Polymer-Assisted Solution-Phase Library Synthesis and Crystal Structure of α-Ketothiazoles as Tissue Factor VIIa Inhibitors

John J. Parlow,*,† Thomas A. Dice,† Rhonda M. Lachance,‡ Thomas J. Girard,‡ Anna M. Stevens,§ Roderick A. Stegeman,§ William C. Stallings,§ Ravi G. Kurumbail,§ and Michael S. South†

Department of Medicinal and Combinatorial Chemistry, Pharmacia Corporation, 800 North Lindbergh Boulevard, St. Louis, Missouri 63167, Department of Cardiovascular and Metabolic Disease, Pharmacia Corporation, 800 North Lindbergh Boulevard, St. Louis, Missouri 63167, and Structure and Computational Chemistry, Pharmacia Corporation, 700 Chesterfield Village Parkway, St. Louis, Missouri 63198

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A solution-phase synthesis of an α-ketothiazole library of the general form D-Phe-L-AA-Arg-α-ketothiazole is described. The five-step synthesis is accomplished using a combination of polymeric reagents and polymer-assisted solution-phase purification concepts, including reactant-sequestering resins, reagent-sequestering resins, and tagged reagents. The multistep synthesis affords desired α-ketothiazole products in excellent purities and yields. A variety of L-amino acid inputs were used to probe the S_2 pocket of tissue Factor VIIa enzyme to influence both potency and selectivity. An X-ray crystal structure of compound **10k** bound to the TF/VIIa complex was obtained that explains the observed selectivity. The α-ketothiazoles were found to be potent, reversible-covalent inhibitors of tissue Factor VIIa, with some analogues demonstrating selectivity over thrombin.

Tissue Factor (TF) VIIa is a serine protease and a key enzyme in the blood coagulation cascade.[1−4] Tissue factor is the essential cofactor for the coagulation protease Factor VIIa, initiating the coagulation cascade. The role of tissue factor in thrombotic diseases is becoming increasingly evident. Recent findings suggest that inhibition of TF/VIIa activity could be important in the prevention of clinical sequelae associated with plaque rupture or vessel damage that exposes tissue factor to blood. Furthermore, selective inhibitors of tissue Factor VIIa may be associated with less bleeding risk than other antithrombotic agents.[5−8]

An approach to the design of serine protease inhibitors has been the replacement of the scissile amide bond by an electron-deficient carbonyl group.[9,10] Series of aldehydes,[11] α-fluoroketones,[12−14] α-keto esters/amides,[15−18] and α-ketothiazoles[19−23] have been incorporated into peptidyl protease inhibitors. Since the report of the X-ray crystal structure of D-Phe-L-Phe-Arg chloromethyl ketone (DFFRCMK) bound to the active site of tissue Factor VIIa,[24−26] comparisons of the various pockets with other closely related proteases such as thrombin and Factor Xa have been possible. The most notable difference is the S_2 pocket of TF/VIIa. The S_2 pocket of TF/VIIa is larger than that of thrombin and Factor Xa and differs by a key residue, Asp 60, contained only in TF/VIIa. We initiated a program to identify a selective tissue Factor VIIa inhibitor. At the outset of the program, we sought to utilize tripeptide transition state analogues closely related to DFFRCMK. The design was of the general form D-Phe-L-AA-Arg-α-ketothiazole, utilizing the DFFRCMK backbone with α-ketothiazole in place of the chloromethyl ketone to provide a covalent-reversible inhibitor. The L-amino acid allows for variation at that position, to probe the S_2 pocket of the enzyme, which is expected to influence both potency and selectivity. In an effort to rapidly prepare libraries of α-ketothiazole peptidyl protease inhibitors in a parallel format, a solution-phase library synthesis was developed utilizing polymer-assisted solution-phase (PASP) technology.[27−29] Herein, we report a five-step PASP synthesis and biological activity of α-ketothiazoles with the structural motif D-Phe-L-AA-Arg-α-ketothiazole.[30]

A summary description of the library synthesis is depicted in Scheme 1. Each of the steps in the synthesis underwent independent validation in order to identify and optimize conditions such that each transformation could be performed in a high-yielding, parallel format. The synthesis was accomplished using a combination of polymeric reagents and polymer-assisted solution-phase purification concepts, including reactant-sequestering resins, reagent-sequestering resins, and tagged reagents. Compound **3** was selected as the starting scaffold in its unoxidized form, as the alcohol, to avoid side reactions during the ensuing steps. As a result, the synthesis was devised such that oxidation of the alcohol to ketone was conducted near the end. The synthesis is general such that variation of either amino acid is easily allowed. The initial library was designed with D-Phe as the terminal amino acid capped as the benzylsulfonamide. The benzylsulfonamide moiety, expected to occupy the S_3 pocket, was selected based on the structure−activity relationship (SAR) from the thrombin literature and the similarity of the S_3 pockets of Factor VIIa and thrombin. Considering the larger size of the S_2 pocket of TF/VIIa compared to thrombin and Factor Xa, a variety of L-amino acids was used to probe the S_2 pocket with the hope of providing potency and selectivity.

