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Design and Synthesis of Phenylpyrrolidine Phenylglycinamides As Highly Potent and Selective TF-FVIIa Inhibitors

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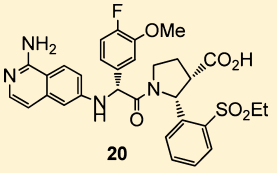
Supporting Information

ABSTRACT: Inhibitors of the Tissue Factor/Factor VIIa (TF-FVIIa) complex are promising novel anticoagulants that show excellent efficacy and minimal bleeding in preclinical models. On the basis of a zwitterionic phenylglycine acylsulfonamide **1**, a phenylglycine benzylamide **2** was shown to possess improved permeability and oral bioavailability. Optimization of the benzylamide, guided by X-ray crystallography, led to a potent TF-FVIIa inhibitor **18i** with promising oral bioavailability, but promiscuous activity in an in vitro safety panel of receptors and enzymes. Introducing an acid on the pyrrolidine ring, guided by molecular modeling, resulted in highly potent, selective, and efficacious TF-FVIIa inhibitors with clean in vitro safety profile. The pyrrolidine acid **20** showed a moderate clearance, low volume of distribution, and a short $t_{1/2}$ in dog PK studies.



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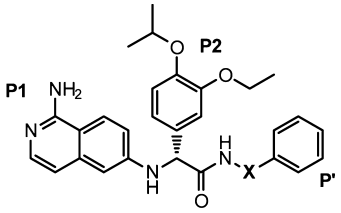
KEYWORDS: *TF-FVIIa inhibitor, anticoagulant, aminoisoquinoline, phenylpyrrolidine, phenylglycinamide, structure-based drug design*

Thromboembolic disorders are the most common cause of morbility and disability in the western world.[1] Thrombus formation is initiated via the extrinsic coagulation cascade by exposure of tissue factor (TF) to circulating coagulation factor VIIa (FVIIa) in blood. Binding of TF to FVIIa, a serine protease, leads to a large enhancement of its catalytic activity.[2] The TF-FVIIa complex initiates the extrinsic coagulation pathway by activating factor IX to IXa and factor X to Xa, which in turn activates prothrombin to thrombin. Thrombin cleaves fibrinogen to fibrin and activates platelets, triggering clot formation.[3,4] Inappropriate clot formation in blood vessels causes cardiovascular diseases such as ischemic stroke, myocardial infarction, and deep venous thrombosis. Recent preclinical studies have shown that selective inhibition of the TF-FVIIa complex provides effective anticoagulation with a low risk of bleeding.[5−9] Herein, we report the design and synthesis of phenylpyrrolidine phenylglycinamides as highly potent and selective TF-FVIIa inhibitors with promising oral bioavailability.

One of the major challenges in the development of small molecule drugs inhibiting TF-VIIa is achieving oral bioavailability; the majority of the reported TF-FVIIa inhibitors have a highly basic benzamidine P1 moiety ($pK_a \approx 12$).[10] The benzamidine forms a strong salt bridge interaction with Asp189 in the active site of the enzyme, resulting in inhibitors that are potent, but poorly orally bioavailable due to protonation and low permeability under physiological conditions. Some reports of weakly potent nonbenzamidine TF-FVIIa inhibitors have appeared in the literature.[11−13] We reported successful replacement of the benzamidine P1 group with a less basic aminoisoquinoline in an acylsulfonamide series (Figure 1).[14]



1: X = SO_2, **2**: X = CH_2

Cmpd. #	1	2
FVIIa K_i (nM)	11	260
Caco-2 (nm/s)	< 15	86
Dog F%	3.5	45
Rat F%	< 1	31

Figure 1. Phenylglycine acylsulfonamide **1** vs benzylamide **2**.

