. Potassium carbonate (0.20 g, 1.5 mmol) was added, followed by dropwise addition of H_2O_2 (1.2 mL of 30%). The cooling bath was removed, and the mixture was stirred at room temperature for 12 h. The reaction was quenched with aqueous $NaHSO_3$ and water. The precipitate formed was filtered and dried to give 1.1 g of the desired amide (75%). MS: 334.2, 336.3 $(M + 1)^+$.

Benzyl 4-Carbamoyl-3′-formylbiphenyl-2-carboxylate (II-8). Benzyl 2-bromo-5-carbamoylbenzoate (**II-4**) (7.2 g, 22 mmol), 3-formylphenylboronic acid (4.8 g, 32 mmol), K_3PO_4 (7.5 g, 36 mmol), and $Pd[PPh_3]_4$ (2.4 g, 10%) were reacted using the same procedure described for **I-3d** to give 7.2 g of the biarylaldehyde (93%). ^{1}H NMR ($CDCl_3$) δ 9.93 (s, 1H), 8.35 (d, 1H), 8.05 (dd, 1H), 7.83 (dd, 1H), 7.75 (s, 1H), 7.55−7.43 (m, 4H), 7.28 (m, 3H), 7.08 (m, 2H), 3.10 (s, 2H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid (16). 4-Aminobenzamidine mono-HCl salt (0.11 g, 0.58 mmol) was suspended in acetonitrile (30 mL). **II-8** (0.21 g, 0.58 mmol) and α-methylstyrene (0.34 mL, 2.9 mmol) were added, followed by indium triflate (0.17 g, 0.29 mmol). Following the procedure described for compound **7**, the desired product was isolated as the TFA salt (80 mg, 22%). MS: 505.3 $(M + 1)^+$. Analytical HPLC purity, 94.1%. ^{1}H NMR (DMSO-d_6) δ 8.61 (s, 2H), 8.18−8.15 (m, 3H), 8.00 (d, 1H), 7.79−7.50 (m, 5H), 7.25 (m, 5H), 7.01 (s, 1H), 6.78 (d, 1H), 4.66 (d, 1H), 1.80−2.10 (m, 2H), 1.74 (s, 3H).

Benzyl 4-Carbamoyl-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-5′-biphenyl-2-carboxylate (II-15). 2-(4-Aminophenyl)-5-methyloxadiazole (0.49 g, 2.8 mmol) was suspended in acetonitrile (20 mL). Benzyl 4-carbamoyl-3′-formyl-5′-biphenyl-2-carboxylate (**II-8**) (1.0 g, 2.8 mmol) and α-methylstyrene (1.8 mL, 14 mmol) were added, followed by indium triflate (0.78 g, 1.4 mmol). The mixture was degassed and heated at 70 °C under N_2 for 6 h. The mixture was concentrated and purified by chromatography (silica gel, 30% EtOAc in hexane and then 3% MeOH in CH_2Cl_2). MS: 635.5 $(M + 1)^+$. The product mixture was separated by chiral HPLC (OD chiracel 250, 100%ACN) to give three products. **II-15a** (226 mg, first peak, R_f = 5.00 min, $[\alpha]_D^{20}$ −85.5 (*c* 0.26, MeOH)). **II-15b** (229 mg, third peak, R_f = 5.48 min, $[\alpha]_D^{20}$ +85.7 (*c* 0.27, MeOH)). **II-15c** (70 mg, second peak, R_f = 5.13 min, racemate trans isomer).

(+)-3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid [(+)-16]. **II-15b** (229 mg, 0.31 mmol) was dissolved in 15 mL of $MeOH/Et_3N$ (8:1). Catalytic amount of 10% Pd/C was added, and the mixture was stirred under 1 atm H_2 for 12 h. The reaction mixture was filtered through Celite, concentrated, and purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 110 mg of the desired product as a TFA salt (57%). MS: 505.4 $(M + 1)^+$. Analytical HPLC purity, 99.6%. $[\alpha]_D^{20}$ +79.5 (*c* 0.21, MeOH). ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 2H), 8.15 (m, 3H), 8.00 (d, 1H), 7.50−7.30 (m, 5H), 7.25 (m, 3H), 7.15 (m, 1H), 7.01 (s, 1H), 6.68 (d, 1H), 4.66 (d, 1H), 2.05 (t, 1H), 1.90 (m, 1H), 1.72 (s, 3H).