* To whom correspondence should be addressed. Phone: 314-274-3494. Fax 314-274-1621. E-mail: john.j.parlow@pfizer.com.
† Department of Medicinal and Combinatorial Chemistry.
‡ Department of Cardiovascular and Metabolic Disease.
§ Department of Crystallography and Molecular Modeling.

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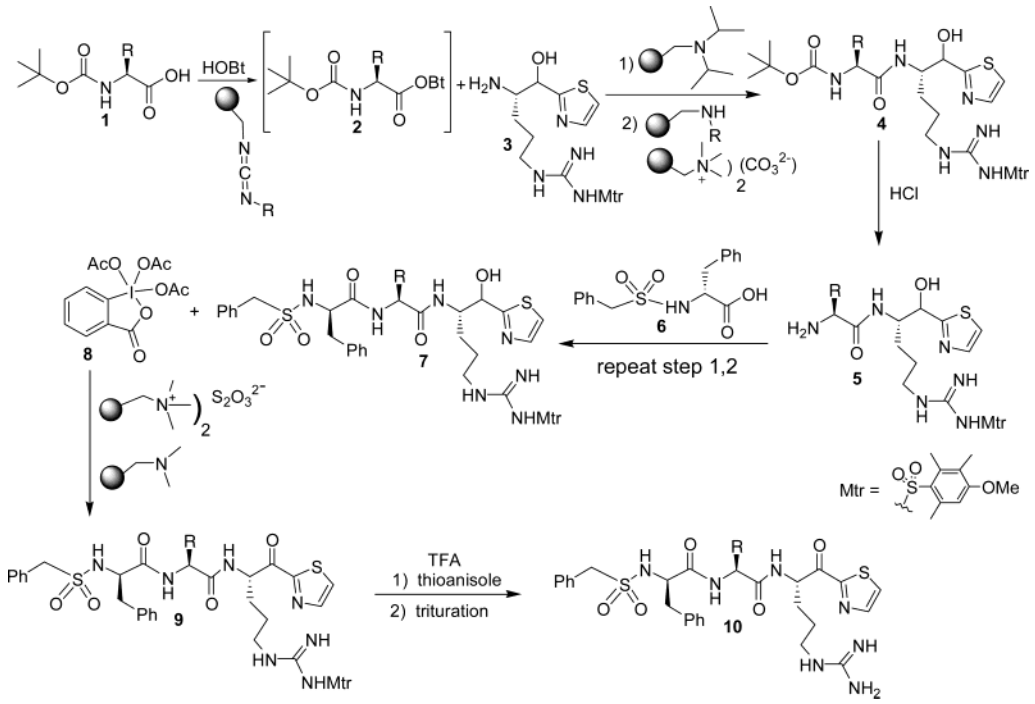
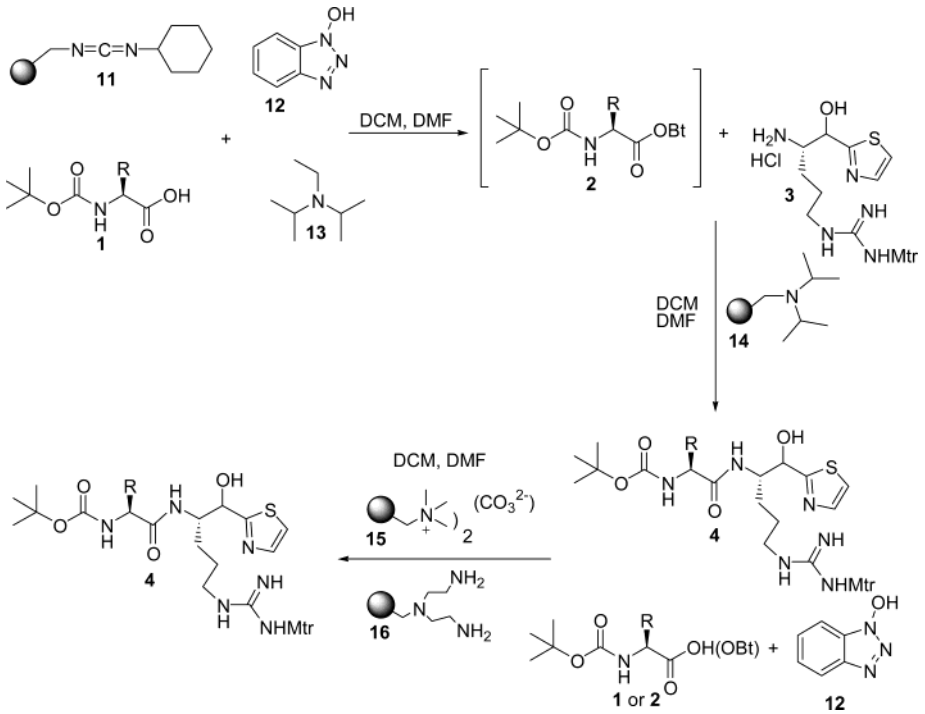
Scheme 1. PASP Synthesis of α-Ketothiazole Library

