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Structure-Based Drug Design of Pyrazinone Antithrombotics as Selective Inhibitors of the Tissue Factor VIIa Complex

Michael S. South,[a,*] Brenda L. Case,[a] Rhonda S. Wood,[a] Darin E. Jones,[a] Michael J. Hayes,[a] Thomas J. Girard,[b] Rhonda M. Lachance,[b] Nancy S. Nicholson,[c] Michael Clare,[d] Anna M. Stevens,[e] Roderick A. Stegeman,[e] William C. Stallings,[e] Ravi G. Kurumbail[e] and John J. Parlow[a]

[a]*Department of Medicinal and Combinatorial Chemistry, Pharmacia Corporation, 800 North Lindbergh Blvd., St. Louis, MO 63167, USA*
[b]*Department of Cardiovascular and Metabolic Disease, Pharmacia Corporation, 800 North Lindbergh Blvd., St. Louis, MO 63167, USA*
[c]*Department of Cardiovascular Pharmacology, Pharmacia Corporation, 4901 Searle Parkway, Skokie, IL 60077, USA*
[d]*Structure and Computational Chemistry, Pharmacia Corporation, 4901 Searle Parkway, Skokie, IL 60077, USA*
[e]*Structure and Computational Chemisty, Pharmacia Corporation, 700 Chesterfield Village Pkwy., St. Louis, MO 63198, USA*

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Abstract—Structure-based drug design coupled with polymer-assisted solution-phase library synthesis was utilized to develop a series of pyrazinone inhibitors of the tissue factor/Factor VIIa complex. The crystal structure of a tri-peptide ketothiazole complexed with TF/VIIa was utilized in a docking experiment that identified a benzyl-substituted pyrazinone as a P_2 surrogate for the tri-peptide. A 5-step PASP library synthesis of these aryl-substituted pyrazinones was developed. The sequence allows for attachment of a variety of P_1 and P_3 moieties, which led to synthesis pyrazinone **23**. Compound **23** exhibited 16 nM IC_{50} against TF/VIIa with $>6250\times$ selectivity versus Factor Xa and thrombin. This potent and highly selective inhibitor of TF/VIIa was chosen for preclinical intravenous proof-of-concept studies to demonstrate the separation between antithrombotic efficacy and bleeding side effects in a primate model of thrombosis.
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Cardiovascular disease is the most common cause of mortality in the western world. The disease is characterized by the acute coronary syndromes unstable angina and myocardial infarction.[1] This inappropriate thrombus formation is initiated via the extrinsic coagulation cascade by a plaque rupture. The plaque rupture exposes tissue factor (TF) to the serine protease Factor VIIa (VIIa) in circulating blood, which forms the TF/VIIa complex. This complex then further activates the serine proteases Factors IX to IXa and X to Xa, which in turn activate prothrombin to thrombin and fibrinogen to fibrin. Upon combination with activated platelets, a fibrin clot may result in a life threatening thrombus formation.[2] There is evidence from our own laboratories as well as others that selective inhibition of the TF/VIIa complex may provide effective anticoagulation while lessening the risk of bleeding side effects. as compared to other antithrombotic mechanisms (Glycoprotein IIb/IIIa antagonists and inhibitors of Factor Xa and thrombin).[3] Warfarin is currently the only approved oral antithrombotic therapy, which is complicated by frequent monitoring due to bleeding side effects, drug-drug interactions, and food effects.[4] Therefore, we sought to develop a series of potent and selective TF/VIIa inhibitors in order to address the large unmet medical need for safe and effective oral anticoagulants.

We recently described the synthesis and SAR of a series of tripeptide-α-ketothiazoles.[5] These reversible-covalent serine protease inhibitors were found to have nanomolar potency against TF/VIIa and exhibited $500\times$ selectivity versus thrombin. These compounds demonstrated that it is possible utilizing structure-based drug design (SBDD) techniques to achieve potent inhibition of the TF/VIIa complex while maintaining selectivity versus the other highly homologous serine proteases in the coagulation cascade. Utilizing the crystal structure of

*Corresponding author. Tel.: +314-274-5104; fax: +314-274-1621; e-mail: michael.s.south@pharmacia.com