Aminoisoquinoline acylsulfonamide **1** retained good potency against TF-FVIIa with a K_i of 11 nM but showed poor Caco-2 permeability and low oral bioavailability in dogs (3.5%) and rats (<1%). The poor permeability of compound **1** is likely due to its zwitterionic nature (measured pK_a: 3.1 and 8.9). We reasoned that replacing the acidic acylsulfonamide with a neutral benzylamide may improve the permeability and thus oral bioavailability. The corresponding benzylamide **2** indeed displayed improved Caco-2 permeability and oral bioavailability in dogs and rats compared to acylsulfonamide **1**. Although the

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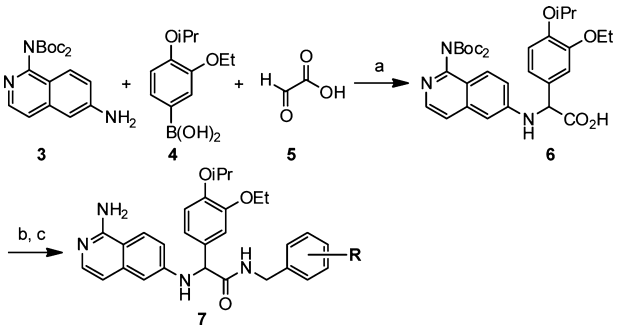
potency of benzylamide **2** is significantly reduced, we considered it to be a good lead that warranted further optimization.

Our initial strategy to improve the potency of benzylamide **2** was to optimize the interactions with the S′ site[15] in analogy to that of the acylsulfonamide series by investigating substitution on the benzyl group.[14] The general synthesis of analogues of compound **2** is shown in Scheme 1. A three component Petasis reaction of 6-aminoisoqunoline **3**,[16] (3-ethoxy-4-isopropoxyphenyl)boronic acid **4**, and glyoxylate **5** gave rise to the phenylglycine derivative **6**.[17] Coupling of compound **6** with a substituted benzylamine followed by deprotection of the Boc groups afforded compound **7** as a racemic mixture for biological testing to determine in vitro potency, selectivity, and permeability (Table 1). Chiral separation of key compounds was carried out if further profiling was needed.

Scheme 1. Synthesis of Compound 7 and Analogues[a]



[a]Reagents and conditions: (a) toluene/MeOH (5:1), 60 °C, 6 h, 78%; (b) EDC, $ArCH_2NH_2$, CH_2Cl_2/DMF (2:1), 15−70%; (c) 4.0 HCl, EtOAc/dioxane, >80%.

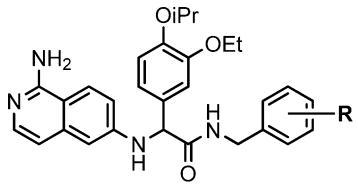
The parent benzylamide **7a** showed moderate potency against TF-FVIIa, weak activity against other coagulation serine proteases (FXa, FXIa and thrombin), and moderate PAMPA permeability (Table 1). A simple acetamide NHAc (**7b**) improved potency by 30-fold, while other polar groups such as $NHSO_2NH_2$ (**7c**), SO_2NH_2 (**7d**), $NHCO_2Me$ (**7e**), OH (**7f**), and NH_2 (**7g**) also improved potency and selectivity compared to the **7a**. These results indicate a strong preference for TF-FVIIa to bind small polar groups at the *meta*-position of the P′ phenyl. The presence of an H-bond donor (NH or OH) is important, as the *N*-methylation of **7b** resulted in an inactive compound **7h**. Although these polar groups improved potency, they afforded compounds that showed no PAMPA permeability.

Improvement of potency relative to **7a** was also achieved with substituents at the *ortho*-position of the P′ phenyl, as observed in the corresponding acylsulfonamide series.[14] Small alkylsulfones (**7i**−**k**) were particularly effective, improving potency by more than 30-fold relative to **7a**. These sulfones also showed low but measurable PAMPA permeability.