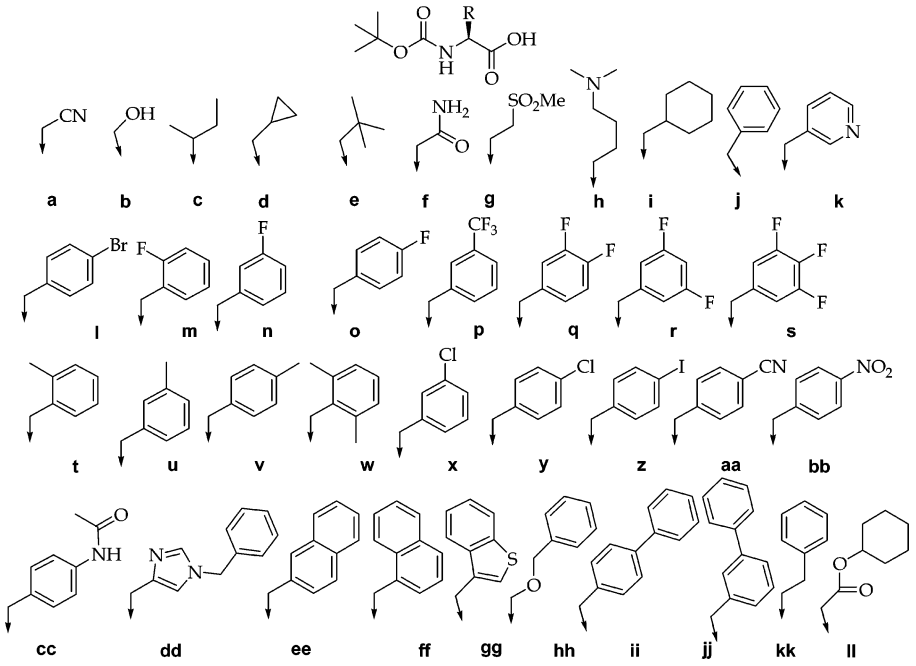


Scheme 2. Synthetic Step 1 of PASP Ketothiazole Synthesis

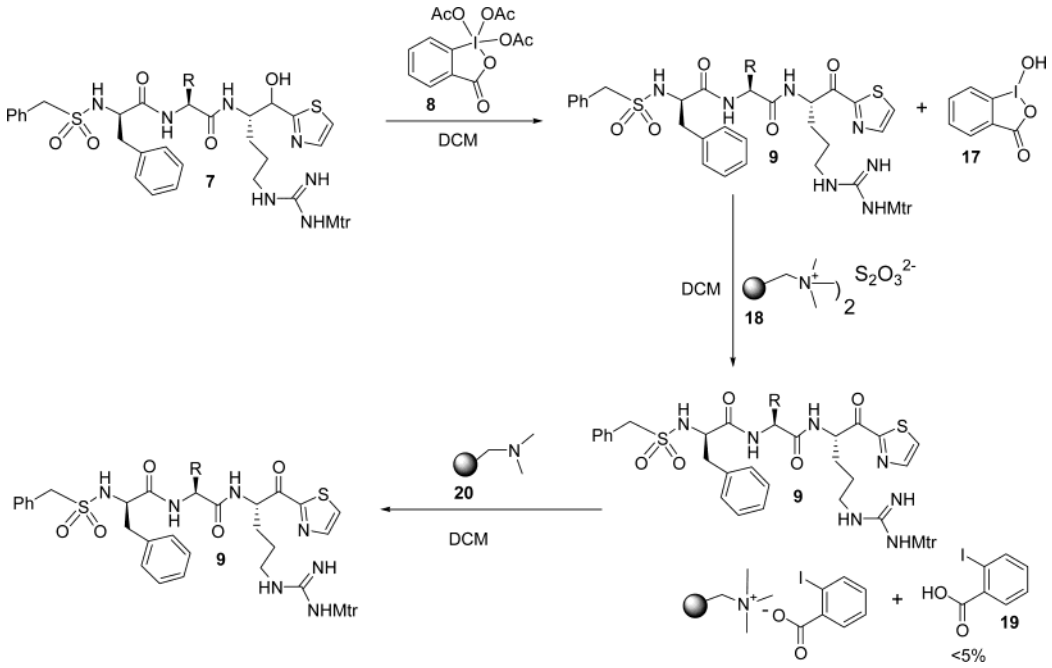


The first step of the synthesis (Scheme 2) involved an amide coupling using the starting scaffold[31] **3** and a variety of BOC protected L-amino acids **1**. The amino acids **1** were incubated with the polymer-bound carbodiimide **11**, hydroxybenzotriazole **12**, and a catalytic amount of Hunig's base **13** to afford the activated esters **2**. Diisopropylaminomethyl resin **14** and a limiting amount of the amine hydrochloride salt **3** were added to each reaction vessel. An excess of the polymer-bound base, diisopropylaminomethyl resin **14**, was used to generate the free amine of scaffold **3** since it existed as a dihydrochloride salt. After total consumption of the scaffold **3** was observed, the reaction mixture was diluted with dimethylformamide to accommodate the addition of sequestering resins. A mixed-resin bed of the polyamine resin **16** and carbonate resin **15** were added to sequester the hydroxybenzotriazole **12**, activated ester **2**, and any remaining amino acid **1**. Acylation of the hydroxy group was observed as a minor impurity (<8%) in some of the product mixtures when using a small amino acid input. As a result, the combination of both basic resins **15** and **16** was used and incubated for a period of 20 h, resulting in hydrolysis of the ester. Simple filtration and rinsing with dimethylformamide yielded a filtrate, whereupon evaporation of the solvents left highly purified product **4** from each parallel reac-

Scheme 3. Amino Acid Inputs



Scheme 4. Oxidation of Alcohol to Ketone



tion. The products were characterized by LC/MS and carried on to the next step of the synthesis. A representative set of BOC protected amino acids used for the amide coupling is depicted in Scheme 3.

The next step of the synthesis involved a straightforward deprotection of the BOC group using 4 N hydrochloric acid in dioxane to afford the amine hydrochloride salts **5** (Scheme 1). The third step of the synthesis was an amide coupling using the amine intermediate **5** and *N*-(benzylsulfonyl)-D-phenylalanine **6** (Scheme 1). The same reaction conditions were applied from step 1 (Scheme 2) except that the sequestration process involved using only the polyamine resin **16**. The carbonate resin **15** was omitted in this step as the desired products **7**, possessing an acidic proton from the sulfonamide, are sequestered by the strongly basic carbonate resin **15**.