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TF/VIIa bound to these tripeptide-α-ketothiazoles, we sought to develop a series of highly selective small molecule inhibitors of TF/VIIa that are non-peptidic and do not interact covalently with the catalytic apparatus of the enzyme.[6] Several reports of small molecule TF/VIIa inhibitors have appeared describing varying degrees of selectivity versus the other plasma proteases in the coagulation cascade.[7] We theorized that a wider selectivity margin over Factor Xa and thrombin was necessary to unequivocally demonstrate that inhibition of the TF/VIIa complex would lead to a lower bleeding side effect in-vivo. These highly selective TF/VIIa inhibitors should then be suitable for pre-clinical intravenous proof-of-concept studies demonstrating the separation between antithrombotic efficacy and bleeding side effects in a primate model of thrombosis.[3a]

Our first attempts at developing small molecule, non-peptidic inhibitors of TF/VIIa centered on the docking experiment shown in Figure 1. Here, an X-ray crystal structure of a tripeptide ketothiazole (*N*-{1-[4-guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-2-pyridin-3-yl-ethyl}-3-phenyl-2-phenylmethanesulfonylamino-propionamide) bound to the TF/VIIa enzyme is shown.[5,8]

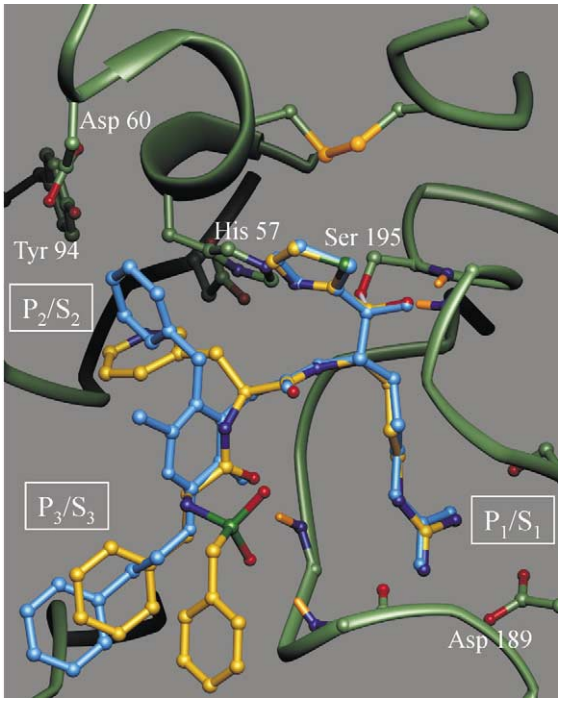


Figure 1. Docking of a pyrazinone inhibitor (compound **10**, cyan) in the active site of TF/VIIa based on the crystal structure of a tripeptide ketothiazole inhibitor (C: gold, N: dark blue; O: red and S: green). Crystals of TF/VIIa complex were obtained by slight modification of the procedure described by Banner et al.[8] Diffraction data of the ketothiazole complex were measured at the Advanced Photon Source to 2.6 Å resolution and the structure has been refined with good agreement between the data and the model (R_{free} of 28.6% and R-Factor: 22.2%). Some of the key side chains of factor VIIa are displayed (C: green, N: dark blue, O: red, S: yellow and H: orange). The carbon atoms of the inhibitor are shown in gold color. The active site serine, Ser 195, forms a covalent bond (thin solid line) with the activated carbon of the inhibitor. This results in the formation of a transition-state analogue with the negatively charged oxygen forming two hydrogen bonds with the peptide nitrogens of Ser 195 and Gly 193 in the oxy-anion hole. The nitrogen atom of the ketothiazole moiety forms a hydrogen bond to the active site histidine, His 57. The locations of P_1/S_1, P_2/S_2 and P_3/S_3 sites are labeled.