X-ray cocrystal structures of compounds **7d** and **7j** with TF-FVIIa were obtained and are shown overlaid in Figure 2.[19] As expected, the aminoisoquinoline group forms a salt bridge interaction with Asp189 in the S1 pocket. The 6-amino group (NH) of the aminoisoquinoline and the carbonyl (CO) of the amide form polar contacts with Ser195 and His57. The ethoxy from the P2 phenyl engages a small hydrophobic pocket defined in part by Thr98−Thr99 backbone and His57 side chain. The benzylamide phenyl is projected into the S′ pocket. The sulfonamide in **7d** forms an intermolecular H-bond to a structural water molecule bridging Asp60 side chain and Thr98 backbone oxygen. Similar hydrophilic interactions with TF-FVIIa were observed for other reported TF-FVIIa inhibitors,[14,20] However, the isopropylsulfone in **7j** was shown to engage in hydrophobic interaction with the Cys42−Cys58 disulfide bridge. This interaction, which provided more than 30-fold potency improvement, was first observed in the acylsulfonamide series.[14]

Overlay of X-ray cocrystal structures of compound **7d** with **7j** suggested 2,5-disubstitution could potentially combine the meta hydrophilic and ortho hydrophobic interactions (Figure 2). A disubstituted benzylamide **7l** was prepared and showed

Table 1. P′ SAR of Phenylglycine Benzylamide 7[a]



7, racemate

compd	R	TF-FVIIa K_i (nM)	FXa K_i (nM)	FXIa K_i (nM)	thrombin K_i (nM)	PAMPA (nm/s)
7a	H	930	5900	3900	7800	48
7b	3-NHAc	27	7200	11000	13000	1
7c	3-$NHSO_2NH_2$	47	4100	11000	9500	0
7d	3-SO_2NH_2	75	8100	11000	8700	0
7e	3-$NHCO_2Me$	84	6200	7900	11000	0
7f	3-OH	170	3900	11000	7800	0
7g	3-NH_2	200	1800	9700	7900	0
7h	3-N(Me)Ac	5400	7600	11000	6700	ND[b]
7i	2-SO_2cPr	12	3500	6700	2400	26
7j	2-SO_2iPr	17	2800	11000	2900	12
7k	2-SO_2Et	26	8200	11000	2800	9
7l	2-SO_2Et, 5-NHAc	4.4	7200	4000	12000	0

[a]K_is for the indicated enzymes were determined by chromogenic substrate assays at 25 °C (n = 2).[18] [b]No data.

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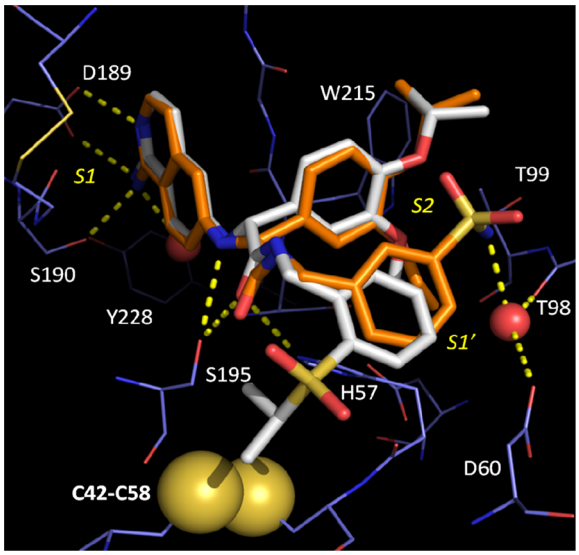
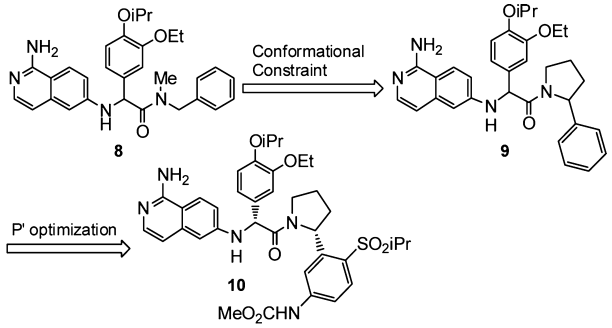


Figure 2. Overlay of X-ray cocrystal structures of **7d** and **7j**. Graphics were generated with PyMol.[21]

further improvement in potency compared to **7d** and **7j** with a K_i of 4.4 nM (Table 1). Compound **7l** is also highly selective against factor Xa, XIa, and thrombin but shows no permeability.