(−)-3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid [(−)-16]. This compound was prepared from **II-15a** following the same procedure as described for (+)-**16**. MS: 505.4 $(M + 1)^+$. Analytical HPLC purity, 99.6%. $[\alpha]_D^{20}$ −80.5 (*c* 0.21, MeOH). ^{1}H NMR (DMSO-d_6) δ 8.63 (s, 2H), 8.20 (m, 3H), 8.03 (d, 1H), 7.52−7.32 (m, 5H), 7.30 (m, 3H), 7.20 (m, 1H), 7.05 (s, 1H), 6.82 (d, 1H), 4.72 (d, 1H), 2.08 (t, 1H), 1.92 (m, 1H), 1.77 (s, 3H).

(*trans*)-3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid (28). This compound was prepared from **II-15c** following the same procedure as described for (+)-**16**. MS: 505.4 $(M + 1)^+$. Analytical HPLC purity, 99%. ^{1}H NMR (DMSO-d_6) δ 8.28−8.08 (m, 2H), 8.00 (d, 1H), 7.73 (s, 1H), 7.58 (m, 1H), 7.50−7.30 (m, 3H), 7.31−7.10 (m, 4H), 7.02 (m, 2H), 6.75 (d, 1H), 6.48 (d, 1H), 3.87 (d, 1H), 2.25 (m, 1H), 1.91 (t, 1H), 1.70 (s, 3H).

Methyl 3′-Formyl-4-nitrobiphenyl-2-carboxylate (III-2). Methyl 2-bromo-5-nitrobenzoate (**III-1**) (0.98 g, 3.8 mmol), 3-

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formylphenylboronic acid (**II-6**) (0.57 g, 3.8 mmol), K_3PO_4 (3.2 g, 15 mmol), and $Pd[PPh_3]_4$ (0.22 g, 5%) were reacted using the same procedure described for **I-3d** to give 0.92 g of the biarylaldehyde (85%). MS: 327.2 $(M + CH_3CN + H)^+$.

Methyl 3′-((2*S*,4*R*)-4-Methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-nitrobiphenyl-2-carboxylate (III-4). 2-(4-Aminobphenyl)-5-methyloxadiazole (**II-10**) (0.31 g, 1.8 mmol) was suspended in acetonitrile (20 mL). Methyl 3′-formyl-4-nitrobiphenyl-2-carboxylate (**III-2**) (0.50 g, 1.8 mmol) and α-methylstyrene (**III-3**) (1.1 mL, 8.8 mmol) were added, followed by indium triflate (0.49 g, 0.88 mmol). The mixture was heated at 70 °C under N_2 for 4 h. The mixture was concentrated and purified by silica gel chromatography (20% EtOAc in hexane) to give 0.60 mg of the desired product (61%). MS: 561.2 $(M + 1)^+$.

Methyl 4-Amino-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-biphenyl-2-carboxylate (III-5). A solution of methyl 3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-nitrobiphenyl-2-carboxylate (**III-4**) (0.56 g, 1.0 mmol) in 15 mL of THF/dioxane mixture (1:1) was added to a mixture of sodium hydrosulfide (0.52 g, 3.0 mmol) in 5 mL of H_2O at room temperature. The mixture was stirred at room temperature under N_2 for 2 h. The mixture was concentrated and dissolved in CH_2Cl_2. It was washed with water and brine, dried over $MgSO_4$, and concentrated to a yellow solid (0.49 g, 92%). MS: 531.3 $(M + 1)^+$.