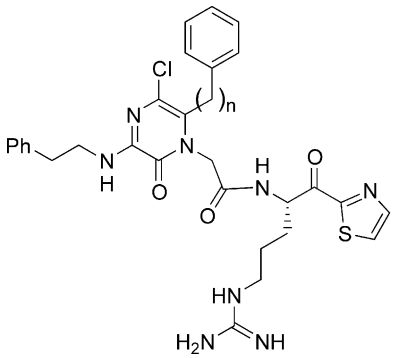
The key feature that is responsible for the good selectivity on TF/VIIa versus thrombin is the interaction of the 3-pyridylphenylalanine at P_2 with the S_2 pocket of TF/VIIa. This S_2 pocket has an aspartic acid residue (Asp 60) that is not present in the other coagulation enzymes and is much larger in size than the corresponding pocket of thrombin, which has an insertion loop in this region.[9] Utilizing these key features of the TF/VIIa crystal structure, we docked (FlexX was used) a series of 6-membered heterocyclic cores with pendant functionality at P_2 that mimicked the structure of the pyridylphenylalanine. We settled on the pyrazinone core with a benzyl functionality at P_2 as a prototype inhibitor to begin our SBDD studies. The benzyl group seemed to occupy much of the space of the pyridylphenylalanine in the peptide series, Figure 1. Also, critical hydrogen bonds between the pyrazinone carbonyl, the NH of the phenethylamine and the NH of the glycine unit on the pyrazinone to Gly 216 and Ser 214 were maintained similar to those in the tripeptide. The pyrazinone core was previously utilized in the design of inhibitors for thrombin[10] and the pyrimidine core for human leukocyte elastase.[11] Both cores are bound in these serine protease enzymes in a similar fashion along the peptide backbone. However, it is clear from Figure 1 that the requirements for P_1, P_2, and P_3 would likely be very different for the TF/VIIa enzyme.

The next step was to prepare the prototype pyrazinone inhibitor in Figure 1 for testing. The phenyl substituted P_2 was concurrently prepared for comparison purposes to probe the depth of the S_2 pocket of the TF/VIIa enzyme. A variation of the Strecker synthesis was utilized for the preparation of the pyrazinone skeleton, Scheme 1.[10d,e,12] Glycine benzyl ester was converted to the pyrazinones via incubation of the aldehyde cyanohydrin with oxalyl chloride in 1,2-dichlorobenzene. This reaction afforded the substituted dichloropyrazinones **1** and **2** in 38% and 60% yields, respectively. Compounds **1** and **2** were converted to the P_3 phenethylamine substituted pyrazinones **3** and **4** in 72% and 96% yields respectively via heating the core and amine in ethyl acetate.

Pyazinones **3** and **4** were then reacted with LiOH to cleave the benzyl ester, followed by coupling with the aminoketothiazole **11** to give **7** and **8**, Scheme 2. After removal of the protecting group with TFA and thioanisole, the target compounds **9** and **10** were isolated in 57% and 63% yields, respectively, after reverse phase chromatography.

Compounds **9** and **10** were tested on the TF/VIIa enzyme as well as Factor Xa, thrombin, and trypsin and the IC_{50} results are shown in Table 1. The benzyl-substituted pyrazinone **10** inhibited TF/VIIa with an IC_{50} of 290 nm and was 2× less potent against the TF/VIIa enzyme than the phenyl substituted pyrazinone **9**. Both

Table 1. Comparison of the biological activity of compounds **9** and **10**

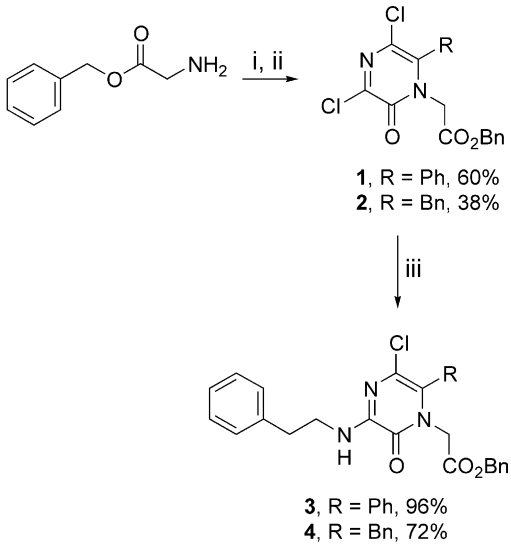


Compd	*n*	IC_{50} (μM)			
		VIIa	Xa	IIa	Trypsin
9	0	0.15	1.41	<0.04	0.42
10	1	0.29	2.90	0.11	0.47

compounds showed some selectivity versus Factor Xa (~10×), but no selectivity versus thrombin and trypsin. The conclusion from this initial study was that the phenyl substituent at P_2 of the pyrazinone was preferred over the benzyl substituent and would be utilized in further SAR studies due to its enhanced potency. Docking of compound **10** in the active site of the TF/VIIa complex is illustrated in Figure 1.