We have successfully improved the potency and selectivity for phenylglycine benzylamide **7a** with substituents at the ortho and meta positions of the P′ phenyl, but the PAMPA permeability was sacrificed for the potency gain. Introducing a methyl group in compound **7a** to form a tertiary amide **8** did not appear to affect the TF-FVIIa potency (Figure 3) but



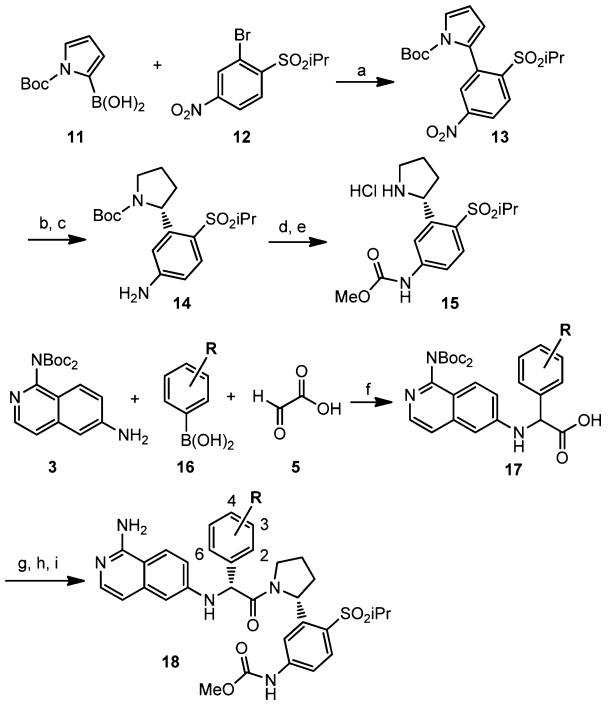
Cmpd #	7a	8	9	10
FVIIa K_i (nM)	930	1200	380	1.8
PAMPA (nm/s)	48	230	81	7

Figure 3. Evolution of phenylpyrrolidine TF-FVIIa inhibitors.

improved the PAMPA permeability. Constraining the tertiary benzylamide to its bioactive conformation with a pyrrolidine ring gave phenyl pyrrolidine amide **9** (a mixture of 4 diastereoisomers) that improved potency and maintained good PAMPA permeability relative to compounds **7a** and **8**. Introducing the potency enhancing meta and ortho substituents in compound **9** and chiral separation gave enantiomerically pure compound **10** that showed excellent TF-FVIIa potency (K_i of 1.8 nM), but a disappointing PAMPA permeability (7 nm/s).

Given the excellent potency demonstrated with compound **10**, SAR was further explored in the P2 region. The synthesis of P2 analogues of **10** is shown in Scheme 2. Suzuki–Miyaura

Scheme 2. Synthesis of Compound 18a–i[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, 1,2-DME, 95 °C, 96%; (b) platinum oxide, H_2, EtOH, 40 psi, 88%; (c) chiralpak AD; (d) methyl chloroformate, pyridine, 0 °C; (e) 4.0 HCl, EtOAc/dioxane, 95% for 2 steps; (f) microwave, 105 °C, 15 min, ACN/DMF (2:1), 20–65%; (g) EDC, **15**, CH_2Cl_2/DMF (2:1), 20–65%; (h) 4.0 HCl, EtOAc/dioxane, >80%; (i) chiral separation.

coupling of pyrrolyl boronic acid **11** and aryl bromide **12** gave rise to 2-substituted pyrrole **13**. Reduction of the pyrrole and nitro groups with platinum oxide under hydrogen pressure gave a substituted phenyl pyrrolidine in good yield. The racemic mixture was separated with a chiralpak AD column at this stage, the active (*R*)-enantiomer **14** was converted to methyl carbamate, and the Boc groups were deprotected to give intermediate **15**. A Petasis reaction of 6-aminoisoqunoline **3**, boronic acid **16**, and glyoxylate **5** gave rise to the phenylglycine derivative **17**. Coupling of compound **17** with intermediate **15**, followed by deprotection of Boc groups and chiral separation afforded phenylpyrrolidine **18** for biological testing. The three component Petasis reaction is particularly versatile in the P2 SAR investigation because a wide variety of phenyl boronic acids are readily available.