4-Amino-3′-(6-carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-biphenyl-2-carboxylic Acid (20). Methyl 4-amino-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**III-5**) (50 mg, 0.094 mmol) was dissolved in MeOH (5 mL) and H_2O (1 mL). LiOH (21 mg, 0.50 mmol) was added. The mixture was refluxed under N_2 for 2 h. It was diluted with water and extracted with EtOAc. The combined organic mixture was washed with water and brine, dried over $MgSO_4$, and concentrated (47 mg, 97%). MS: 517.3 $(M + 1)^+$. The resulting acid (46 mg, 0.090 mmol) was dissolved in EtOH and HOAc (21 mL/3 mL). Catalytic amount of Raney Ni was added, and the mixture was stirred under 50 psi of H_2 for 12 h. The mixture was filtered through Celite, concentrated, and purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 13 mg of the desired product as a TFA salt (24%). MS: 477.3 $(M + 1)^+$. Analytical HPLC purity, 90%. ^1H NMR (CD_3OD) δ 7.80 (m, 2H), 7.41−7.10 (m, 9H), 7.05 (m, 2H), 6.77 (d, 2H), 4.70 (m, 1H), 2.20 (t, 1H), 1.98 (m, 1H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-(3-methylureido)biphenyl-2-carboxylic Acid (17). Methyl 4-amino-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**III-5**) (100 mg, 0.19 mmol) was dissolved in 5 mL of CH_2Cl_2. Triethylamine (100 mg, 1.0 mmol) was added, followed by methyl isocyanate (29 mg, 0.50 mmol). The mixture was stirred at room temperature under N_2 for 12 h. It was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated (130 mg, 100%). MS: 588.4 $(M + 1)^+$. The ester was hydrolyzed and then converted to the benzamidine following the same procedures described for compound **20** (32 mg, 26%). MS: 534.4 $(M + 1)^+$. Analytical HPLC purity, 98%. ^1H NMR (CD_3OD) δ 7.79 (m, 1H), 7.66 (m, 1H), 7.40−7.10 (m, 11H), 7.02 (m, 1H), 6.75 (d, 1H), 4.72 (m, 1H), 2.75 (s, 3H), 2.20 (m, 1H), 1.98 (m, 1H), 1.80 (s, 3H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-methanesulfonylaminobiphenyl-2-carboxylic Acid (18). Methyl 4-amino-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**III-5**) (100 mg, 0.19 mmol) was dissolved in 5 mL of CH_2Cl_2. Triethylamine (100 mg, 1.0 mmol) was added, followed by methanesulfonyl chloride (46 mg, 0.40 mmol). The mixture was stirred at room temperature under N_2 for 4 h. It was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated (48 mg, 42%). MS: 608.2 $(M + 1)^+$. The ester was hydrolyzed and then converted to the benzamidine following the same procedures described for **20** (10 mg, 7.9%). MS: 555.4 $(M + 1)^+$. Analytical HPLC purity, >98%. ^1H NMR (CD_3OD) δ 7.62 (m, 1H), 7.41−7.10 (m, 12H), 7.05 (m, 1H), 6.77 (d, 1H), 4.73 (m, 1H), 2.97 (s, 3H), 2.20 (t, 1H), 1.98 (m, 1H), 1.79 (s, 3H).