The ultimate goal was to obtain high selectivity levels for TF/VIIa versus Factor Xa and thrombin. We theorized that the ketothiazole moiety was contributing to a loss of selectivity since this moiety captures the catalytic apparatus of all of the homologous serine proteases. Therefore, our next study was to remove the ketothiazole and modify P_1, P_2, and P_3 in a library format to obtain the potency for TF/VIIa and selectivity levels versus other proteases that were desired for our preclinical studies.

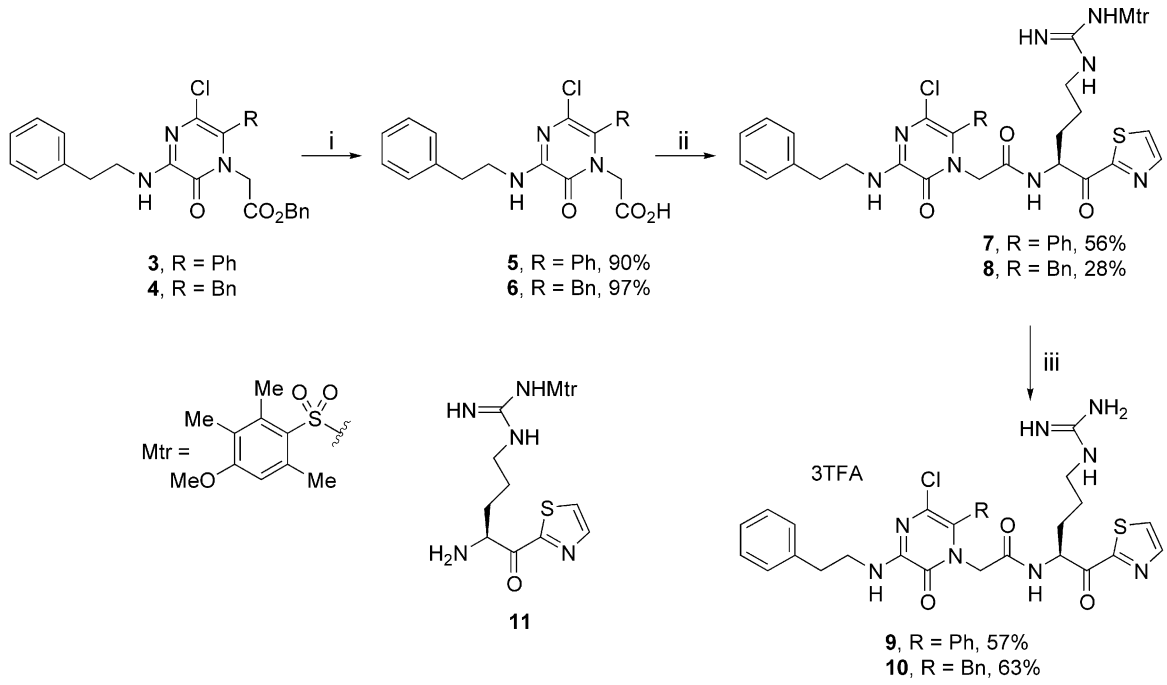
A general Scheme for the 5-step PASP library synthesis of pyrazinone TF/VIIa inhibitors is shown in Scheme 3.[13] This library synthesis allows for the attachment of any P_1 and P_3 for SAR studies. Core molecules **12**, **13**, and **14** were prepared as shown in Scheme 1. The first step was to incorporate the P_3 moiety. Pyrazinones **15** were prepared by treatment of **12**–**14** with 3 equiv of a primary amine in acetonitrile at 70 degrees centigrade. Excess amine and amine hydrochloride were left in the reaction mixture and carried on to the next step. The next step involved the hydrolysis of the benzyl ester with excess KOH followed by an acidification leaving the crude pyrazinone acid **16** as a mixture with excess amine hydrochloride and benzyl alcohol. Resin capture of the pyrazinone acids **17** was accomplished by treatment with a polyamine resin followed by repeated washings with DMF, dichloromethane, MeOH and dichloromethane, which removed excess amine, benzyl alcohol and any other non-acid impurities from the reaction mixture. The pyrazinone acids **18** were then removed from the resin with 4N HCl in dioxane. This sequence allowed pyrazinone acids **18** to be prepared in a parallel



Scheme 1. Preparation of prototype pyrazinone inhibitors. Reagents and conditions: (i) TMSCN, RCHO, CH_2Cl_2; (ii) $(ClCO)_2$,1,2-dichlorobenzene; (iii) Phenethylamine (3 equiv), EtOAc.