The oxidation of the alcohol **7** to ketone **9** using a PASP purification protocol is shown in Scheme 4.[32] A mild oxidizing agent was required that would tolerate the functionalities present within the library members. Several oxidizing conditions were attempted and the periodinane Dess−Martin reagent **8** proved superior. The alcohol **7** was oxidized with an excess of the periodinane reagent **8** to drive the reaction to completion, affording a product mixture containing the desired ketone **9**, excess oxidizing agent **8**, and a reactant byproduct **17**. The thiosulfate resin **18** was added to the product mixture, which reduced the excess Dess−Martin reagent **8** and the I^{III} byproduct species **17** to the sequesterable 2-iodobenzoic acid **19** (I^{I} species). In addition, the thiosulfate resin **18** sequestered the majority of the 2-iodobenzoic acid **19**. Amberlyst A-21 **20** was

Table 1. IC_{50} Values of α-Ketothiazoles **10**

	IC_{50} (uM)			
compd **10**	VIIa	IIa	Xa	VIIa/IIa
a	1.45	100	2.4	69
b	0.11	0.04	0.24	0.4
c	0.30	19.3	0.38	64
d	0.82	9.20	2.12	11
e	0.70	0.44	1.03	0.6
f	1.03	60	2.1	58
g	13.7	12.9	2.0	1
h	2.82	15.4	1.7	5
i	3.30	24.2	2.70	7
j	0.042	4.0	0.027	95
k	0.20	100	0.29	500
l	0.76	3.19	0.38	4
m	0.09	>30	0.21	>333
n	0.20	15	0.25	75
o	0.17	3.15	0.185	19
p	0.80	84.9	1.0	106
q	0.16	11.2	0.21	70
r	0.19	6.82	0.18	36
s	0.20	-	0.25	-
t	0.24	21.7	0.33	90
u	0.17	12.0	0.16	71
v	1.29	7.48	0.57	6
w	0.70	28.1	2.77	40
x	0.23	14.6	0.27	63
y	0.68	3.42	0.61	5
z	1.56	6.3	0.50	4
aa	0.34	50	0.90	147
bb	5.88	>30	2.18	>5
cc	0.57	4.59	0.30	8
dd	9.97	9.92	2.4	1
ee	1.95	2.4	0.77	1
ff	5.6	>30	1.8	>5
gg	0.50	15.4	0.15	3
hh	1.53	9.89	0.31	6
ii	17.8	11.2	3.14	1
jj	1.83	1.68	1.07	1
kk	0.90	10.4	0.54	12
ll	3.18	4.99	1.25	2

added to sequester the remaining acid **19**. Strongly basic resins, such as polymer-bound 1,3,5-triazabicylcodec-5-ene (TBD), were avoided at this step due to sequestration of the product. Simple filtration and rinsing with dichloromethane yielded a filtrate, whereupon evaporation of the solvents left purified products **9** from each parallel reaction. The products were characterized by LC/MS and carried on to the next step of the synthesis.