4-Acetylamino-3′-(6-carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylic Acid (23). Methyl 4-amino-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**III-5**) (100 mg, 0.19 mmol) was dissolved in 5 mL of CH_2Cl_2. Triethylamine (100 mg, 1.0 mmol) was added, followed by acetyl chloride (39 mg, 0.50 mmol). The mixture was stirred at room temperature under N_2 for 2 h. It was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated (160 mg, 100%). MS: 573.4 $(M + 1)^+$. The ester was hydrolyzed and then converted to the benzamidine following the same procedures described for **20** (31 mg, 26%). MS: 519.4 $(M + 1)^+$. Analytical purity, 98%. ^1H NMR (CD_3OD) δ 7.98 (m, 1H), 7.22 (m, 1H), 7.41 (m, 11H), 7.02 (m, 1H), 6.77 (d, 1H), 4.72 (m, 1H), 2.20 (m, 1H), 2.11 (s, 3H), 1.97 (m, 1H), 1.81 (s, 3H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-cyanobiphenyl-2-carboxylic Acid (19). Benzyl 2-bromo-5-cyanobenzoate (**II-3**) (0.32 g, 1.0 mmol), 3-formylphenylboronic acid (0.23 g, 1.5 mmol), K_3PO_4 (0.32 g, 1.5 mmol), and $Pd[PPh_3]_4$ (0.12 g, 10%) were reacted using the same procedure described for **I-3d** to give 0.21 g of benzyl 4-cyano-3′-formylbiphenyl-2-carboxylate. This intermediate (55 mg, 0.16 mmol) was added together with 4-aminobenzamidine mono-HCl salt (30 mg, 0.16 mmol), α-methylstyrene (0.12 mL, 0.81 mmol), indium triflate (50 mg, 0.08 mmol) with 5 mL of acetonitrile. Following the procedure described for compound **7**, the desired product was isolated as the TFA salt (16 mg, 17%). MS: 487.5$(M + 1)^+$. Analytical purity, 92%. ^1H NMR (DMSO-d_6) δ 8.60 (s, 2H), 8.20(s, 2H), 8.11 (s, 1H), 7.98 (d, 1H), 7.58 (d, 1H), 7.40 (m, 3H), 7.26 (m, 3H), 7.15 (m, 1H), 7.00 (m, 1H), 6.77 (d, 1H), 4.68 (d, 1H), 2.05 (t, 1H), 1.88 (m, 1H), 1.72 (s, 3H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylic Acid (22). This compound was prepared following the same methods described for compound **8**. MS: 463.3 $(M + 1)^+$. Analytical purity, 93%. ^1H NMR (CD_3OD) δ 7.78 (d, 1H), 7.50 (m, 1H), 7.40−7.10 (m, 12), 7.02 (d, 1H), 6.77 (d, 1H), 4.72 (d, 1H), 2.20 (t, 1H), 1.95 (m, 1H), 1.80 (s, 3H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2,4-dicarboxylic Acid 4-Methyl Ester (21). This compound was prepared following the same procedures described for compound **13**. MS: 520.4 $(M + 1)^+$. Analytical purity, 100%. ^1H NMR (CD_3OD) δ 8.42 (s, 1H), 8.18 (d, 1H), 7.55−7.25 (m, 10), 7.20 (m, 1H), 7.09 (d, 1H), 6.80 (d, 1H), 4.79 (m, 1H), 3.95 (s, 3H), 2.22 (t, 1H), 2.00 (m, 1H), 1.82 (s, 3H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-methylcarbamoylbiphenyl-2-carboxylic Acid (24). This compound was prepared following the same procedures described compound **11**. MS: 519.3 $(M + 1)^+$. Analytical purity, 99.9%. ^1H NMR (DMSO-d_6) δ 8.59 (m, 2H), 8.18 (m, 2H), 7.95 (d, 1H), 7.40 (m, 4H), 7.20 (m, 4H), 7.01 (s, 1H), 6.78 (d, 1H), 4.65 (d, 1H), 2.77 (d, 3H), 2.04 (t, 1H), 1.86 (m, 1H), 1.72 (s, 3H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-isopropylcarbamoylbiphenyl-2-carboxylic Acid (25). This compound was prepared following the same methods described for compound **11**. MS: 547.4 $(M + 1)^+$. Analytical purity, 99.5%. ^1H NMR (DMSO-d_6) δ 8.60 (s, 2H), 8.38 (d, 1H), 8.18 (m, 2H), 7.98 (d, 1H), 7.40 (m, 4H), 7.23 (m, 3H), 7.00 (m, 1H), 6.77 (d, 1H), 4.68 (m, 1H), 4.08 (m, 1H), 2.05 (t, 1H), 1.88 (m, 1H), 1.73 (s, 3H), 1.12 (d, 6H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-*tert*-butylcarbamoylbiphenyl-2-carboxylic Acid (27). This compound was prepared following the same methods described for compound **11**. MS: 561.3 $(M + 1)^+$. Analytical purity, 91%. ^1H NMR (DMSO-d_6) δ 8.67 (s, 2H), 8.25 (s, 1H), 8.15 (s, H), 8.01 (m, 1H), 7.42 (m, 4H), 7.28 (m, 4H), 7.08 (s, 1H), 6.83 (d, 1H), 4.73 (m, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.79 (s, 3H), 1.40 (s, 9H).

Methyl 5-((Dimethylamino)methyl)-2-(trifluoromethylsulfonyloxy)benzoate (IV-3). 2-Hydroxy-5-formylbenzoic acid (**IV-1**) (2.0 g, 12 mmol) was dissolved in 30 mL of DMF. Potassium

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bicarbonate (1.3 g, 13 mmol) was added, followed by benzyl bromide (1.6 mL, 13 mmol). The mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with EtOAc. The combined extract was washed with brine, dried over Na_2SO_4, concentrated to a light brown oil. This oil was dissolved in 10 mL of MeOH, and dimethylamine (25 mL, 2.0 N in MeOH) was added. The mixture was stirred at room temperature for 30 min, and the sodium cyanoborohydride (1.3 g, 20 mmol) was added. The mixture was stirred at room temperature for 12 h. It was diluted with water and extracted with EtOAc. The combined extract was washed with brine, dried over Na_2SO_4, concentrated to light brown oil. This material was dissolved in CH_2Cl_2 (100 mL) and cooled at 0 °C. Pyridine (4.0 g, 50 mmol) was added, followed by triflic anhydride (2.5 mL, 15 mmol). The reaction mixture was stirred at 0 °C for 30 min and then poured into water. The mixture was extracted with EtOAc. The combined extract was washed with brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (silica, 1:1 EtOAc/hexane) to give 0.88 g of brown oil (22%). MS: 342.2 $(M + 1)^+$.