format without chromatography in >95% purity. Scheme 3 takes a slightly different course when R_1 and R_2 were NO_2 and CO_2Me respectively since selective deprotection of only the benzyl ester was desired for the resin capture step. Pyrazinone **15** was treated with hydrogen and Pd-C to simultaneously reduce the nitro group to the aniline and remove the benzyl ester. The synthesis then proceeds as described above to give compound **18**. The P_1 moiety was then coupled to the pyrazinone **18** by treatment with polymer bound carbodiimide and HOBt. Excess amine and starting acid **18** were removed from the solution by simultaneously utilizing the polyamine and aldehyde resins leaving pure **19** in solution. The CBZ protecting group was then removed via treatment with TMSCl and NaI followed by a MeOH quench. Any excess TMSCl was scavenged by polymer bound pyridine. Alternatively, a low-pressure catalytic reduction will remove the CBZ protecting group without concomitant reduction of the pyrazinone chloro-group. In general, the 5-step PASP synthesis of pyrazinones gave good yields (8–86% yields) and very high purities (>95%) of final products **20**, which were suitable for in-vitro enzymatic testing. Scheme 3 allowed for a variety of P_1 and P_3 substituents to rapidly be incorporated into the molecules without chromatography. Three molecules were synthesized to illustrate how SBDD was coupled with PASP synthesis to optimize activity and selectivity for TF/VIIa complex versus the other coagulation enzymes. A more detailed account of this synthesis with SAR data will appear elsewhere.

One of the first analogues that was prepared via the 5-step PASP library synthesis of pyrazinones (Scheme 3) was compound **21** (65% overall yield). Compound **21** has a *p*-aminomethyl-benzamidine group at P_1, a phenyl group at P_2 and a phenethyl group at P_3. This compound, which is shown in Table 2, was found to inhibit TF/VIIa with an IC_{50} of 620 nM with no selectivity versus Factor Xa and trypsin. A docking experiment based on the X-ray crystal structure of the des-Cl ana-



Scheme 2. Preparation of protoype pyrazinone inhibitors. Reagents and conditions: (i) LiOH, THF:MeOH:H_2O (3:3:1); (ii) **11**, EDC, HOBt, DIEA, THF; (iii) TFA, thioanisole.

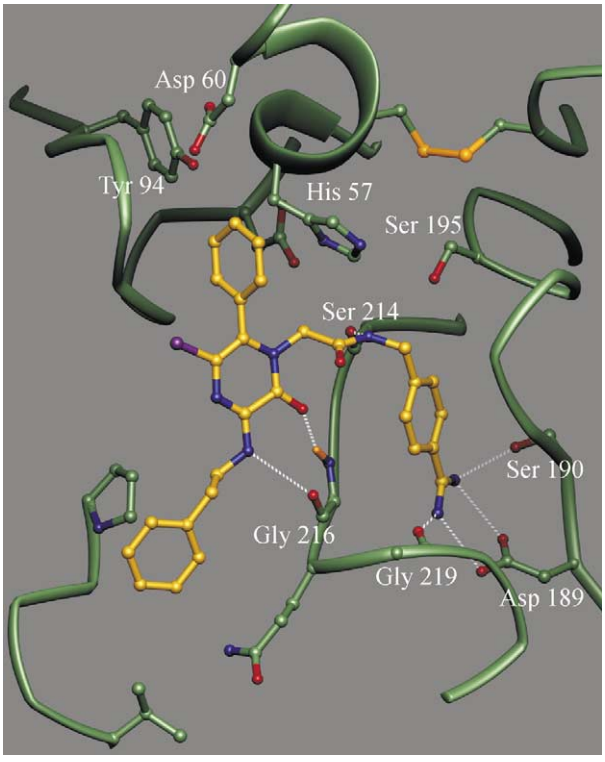


Figure 2. Docking of compound **21** in the active site of TF/VIIa based on the crystal structure of the complex with des-Cl analogue of **21**(structure not shown). The crystal structure of the des-Cl analogue was refined to an R_{free} of 28.2% at 2.3 Å resolution. The atoms are colored as in Figure 1. Some of the key side chains of Factor VIIa are displayed. The hydrogen bonds formed by the inhibitor are shown in dotted white line.