The last step of the synthesis involved deprotection of the 2,3,6-trimethyl-4-methoxybenzenesulfonyl (Mtr) protecting group to afford the unprotected guanidine. Thioanisole was added to the ketones **9** in trifluoroacetic acid. Upon completion of the reaction, the solvent was evaporated and the residue was triturated to afford desired product **10** from each reaction chamber. The HPLC purities and overall yields for the desired α-ketothiazoles **10** are listed in Table 2 in Supporting Information. Purity levels ranged from 70 to 99% with an average purity level of 82%. The yields ranged from 9 to 45% based on mass recovery. Considering that this is a five-step synthesis, with a portion of the sample taken for characterization of each intermediate and the physical manipulation of the reaction mixtures to and from the reaction block, these are quite acceptable overall yields (i.e., 80% yield for each reaction of a five step synthesis affords an overall 33% yield).

The compounds **10a**−**ll** were screened for potency on TF/VIIa and for other enzymes affecting coagulation, such as Factor Xa and Thrombin (IIa), to determine specificity (Table 1). Each enzyme assay consisted of the specific enzyme and chromogenic substrate for that

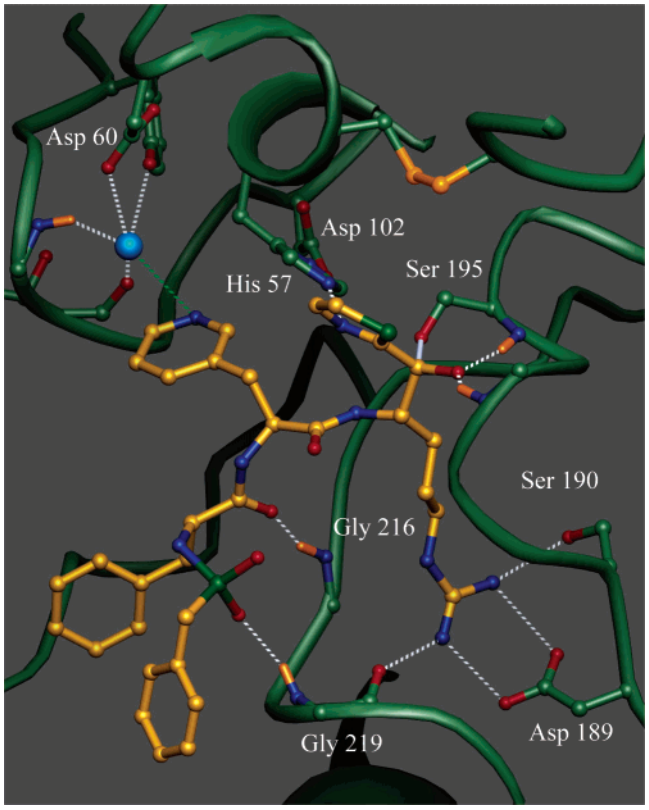


Figure 1. Crystal structure of ketothiazole inhibitor **10K** bound in the active site of TF/VIIa complex. Some of the key side chains of Factor VIIa are displayed (C: green, N: dark blue, O: red, S: yellow, H: orange). The carbon atoms of the inhibitor are shown in gold color. The hydrogen bonds formed by the inhibitor and a bound water molecule in the S_2 site are shown in dotted white lines. The close interaction between the bound solvent and the pyridyl nitrogen of the inhibitor is shown in the dotted green line. The active site serine, Ser 195, forms a covalent bond (thin solid line) with the activated carbon of the inhibitor.

enzyme. Enzyme activity was determined by monitoring the increase in absorbance at 405 nm caused by the release of *p*-nitroaniline when the substrate is hydrolyzed. Inhibition of the enzyme reduces the change in absorbance with the data reported as IC_{50} values. Several of the intermediate alcohols **7** were not oxidized to the ketone and tested as α-hydroxythiazoles. As anticipated, the unoxidized compounds showed no biological activity. All of the α-ketothiazoles **10** prepared were active against TF/VIIa with IC_{50} values ranging from 0.042 to 17.8 uM. The most potent compound of the library was **10j** with the L-amino acid as phenylalanine. The TF/VIIa activity was fairly flat across the set of compounds with the substituted phenylalanine derivatives exhibiting consistent activity with IC_{50}'s below 1 uM. A key requirement for the program was to demonstrate that selectivity of TF/VIIa over thrombin could be achieved. Several compounds, **10k**,**m**,**p**,**aa**, have selectivity ratios (VIIa/IIa) of greater than 100, with **10k** having a selectivity factor of 500. These selectivity factors confirmed that a potent TF/VIIa inhibitor with selectivity versus thrombin could be attained.