Methyl 4-((Dimethylamino)methyl)-3′-formylbiphenyl-2-carboxylate (IV-4). Methyl 5-((dimethylamino)methyl)-2-(trifluoromethylsulfonyloxy)benzoate (**IV-3**) (0.44 g, 1.3 mmol), 3-formylphenylboronic acid (0.29 g, 1.9 mmol), K_3PO_4 (0.41 g, 1.9 mmol), and $Pd[PPh_3]_4$ (0.15 g, 10%) were reacted using the same procedure described for **I-3d** to give 0.33 g of the biarylaldehyde (86%). MS: 298.3 $(M + 1)^+$.

Methyl 4-((Dimethylamino)methyl)-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (IV-5). 2-(4-Aminophenyl)-5-methyloxadiazole (**II-10**) (59 mg, 0.34 mmol) was suspended in acetonitrile (10 mL). Methyl 4-((dimethylamino)methyl)-3′-formylbiphenyl-2-carboxylate (**IV-4**) (100 mg, 0.34 mmol) and α-methylstyrene (**III-3**) (0.22 mL, 1.7 mmol) were added, followed by indium triflate (95 mg, 0.17 mmol). The mixture was heated at 70 °C under N_2 for 4 h. The mixture was concentrated and taken into the next step without purification. MS: 537.4 $(M + 1)^+$.

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-dimethylaminomethylbiphenyl-2-carboxylic Acid (26). Methyl 4-((dimethylamino)methyl)-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**IV-5**) was dissolved in MeOH (5 mL), THF (5 mL), and H_2O (2 mL). LiOH (42 mg) was added. The mixture was refluxed under N_2 for 8 h. It was concentrated and purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 180 mg of TFA salt of the desired acid (77%). MS: 559.4 $(M + 1)^+$. Part of the product (86 mg, 0.15 mmol) was dissolved in EtOH and HOAc (21 mL/3 mL). Catalytic amount of Raney Ni was added, and the mixture was stirred under 50 psi of H_2 for 12 h. The mixture was filtered through Celite, concentrated, and purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 36 mg of TFA salt of the desired product (38%). MS: 519.4 $(M + 1)^+$. Analytical purity, 97.8%. ^1H NMR (CD_3OD) δ 7.94 (s, 1H), 7.68 (m, 1H), 7.50−7.25 (m, 10), 7.18 (m, 1H), 7.05 (m, 1H), 6.78 (d, 1H), 4.76 (m, 1H), 4.37 (s, 2H), 2.86 (s, 6H), 2.20 (m, 1H), 1.98 (m, 1H), 1.81 (s, 3H).

2′-(Benzyloxycarbonyl)-4′-carbamoyl-5-nitrobiphenyl-3-carboxylic Acid (II-7). Benzyl 2-bromo-5-carbamoylbenzoate (**II-4**) (4.7 g, 14 mmol), 3-carboxyl-5-nitrophenylboronic acid (3.0 g, 14 mmol), K_3PO_4 (4.5 g, 21 mmol), and $Pd[PPh_3]_4$ (0.82 g, 5%) were added together with 50 mL of DMF. The mixture was degassed and heated at 100 °C under N_2 for 8 h. The reaction mixture was cooled and poured into water. It was extracted with EtOAc. The combined organic solution was washed with brine and dried over $MgSO_4$. It was concentrated and recrystallized from EtOAc and CH_2Cl_2 to give 1.6 g of the biaryl product (27%). MS: 421.2 $(M + 1)^+$.