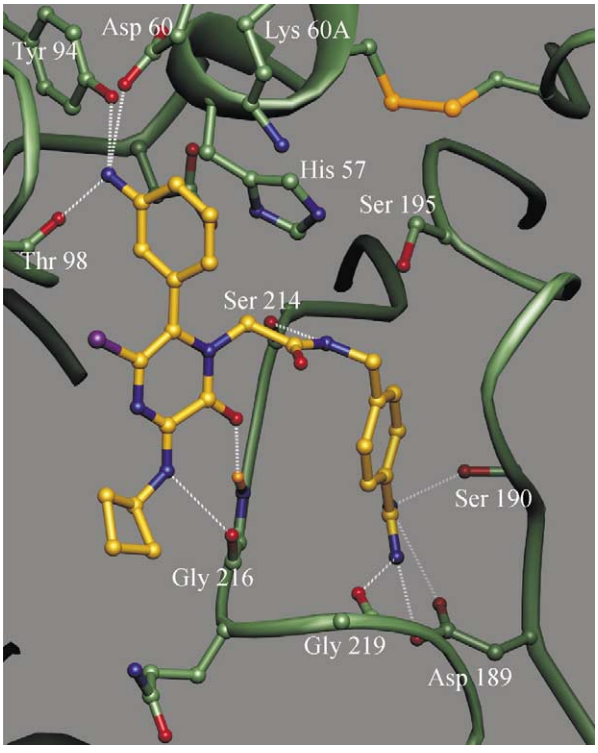
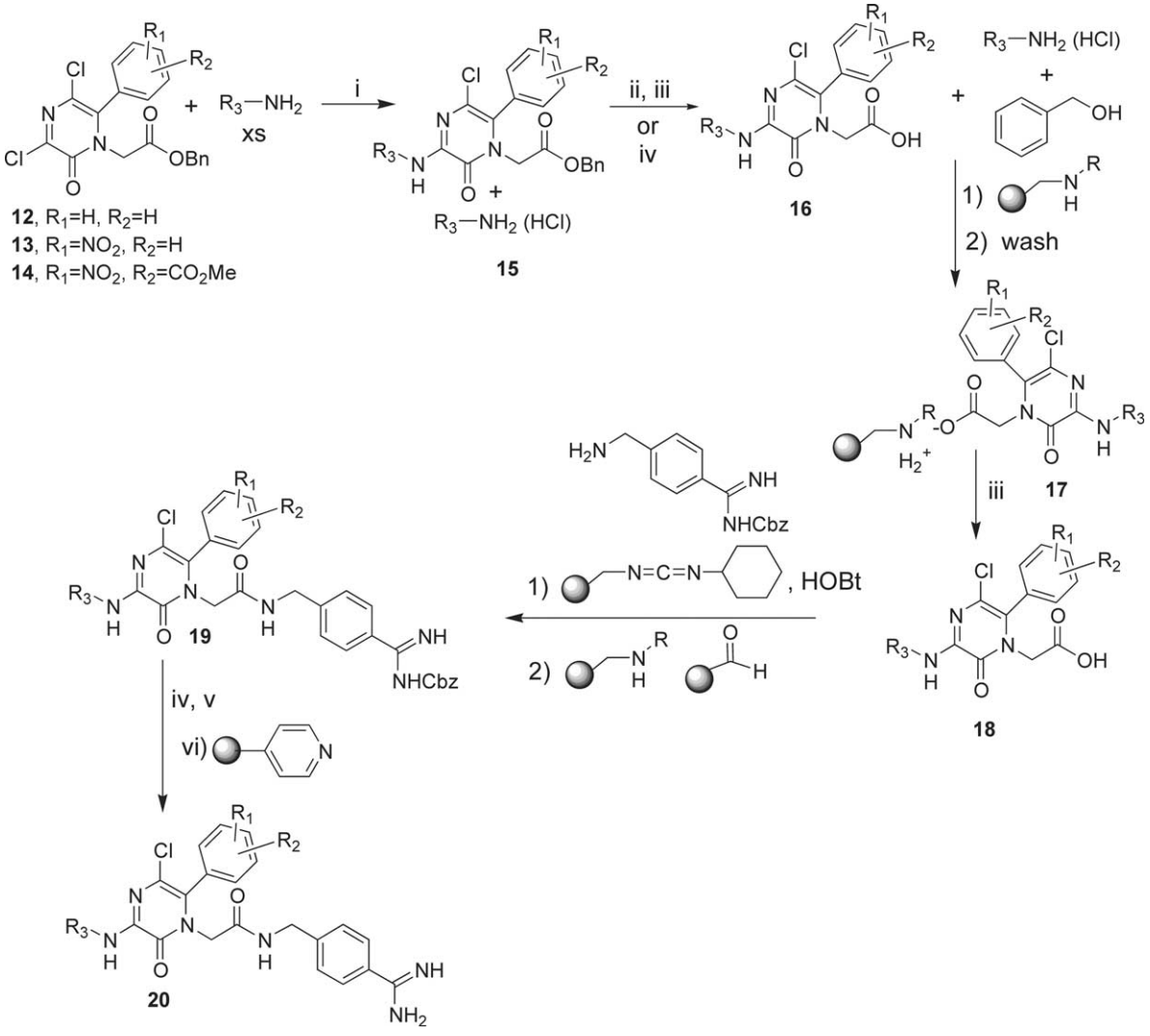