An X-ray crystal structure of compound **10k** bound in the active site of TF/VIIa complex was obtained to gain a better understanding of the structural differences responsible for selectivity (Figure 1). The ketothiazole

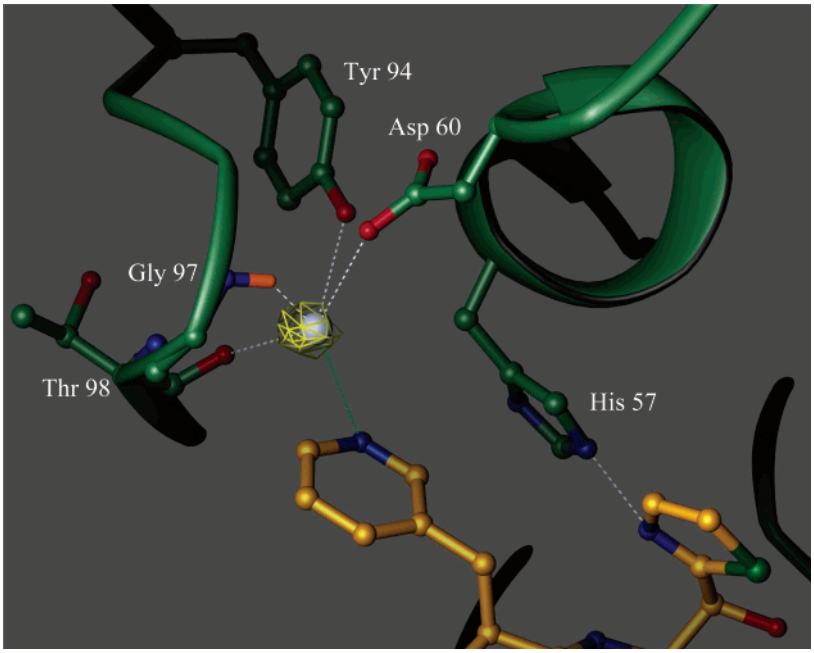


Figure 2. Expanded view of the bound solvent molecule in the S_2 pocket. Shown in yellow is the $|F_o| - |F_c|$ electron density contoured at 3.0σ. The atoms are colored as in Figure 1. The hydrogen bonds formed by the solvent are shown in dotted white lines while the close interaction between the water molecule and the pyridyl nitrogen is shown in the dotted green line.

inhibitor **10k** is bound well in the active site of TF/VIIa, forming several hydrogen bonding interactions with the protein atoms. The arginine side chain at P_1 forms four strong hydrogen bonds at the bottom of the S_1 pocket with the side chains of Asp 189 and Ser 190 as well as to the backbone carbonyl oxygen of Gly 219. The active site serine, Ser 195, forms a covalent bond to the activated carbon of the inhibitor as expected. This results in the formation of a transition state analogue. The resulting hydroxyl group binds in the oxyanion hole, forming two hydrogen bonds with the amide nitrogen of Gly 193 and Ser 195. The thiazole ring stacks parallel to the side chain of active site histidine, His 57, with a hydrogen bond between the nitrogen of the thiazole and one of the nitrogens of the histidine side chain. The inhibitor forms two other hydrogen bonds with peptide nitrogens of Gly 216 and Gly 219.

The side chain pyridyl ring traps a water molecule at the S_2 site of the enzyme active site (Figure 2). The bound solvent molecule forms hydrogen bonding interactions with the side chains of Asp 60 and Tyr 94. In addition, two other hydrogen bonds are formed by the solvent molecule with the backbone atoms of Gly 97 and Thr 98. Moreover, the pyridyl nitrogen of the inhibitor is 3.0 Å away from the water molecule although the geometry is not appropriate for a direct hydrogen bond. The pyridyl ring of the inhibitor is almost orthogonal to the plane of the His 57 side chain. The S_2 pocket of Factor VIIa is relatively open and has a negative potential due to the presence of Asp 60. The pyridyl group of the inhibitor takes advantages of these structural features to form strong interactions in the S_2 pocket of VIIa. Among the coagulation proteases, only Factor VIIa has a negatively charged residue at position 60. Thrombin has a large insertion in the S_2 pocket with a number of aromatic amino acid residues. These structural differences would account for the enhanced selectivity of compound **10k** for TF/VIIa over thrombin.

Conclusion

A series of α-ketothiazoles with the structure $BzSO_2$-D-Phe-L-AA-Arg- α-ketothiazole was synthesized using combinations of polymer-assisted solution-phase purification concepts. The compounds were screened for potency on TF/VIIa and for other enzymes affecting coagulation to determine specificity (Table 1). All of the compounds exhibited activity on tissue Factor VIIa with IC_{50}'s ranging from 0.042 to 17 uM. Several compounds have excellent selectivity for TF/VIIa over thrombin, such as compound **10k** with a selectivity ratio (IIa/VIIa) of 500, demonstrating that selectivity of TF/VIIa over thrombin can be achieved. The structural information from the X-ray crystal structure of compound **10k** from this study, combined with the crystal structure of other related serine proteases such as thrombin and Factor Xa, facilitated the development of a noncovalent-reversible nonpeptidic tissue Factor VIIa inhibitor which will be the topic of a future publication.