Benzyl 4-Carbamoyl-3′-formyl-5′-nitrobiphenyl-2-carboxylate (II-9). 2′-(Benzyloxycarbonyl)-4′-carbamoyl-5-nitrobiphenyl-3-carboxylic acid (**II-7**) (0.80 g, 1.9 mmol) was dissolved in 20 mL of THF at room temperature. Triethylamine (0.32 mL, 2.1 mmol) was added, followed by isobutyl chloroformate (0.30 mL, 2.1 mmol). The mixture was stirred at room temperature under N_2 for 20 min. $NaBH_4$ (0.28 g) was added, followed by a few drops of water. The reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with 1 N HCl and water. It was extracted with EtOAc. The combined EtOAc solution was washed with water and brine, dried over $MgSO_4$, concentrated, and purified by chromatography (silica gel, 1−5% MeOH in CH_2Cl_2) to give 0.28 g of the corresponding alcohol (36%). MS: 407.2 $(M + 1)^+$. This alcohol (0.25 g, 0.62 mmol) and MnO_2 (0.43 g, 4.9 mmol) were then refluxed with benzene (15 mL) under N_2 for 20 h. It was filtered through Celite, concentrated, and purified by chromatography (silica gel, 3−4% MeOH in CH_2Cl_2) to give 0.18 g of the corresponding aldehyde (72%). ^1H NMR ($CDCl_3$)δ 9.96 (s, 1H), 8.48 (d, 2H), 8.30 (d, 1H), 8.13 (m, 1H), 8.00 (m, 1H), 7.45 (dd, 1H), 7.26 (m, 3H), 7.08 (m, 2H), 5.11 (s, 2H).

5′-Amino-3′-(6-carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid (30). 4-Aminobenzamidine mono-HCl salt (16 mg, 0.09 mmol), benzyl 4-carbamoyl-3′-formyl-5′-nitrobiphenyl-2-carboxylate (**II-9**) (33 mg, 0.09 mmol), α-methylstyrene (0.05 mL, 0.47 mmol), and indium triflate (25 mg, 0.05 mmol) were reacted following the procedure described for compound **7**. The desired product was isolated as a TFA salt (6.2 mg, 11%). MS: 520.3 $(M + 1)^+$. Analytical purity, 100%. ^1H NMR (DMSO-d_6) δ 8.59 (s, 2H), 8.16 (s, 2H), 8.11 (s, 1H), 8.09 (s, 1H), 7.97 (d, 1H), 7.45−7.30 (m, 3H), 7.22 (m, 3H), 7.17 (m, 1H), 7.01 (s, 1H), 6.77 (d, 1H), 6.71 (s, 1H), 6.61 (s, 1H), 6.53 (s, 1H), 4.50 (m, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.72 (s, 3H).

5′-Amino-3′-(6-carbamimidoyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylic Acid (29). This compound was prepared following the same methods described for compound **30**. MS: 463.2$(M + 1)^+$. Analytical purity, 98.6%. ^1H NMR (DMSO) δ 8.64 (s, 2H), 8.21 (s, 2H), 7.67 (d, 1H), 7.55 (m, 1H), 7.42−7.20 (m, 8H), 6.92 (s, 1H), 6.85−6.70 (m, 4H), 6.66 (s, 1H), 6.53 (s, 1H), 4.60 (m, 1H), 4.30 (m, 1H), 2.16 (m, 1H), 1.89 (m, 1H).

Benzyl 4-Carbamoyl-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-5′-nitrobiphenyl-2-carboxylate (II-12). 2-(4-Aminobphenyl)-5-methyloxadiazole (72 mg, 0.41 mmol) (**II-10**) was suspended in acetonitrile (10 mL). Benzyl 4-carbamoyl-3′-formyl-5′-nitrobiphenyl-2-carboxylate (**II-9**) (150 mg, 0.37 mmol) and α-methylstyrene (0.25 mL, 1.86 mmol) were added, followed by indium triflate (104 mg, 0.20 mmol). The mixture was degassed and heated at 70 °C under N_2 for 6 h. The mixture was concentrated and purified by chromatography (silica gel, 30% EtOAc in hexane and then 3% MeOH in CH_2Cl_2) to give 0.17 g of the desired product (61%). MS: 680.3 $(M + 1)^+$.

Benzyl 3′-Amino-4-carbamoyl-5′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (II-13). Benzyl 4-carbamoyl-3′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-5′-nitrobiphenyl-2-carboxylate (**II-12**) (63 mg, 0.09 mmol) was added with Fe (28 mg) and HOAc (0.2 mL)/EtOH (4 mL)/H_2O (0.8 mL). The mixture was heated at 80 °C for 30 min under N_2. It was diluted with EtOH and filtered through Celite. The filtrate was concentrated and redissolved in EtOAc. The EtOAc solution was washed with water and brine, dried over $MgSO_4$, concentrated to give 55 mg of crude amine (91%). This material was used in the next step without further purification. MS: 650.4 $(M + 1)^+$.