Figure 3. Crystal structure of compound **22** bound in the active site of TF/VIIa complex. The structure was refined to an R_{free} of 29.0% at 2.8 Å resolution. The atoms are colored as in Figure 1. Some of the key side chains of Factor VIIa are displayed. The hydrogen bonds formed by the inhibitor are shown in dotted white line. The *meta*-amino group on the phenyl group of the inhibitor forms strong interactions with Asp 60, Tyr 94, and the carbonyl oxygen of Thr 98 in the S_2 pocket.

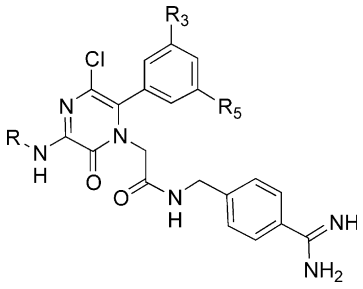
logue of **21** (data not shown) is depicted in Figure 2. The benzamidine P_1 interacts with the Asp 189 at the bottom of the S_1 pocket. Key hydrophobic interactions of the P_2 phenyl group are noted with the S_2 pocket of TF/VIIa, which is bounded by Asp 60, Tyr 94, Gly 97, and Thr 98. The phenethylamine P_3 forms a hydrophobic interaction with the S_3 pocket, which includes residues Val 170E, Pro 170I, and Gln 217. We theorized that since the P_2 pocket is larger in size and Asp 60 is unique to TF/VIIa, we might potentially be able to gain potency and selectivity versus the other enzymes in the coagulation cascade by placing a proton donor at the meta-position of the P_2 phenyl ring. This SBDD hypothesis led to the synthesis of compound **22**, which was prepared according to the library synthesis in Scheme 3 in 40% overall yield. We were pleased to learn that compound **22** exhibited 20 nM activity on TF/VIIa, which is a 10× boost in potency over **21**. Also note that compound **22** exhibited 400× selectivity versus thrombin and >5000× selectivity versus Factor Xa, which is an improvement over the unsubstituted phenyl P_2 present in **21**. An X-ray crystal structure of compound **22** bound to TF/VIIa is shown in Figure 3. It is very clear from the crystal structure of **22** that there is a 3-centered H-bonding interaction between the *m*-amino P_2 of **22** and Asp 60, Tyr 94, and Thr 98. These key H-bonding interactions with the S_2 pocket of TF/VIIa are likely responsible for the observed 10× boost in potency and the increases in selectivity versus thrombin. Selectivity versus Factor Xa is probably due to a collision of the P_2 phenyl ring with Tyr 99 of Factor Xa (data not shown).

In general, our SAR studies indicate that the S_3 pocket of TF/VIIa seems to prefer small alkyl groups for lipophilic interaction with Gln 217 and residues from the peptide segment 170E-170I (including Pro 170I). We felt that the 400× selectivity versus thrombin exhibited by compound **22** would not be sufficient for our intravenous proof-of-concept study in primates. Further docking experiments indicated that placement of a carboxylic acid moiety as a second meta-substituent on the P_2 phenyl ring should lead to a favorable interaction with Lys 60A. Synthesis of this compound was achieved as



Scheme 3. Polymer-assisted solution-phase (PASP) pyrazinone synthesis. Reagents and conditions: (i) 3 equiv $R'NH_2$, AcCN; (ii) aq KOH, MeOH; (iii) 4 N HCl/dioxane; (iv) H_2, Pd/C, MeOH; (v) TMSCl, NaI, acetonitrile; (vi) MeOH.