Experimental Section

General. Solvents and chemicals were reagent grade or better and were obtained from commercial sources. All BOC protected amino acids were obtained from commercial sources. PS-carbodiimide resin, PS-DIEA, PS-polyamine resin, and MP-carbonate resin were purchased from Argonaut Technologies. Amberlyst A-21 was purchased from Sigma-Alrich Chemical Company. ^1H and ^{13}C NMR spectra were recorded using a 300 or 400 MHz NMR spectrometer. Sample purities were determined by HPLC analysis equipped with a mass spectrometer detector using a C18 3.5 μm 30 × 2.1 mm column, eluting with a gradient system of 5/95 to 95/5 acetonitrile/H_2O with a buffer consisting of 0.1% TFA over 4.5 min at 1 mL/min and detected by ELS. Reported yields are not optimized, with emphasis on purity of products rather than quantity. Recombinant soluble TF, consisting of amino acids 1−219 of the mature protein sequence was expressed in *E. coli* and purified using a Mono Q Sepharose FPLC. Recombinant human VIIa was purchased from American Diagnostica, Greenwich CT. Chromogenic substrate *N*-methylsulfonyl-D-phe-gly arg-*p*-nitroaniline was

prepared by American Peptide Company, Inc., Sunnyvale, CA. Factor Xa was obtained from Enzyme Research Laboratories, South Bend IN, thrombin from Calbiochem, La Jolla, CA, and trypsin and L-BAPNA from Sigma, St. Louis, MO. The chromogenic substrates S-2765 and S-2238 were purchased from Chromogenix, Sweden.

General Procedure A. Coupling of Amino Acids 1 with Amine Scaffold 3 to Afford Product 4. The amino acid **1** (0.60 mmol) was added to each reaction vessel containing hydroxybenzotriazole **12** (0.65 M in dimethylformamide) (1.0 mL, 0.65 mmol), *N*,*N*-diisopropylethylamine (0.20 M in dimethylformamide) (0.25 mL, 0.05 mmol), and PS-carbodiimide resin **11** (1.91 mequiv/g) (0.34 g, 0.658 mmol). Dichloromethane (2.0 mL) was added to each well to ensure effective mixing. The vials were agitated by orbital shaking for 15 min. The amine scaffold **3** (0.30 M in dimethylformamide) (1.0 mL, 0.30 mmol) was added along with PS-DIEA resin **14** (3.86 mequiv/g) (0.35 g, 1.35 mmol), and the vials were agitated by orbital shaking for 3.5 h. Additional dimethylformamide (2.0 mL) was added along with PS-polyamine resin **16** (4.78 mequiv/g) (0.50 g, 2.4 mmol) and MP-carbonate resin **15** (2.81 mequiv/g) (0.50, 1.4 mmol), and the vials were agitated by orbital shaking overnight (approx 20 h). The reaction mixtures were filtered and rinsed four times with 2.0 mL of dimethylformamide. The combined filtrate and washings were evaporated to afford pure product **4**.

General Procedure B. Deprotection of the BOC Group of Compounds 2 to Afford the Amine Hydrochloride Salts 5. Hydrochloric acid in 1,4-dioxane (4.0 N, 3 mL) was added to the BOC protected amine **4** (∼0.3 mmol) in a reaction vessel, and the solution was agitated on an orbital shaker at room temperature for 3 h. Evaporation of the solvents afforded the product **5**.

General Procedure C. Coupling of *N*-(Benzylsulfonyl)-D-phenylalanine 6 with Amine 5 to Afford Product 7. The *N*-(benzylsulfonyl)-D-phenylalanine **6** (0.60 mmol) was added to each reaction vessel containing hydroxybenzotriazole **12** (0.60 M in 1/1 dimethylformamide/dichloromethane) (1.0 mL, 0.60 mmol), *N*,*N*-diisopropylethylamine (0.20 M in dimethylformamide) (0.25 mL, 0.05 mmol), and PS-carbodiimide resin **11** (1.91 mequiv/g) (0.34 g, 0.658 mmol). Dichloromethane (2.0 mL) was added to each well to ensure effective mixing. The vials were agitated by orbital shaking for 15 min. The amine **5** (0.20 M in dimethylformamide) (1.5 mL, ∼0.3 mmol) was added along with PS-DIEA resin **14** (3.86 mequiv/g) (0.35 g, 1.35 mmol), and the vials were agitated by orbital shaking for 6 h. Additional dimethylformamide (3.0 mL) was added along with PS-polyamine resin **16** (4.78 mequiv/g) (1.28 g, 6.1 mmol), and the vials were agitated by orbital shaking overnight (approx 17 h). The reaction mixtures were filtered and rinsed four times with 2.0 mL of dimethylformamide. The combined filtrate and washings were evaporated to afford pure product **7**.