Small alkoxyl, alkyl, Cl, and F substituted phenyl P2 all gave potent and selective TF-FVIIa inhibitors (**18a–i**, Table 2). The anticlotting activity of these potent compounds were evaluated in a FVII deficient prothrombin time (dVII PT) assay.[18] Compound **18c** with a 3,4-dimethoxy phenyl P2 showed the best activity (EC_{2x}, 3.5 μM), but unfortunately it had a very low PAMPA permeability (2.0 nm/s). Interestingly, 6-F substitution on P2 phenyl (**18f–i**) appeared to have a beneficial effect on PAMPA permeability, with 3-OEt/6-F affording the best combination (**18i**). Compound **18i** showed excellent potency (K_i, 1.9 nM), good anticlotting activity (EC_{2x}, 9.5 μM), excellent selectivity (>2000-fold against FXa, FXIa, and thrombin), and good PAMPA permeability (140 nm/s). It is also more than 300-fold selective against nine other serine proteases.[22] The pharmacokinetic properties of **18i** were

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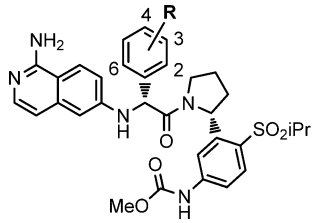
Table 2. Phenylpyrrolidine P2 SAR



18, homochiral

compd	R	TF-FVIIa K_i (nM)	dVII PT (EC_{2x}, μM)[a]	FXa K_i (nM)	FXIa K_i (nM)	thrombin K_i (nM)	PAMPA (nm/s)
18a	H	14	19	6000	11000	3400	58
18b	3-$OCHF_2$	4.5	19	2900	11000	6400	7.0
18c	3,4-di-OMe	1.8	3.5	9000	10000	5600	2.0
18d	3-OMe, 4-Cl	1.2	15	3700	2700	4900	25
18e	3-OMe, 4-F	1.1	11	6400	11000	6700	25
18f	3-Me, 6-F	2.1	12	5400	11000	3600	46
18g	3-OMe, 6-F	2.2	11	5200	11000	4400	64
18h	3-OEt, 4,6-di-F	1.9	9.5	4500	11000	5700	49
18i	3-OEt, 6-F	1.9	9.5	5200	7100	4400	140

[a]dVII PT: FVII deficient prothrombin time.[18]

evaluated (Table 3). It shows a high clearance but a promising oral bioavailability in dogs and moderate clearance and oral bioavailability in rats. Protein binding of compound **18i** in human plasma was measured to be 96.8%. A dose projection based on potency, protein binding, and PK suggested compound **18i** was not suitable for further in vivo evaluation.

Table 3. Pharmacokinetic Profile of Compound 18i

PK	dog[a]	rat[b]
CL (mL/min/kg)	41 ± 17	26 ± 8.1
Vss (L/kg)	4.2 ± 3.3	5.6 ± 2.1
$t_{1/2}$ (h)	2.2 ± 0.8	4.9 ± 1.1
F (%)	45 ± 33	7.9 ± 4.3

[a]Dogs (n = 3) were dosed 0.2 mg/kg iv and 1.0 mg/kg po. [b]Rats (n = 3) were dosed 0.5 mg/kg iv and 1.0 mg/kg po.