5′-Acetylamino-3′-(6-carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid (31). Benzyl 3′-amino-4-carbamoyl-5′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**II-13**) (70 mg, 0.11 mmol) was dissolved in 10 mL of CH_2Cl_2. It was cooled at 0 °C, and triethylamine (0.1 mL) was added, followed by acetyl chloride (21 μL). The mixture was stirred at 0 °C under N_2 for 1.5 h. Water and CH_2Cl_2 were added. The two layers were separated. The CH_2Cl_2 layer was washed with water and brine, dried over $MgSO_4$, and concentrated to give 80 mg of crude product (100%, MS: 692.0 $(M + 1)^+$). This material was dissolved in 10 mL of EtOH and HOAc (7:1). Catalytic amount of Raney Ni was added, and the mixture was stirred under 50 psi of H_2 for 2 h. The mixture was filtered through Celite and concentrated. The resulting solid was dissolved in 10 mL of EtOH and HOAc (7:1). Catalytic amount of 10% Pd/C was added, and the mixture was stirred

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under 40 psi of H_2 for 2 h. The mixture was filtered through Celite and concentrated. The crude product was purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 10 mg of the desired product as a TFA salt (13%). MS: 562.4 $(M + 1)^+$. Analytical purity, 93.9%. ^1H NMR (CD_3OD) δ 8.34 (s, 1H), 8.04 (d, 1H), 7.79 (s, 1H), 7.48 (m, 3H), 7.38−7.25 (m, 4H), 7.20 (m, 2H), 7.11 (s, 1H), 6.80 (d, 1H), 4.75 (m, 1H), 2.27 (m, 1H), 2.13 (s, 3H), 2.02 (m, 1H), 1.83 (s, 3H).

3′-((2*S*,4*R*)-6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoyl-5′-propionamidobiphenyl-2-carboxylic Acid (32). This compound was prepared followed the same procedures described for compound **31**. MS: $(M + 1)^+$. Analytical purity, 95%. ^1H NMR (DMSO-d_6) δ 10.0 (s, 2H), 8.69 (s, 2H), 8.23 (m, 3H), 8.05 (m, 1H), 7.76 (s, 1H), 7.56 (m, 2H), 7.47 (m, 2H), 7.32 (m, 2H), 7.22 (m, 1H), 7.10 (d, 2H), 6.83 (m, 1H), 4.65 (d, 1H), 2.31 (m, 2H), 2.03 (t, 1H), 1.94 (m, 1H), 1.79 (s, 3H), 1.07 (t, 3H).

3′-Butyramido-5′-((2*S*,4*R*)-6-carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoylbiphenyl-2-carboxylic Acid (33). This compound was prepared followed the same procedures described for compound **31**. MS: $(M + 1)^+$. Analytical purity, 94.9%. ^1H NMR (DMSO-d_6) δ 10.0 (s, 1H), 8.69 (s, 2H), 8.23 (m, 3H), 8.05 (d, 1H), 7.76 (s, 1H), 7.57 (m, 2H), 7.47 (m, 2H), 7.32 (m, 2H), 7.22 (m, 1H), 7.10 (d, 2H), 6.83 (m, 1H), 4.70 (d, 1H), 2.27 (t, 2H), 2.05 (t, 1H), 1.96 (m, 1H), 1.79 (s, 3H), 1.59 (m, 2H), 0.91 (t, 3H).

3′-((2*S*,4*R*)-6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoyl-5′-(cyclopropanecarboxamido)biphenyl-2-carboxylic Acid (34). This compound was prepared followed the same procedures described for compound **31**. MS: $(M + 1)^+$. Analytical purity, 90%. ^1H NMR (DMSO-d_6) δ 10.36 (s, 1H), 8.69 (s, 2H), 8.23 (m, 4H), 8.05 (m, 1H), 7.77 (s, 1H), 7.55 (m, 2H), 7.47 (m, 2H), 7.32 (m, 2H), 7.22 (m, 1H), 7.10 (d, 2H), 6.83 (m, 1H), 4.72 (d, 1H), 2.40 (m, 1H), 2.05 (t, 1H), 1.96 (m, 1H), 1.79 (s, 3H), 0.78 (m, 4H).