General Procedure D. Oxidation of Alcohol 7 to Afford Ketone Product 9. The Dess−Martin periodinane reagent **8** (0.30 M in dichloromethane) (1.0 mL, 0.30 mmol) was added to the alcohol **7** (∼0.30 mmol) in 2.0 mL of dichloromethane, and the vials were agitated by orbital shaking for 2 h. Upon completion of the reaction, the thiosulfate resin **18** (1.73 mmol/g) (1.0 g, 1.7 mmol) was added followed by 3.0 mL of dichloromethane, and the vials were agitated by orbital shaking for 3 h. The Amberlyst A-21 resin **20** (4.81 mmol/g) (0.40 g, 1.9 mmol) was added followed by 3.0 mL of dichloromethane, and the vials were agitated by orbital shaking for 3 h. The reaction mixtures were filtered and rinsed four times with 2.0 mL of dimethylformamide. The combined filtrate and washings were evaporated to afford pure product **9**.

General Procedure E. Deprotection of the Mtr Group to Afford Desired α-Ketothiazole 10. Thioanisole (100 uL, 0.85 mmol) was added to the ketone (∼0.3 mmol) in trifluoroacetic acid (2.0 mL), and the vials were agitated by orbital shaking for 5 h. Upon completion of the reaction, the product mixture was evaporated by a stream of nitrogen and placed under high vacuum for 24 h to afford the crude product **10**. The product was purified by trituration with ether and then ethyl acetate followed by filtration to afford the pure product **10**. The products were characterized by LC/MS and HRMS with yields based on mass recovery as shown in Table 2 in Supporting Information.

Assays for Biological Activity. TF−VIIa Assay. Recombinant soluble tissue factor (100 nM) and recombinant human Factor VIIa (2 nM) were added to a 96-well assay plate containing 0.4 mM of the substrate, *N*-methylsulfonyl-D-phegly arg-*p*-nitroaniline, and either inhibitor or buffer (5 mM $CaCl_2$,50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 μL, was measured immediately at 405 nm to determine background absorbance. The plate was incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate was measured by monitoring the reaction at 405 nm for the release of *p*-nitroaniline. All compounds were assayed in duplicate at seven concentrations. Percent inhibition at each concentration was calculated from $OD_{405\ nm}$ value from the experimental and control sample. IC_{50} values were calculated from a four-parameter logistic regression equation. For each compound the individual IC_{50} values were within 10% of each other. The reported IC_{50} represents an average of the duplicates.

Xa Assay. Human Factor Xa (0.3 nM) and *N*-α-benzyloxycarbonyl-D-arginyl-L-glycyl-L-arginine-*p*-nitroaniline dihydrochloride (S-2765) (0.15 mM) were added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 uL, was measured immediately at 405 nm to determine background absorbance. The plate was incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate is measured by monitoring the reaction at 405 nm for the release of *p*-nitroaniline. All compounds were assayed in duplicate at seven concentrations. Percent inhibition at each concentration was calculated from $OD_{405\ nm}$ value from the experimental and control sample. IC_{50} values were calculated from a four-parameter logistic regression equation. For each compound the individual IC_{50} values were within 10% of each other. The reported IC_{50} represents an average of the duplicates.

Thrombin Assay. Human thrombin (0.28 nM) and *H*-D-phenylalanyl-L-pipecolyl-L-arginine-*p*-nitroaniline dihydrochloride (0.06 mM) were added to a 96-well assay plate containing either inhibitor or buffer (50 mM Tris-HCl, pH 8.0, 100 mM NaCl, 0.1% BSA). The reaction, in a final volume of 100 μL, was measured immediately at 405 nm to determine background absorbance. The plate was incubated at room temperature for 60 min, at which time the rate of hydrolysis of the substrate was measured by monitoring the reaction at 405 nm for the release of *p*-nitroaniline. All compounds were assayed in duplicate at seven concentrations. Percent inhibition at each concentration was calculated from OD_{405nm} value from the experimental and control sample. IC_{50} values were calculated from a four-parameter logistic regression equation. For each compound the individual IC_{50} values were within 10% of each other. The reported IC_{50} represents an average of the duplicates.

Crystal Structure. Crystals of TF/VIIa complex were obtained by slight modification of the procedure described by Banner et al. (ref 20). Diffraction data 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_{work}: 22.2%).

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ported by the corporate members of the IMCA and through a contract with Illinois Institute of Technology (IIT), executed through the IIT's Center for Synchrotron Radiation Research and Instrumentation. Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under Contract No. W-31-109-Eng-38.

Supporting Information Available: A table of yields and HPLC purities of α-ketothiazole products **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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