Despite compound **18i** displaying an impressive selectivity against a panel of 12 serine proteases, profiling revealed promiscuous activity in an in vitro safety panel of receptors and enzymes.[23]

To address the promiscuous activity in the in vitro safety panel and to further improve the anticlotting activity, we sought to install an acid on the pyrrolidine ring. We anticipated that we could use an ester prodrug approach to obtain permeable compounds. Molecular modeling of a simple phenylpyrrolidine suggested a likely interaction between an acid on the pyrrolidine and Lys60A (Figure 4).[24] Phenylpyrrolidine acid **19** was prepared and showed excellent potency and anticlotting activity with K_i of 0.9 nM and dVII PT EC_{2x} of 1.5 μM (Table 4). The acid group on the pyrrolidine improved the anticlotting activity by 6-fold compared to **18i**. With an acid on the pyrrolidine ring, removal of the methyl carbamate on the P′ phenyl still afforded potent TF-FVIIa inhibitors, e.g., a simple acid **20** showed anticlotting activity similar to that of compound **19**. Both compounds are highly selective against a panel of 11 other serine proteases and cytochrome P450 enzymes.[25] Compound **20** revealed a clean profile in the in vitro safety panel of receptors and enzymes. The acids are not permeable, but the corresponding esters showed reasonable PAMPA permeability (Table 4). Unfortunately, the parent acids did not possess the desired pharmacokinetic profile for a pro-drug

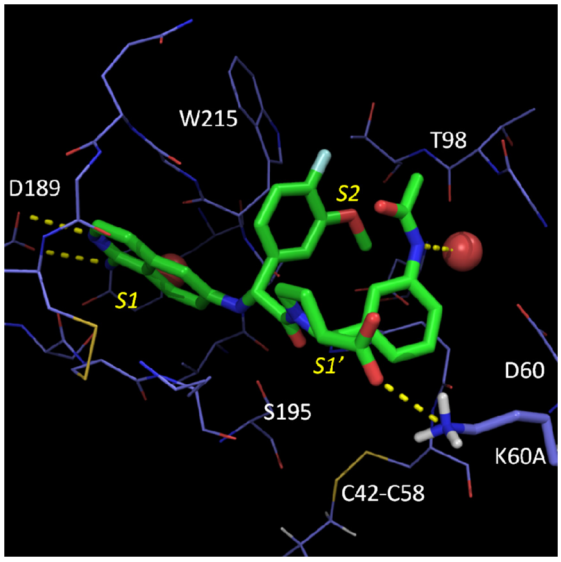
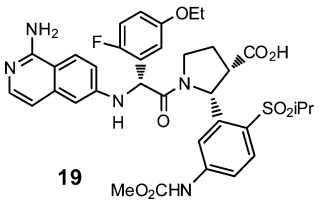
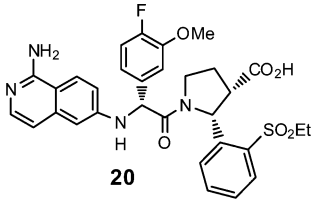


Figure 4. Binding model of a pyrrolidine acid with Lys60A. Graphics were generated with PyMol.[21]

Table 4. Summary of Phenylpyrrolidine Acid 19 and 20



19



20

compd	TF-FVIIa K_i (nM)	dVII PT (EC_{2x}, μM)	selectivity vs 11 other serine proteases, fold	PAMPA (nm/s)
19	0.9	1.5	>500	0, 80 (methyl ester)
20	5.6	2.2	>900	0, 56 (ethyl ester)

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approach due to the short half-life. Compound **20** showed a moderate clearance (14 mL/min/kg), very low V_{ss} (0.65 L/kg), and short $t_{1/2}$ life (1.1 h) in dog iv PK studies.

In summary, a series of phenylglycine benzylamide TF-FVIIa inhibitors was designed to improve permeability and oral bioavailability of a zwitterionic phenylglycine acylsulfonamide lead. Optimization of the benzylamide, guided by X-ray crystallography and conformational constraint, lead to a potent TF-FVIIa inhibitor **18i** with promising oral bioavailability, but promiscuous activity in an in vitro safety panel of receptors and enzymes. Introducing an acid on the pyrrolidine ring resulted in highly potent, selective TF-FVIIa inhibitors **19** and **20** with improved anticlotting activity, and clean profile in an in vitro safety panel of assays. The pyrrolidine acid **20** showed a moderate clearance, low volume of distribution, and short $t_{1/2}$ in dogs.

■ ASSOCIATED CONTENT

Supporting Information

Syntheses and characterization data for new compounds. 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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