Table 2. IC_{50}'s in μM of pyrazinone antithrombotics



Compd				IC_{50} (μM)			
	R	R_3	R_5	VIIa	Xa	IIa	Trypsin
21	$PhCH_2CH_2$	H	H	0.62	—	0.15	0.24
22	*cyclo*-Bu	NH_2	H	0.020	>100	8.0	0.032
23	*i*-Pr	NH_2	CO_2H	0.016	>100	>100	0.064

shown in Scheme 3, which gave **23** in 25% overall yield. The activity of **23** on TF/VIIa was relatively unchanged versus **22**, however the selectivity versus thrombin was dramatically increased to >6250×. An X-ray crystal structure of **23** revealed that the carboxylate group of the inhibitor approaches the side chain of Lys 60A, although the electron density for the lysine side chain is not well defined, Figure 4. The dual substitution of the P_2 phenyl group and consequent steric clashes impart excellent selectivity against both thrombin and Factor Xa. Compound **23** was deemed selective enough versus Factor Xa and thrombin to proceed with our pre-clinical IV-proof of concept studies.

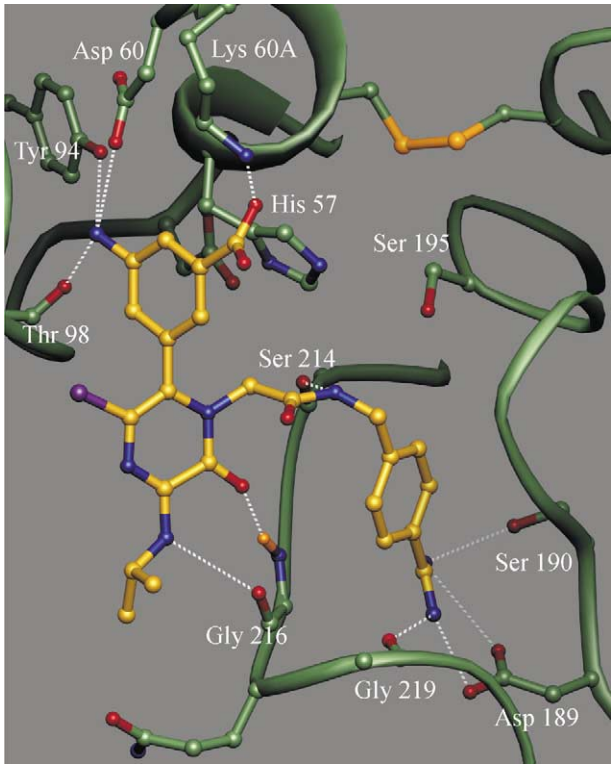


Figure 4. Crystal structure of compound **23** complexed with TF/VIIa. The structure was refined to an R_{free} of 31.1% at 2.1 Å resolution. The atoms are colored as in Figure 1 with some of the key side chains of Factor VIIa shown. The hydrogen bonds formed by the inhibitor are shown in dotted white line. Consistent with the structure of compound **22**, the *meta*-amino group forms close interactions in the S_2 pocket. As predicted, the carboxylate group at 5-position of the phenyl group approaches the side chain of Lys 60A, although the electron density is not well defined for the surface exposed lysine side chain.

In conclusion, we have demonstrated that high levels of activity and selectivity for TF/VIIa are possible by utilizing SBDD coupled with a 5-step PASP library synthesis of pyrazinones. Starting from a tripeptide ketothiazole that was active on TF/VIIa, we were able to design a series of active and selective pyrazinone inhibitors of TF/VIIa that were reversible and did not covalently capture the catalytic apparatus of the enzyme. These inhibitors exhibited sufficient levels of activity and selectivity for TF/VIIa versus Factor Xa and thrombin to proceed with our pre-clinical intravenous proof-of-concept studies of the separation between antithrombotic efficacy and bleeding side effects in a primate model of thrombosis. We are currently continuing to refine the SAR in the pyrazinone series. We are also studying a large variety of core molecules as alternative central templates for the selective inhibition of TF/VIIa, which will be reported in due course.[14]

Acknowledgements

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