3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoyl-5′-(3-methylbutyrylamino)-biphenyl-2-carboxylic Acid (35). This compound was prepared followed the same procedures described for **31**. MS: 604.4 $(M + 1)^+$. Analytical purity, 93.4%. ^1H NMR (DMSO-d_6) δ 9.88 (s, 1H), 8.31 (s, 2H), 8.00 (m, 1H), 7.80 (s, 1H), 7.35−7.48 (m, 4H), 7.20−7.32 (m, 4H), 7.15 (m, 2H), 7.08 (m, 1H), 6.78 (m, 1H), 4.68 (m, 1H), 2.20 (m, 2H), 2.10 (m, 1H), 2.00 (m, 1H), 1.96 (m, 1H), 1.79 (s, 3H), 0.96 (m, 6H).

(+)-3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoyl-5′-(3-methylbutyrylamino)-biphenyl-2-carboxylic Acid (1) and (−)-3′-(6-Carbamimidoyl-4-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)-4-carbamoyl-5′-(3-methylbutyrylamino)biphenyl-2-carboxylic Acid (36). Benzyl 3′-amino-4-carbamoyl-5′-((2*S*,4*R*)-4-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl)-4-phenyl-1,2,3,4-tetrahydroquinolin-2-yl)biphenyl-2-carboxylate (**II-13**) (2.39 g, 3.68 mmol) was dissolved in 350 mL of CH_2Cl_2. It was cooled at 0 °C, and triethylamine (5.0 mL) was added, followed by isovaleryl chloride (3.3 mL). The mixture was stirred at 0 °C under N_2 for 1.5 h. Water and CH_2Cl_2 were added. The two layers were separated. The CH_2Cl_2 layer was washed with water and brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica, 50−100 EtOAc/hexane) to give 1.73 g of the desired product (64%, MS: 734.4 $(M + 1)^+$). This material was separated by chiral HPLC (Chiralcel OD 4.6 × 250, 50% IPA/50% heptane) to give 0.90 g of the dextrorotatory enantiomer and 0.80 g of the levorotary enantiomer. The dextrorotatory enantiomer was dissolved in 130 mL of MeOH/Et_3N (8:1). Catalytic amount of 10% Pd−C was added, and the mixture was stirred under 1 atm H_2 for 12 h. The mixture was filtered through Celite and concentrated. The crude product was purified by reverse phase HPLC (0.5% TFA in CH_3CN/H_2O) to give 0.80 g TFA salt of **1** (91%). MS: 604.4 $(M + 1)^+$. $[\alpha]_D^{20}$ +63.9 (*c* 0.25, MeOH). Analytical purity, 96.4%. ^1H NMR (DMSO-d_6) δ 9.92 (s, 1H), 8.60 (s, 2H), 8.15 (m, 3H), 7.98 (d, 1H), 7.69 (s, 1H), 7.51 (s, 1H), 7.40 (m, 2H), 7.38 (m, 3H), 7.25 (m, 3H), 7.13 (m, 1H), 7 (d, 2H), 6.78 (d, 1H), 4.58 (m, 1H), 2.11 (m, 2H), 2.00 (m, 2H), 1.85 (m, 1H), 1.72 (s, 3H), 0.86 (m, 6H). Compound **36** was prepared from the levorotary enantiomer using the same procedures as described for **1**. MS: 604.4 $(M + 1)^+$. $[\alpha]_D^{24}$ −87.0 (*c* 0.10, MeOH). Analytical purity, 100%. ^1H NMR (DMSO-d_6) δ 9.99 (s, 1H), 8.67 (s, 2H), 8.27 (s, 2H), 8.23 (s, 1H), 8.18 (s, 1H), 8.05 (d, 1H), 7.75 (s, 1H), 7.59 (s, 1H), 7.47 (s, 1H), 7.44 (m, 3H), 7.31 (m, 4H), 7.22 (m, 1H), 7.10 (m, 2H), 6.84 (d, 1H), 4.66 (m, 1H), 2.17 (d, 2H), 2.06 (m, 2H), 1.92 (m, 1H), 1.79 (s, 3H), 0.93 (d, 6H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data and refinement statistics for X-ray crystal structures of the FXIa complexes with compounds **1** and **16** and FVIIa complex with compound **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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