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Novel, Potent Non-Covalent Thrombin Inhibitors Incorporating P_3-Lactam Scaffolds

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Abstract—Evolution of P_1-argininal inhibitor prototypes led to a series of non-covalent P_3-7-membered lactam inhibitors **1a**–**w**, featuring novel peptidomimetic units that probe each of the S_1, S_2, and S_3 specificity pockets of thrombin. Rigid P_1-arginine surrogates possessing a wide range of basicity (calcd pK_a's ~ neutral–14) were surveyed. The design, synthesis, and biological activity of these targets are presented.

Thrombin (fIIa), a multifunctional serine protease with trypsin-like specificity, plays a central role in hemostasis by regulating the blood coagulation cascade and platelet activation.[1] It also promotes numerous cellular events including chemotaxis, proliferation, extracellular matrix turnover and the release of cytokines. These actions have been implicated in tissue repair processes and in the pathogenesis of inflammatory and fibroproliferative disorders such as pulmonary fibrosis and atherosclerosis.[2] Thrombin is formed by prothrombinase-mediated (PTase, complex of fXa-fVa-phospholipid-Ca^{+2}) cleavage of the zymogen prothrombin following tissue injury. Serving as the terminal enzyme of the coagulation pathway, thrombin cleaves fibrinogen to fibrin, which in combination with fXIII and platelets aggregates to a gel-like matrix, ultimately leading to the formation of blood clots.[3] Thromboembolic diseases are a major cause of morbidity and mortality in the industrialized world. Limited efficacy and side effects of common antithrombotic drugs including heparin,

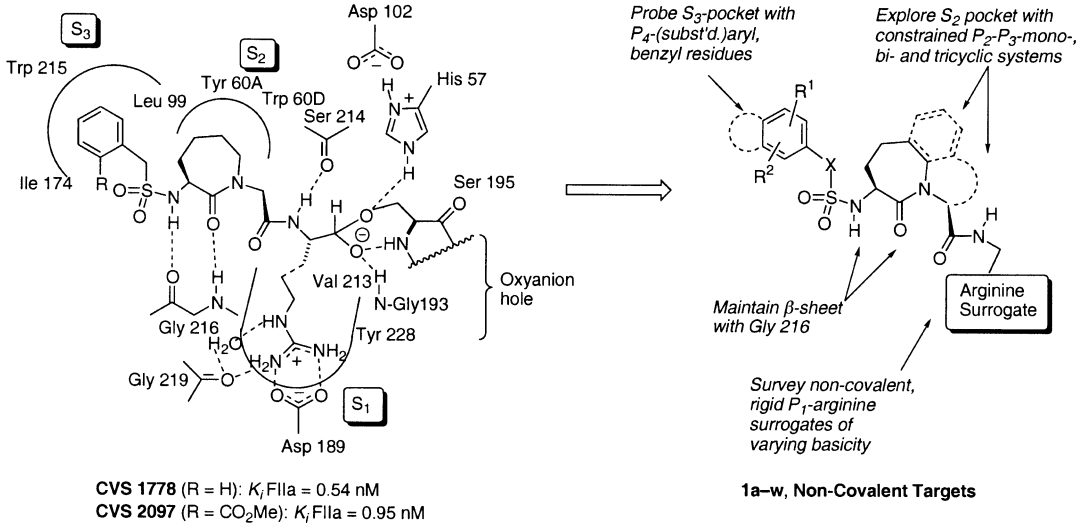

Figure 1. Design of P_3-lactam thrombin inhibitors **1a**–**w**.

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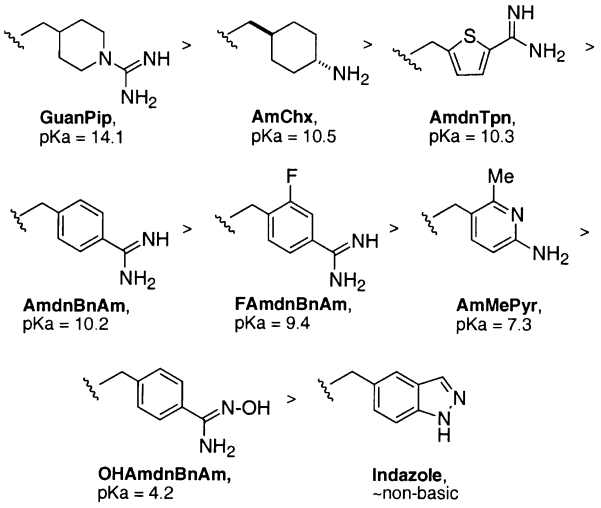


Figure 2. Acronyms and calculated pK_a values for representative rigidified P_1-arginine surrogates.

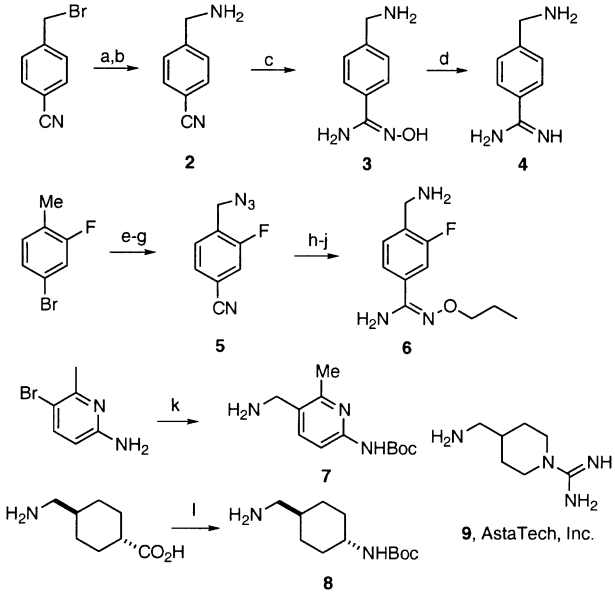
warfarin, and aspirin has provided an impetus for the development of alternate classes of antithrombotic agents.[4] Thus, direct inhibitors of thrombin, factor Xa (fXa) and prothrombinase (PTase) are deemed attractive targets for therapeutic intervention.[4,5] In this letter, we detail our foray into the design, synthesis, and SAR study of non-covalent thrombin inhibitors that resulted in the identification of the novel, potent P_3-lactam-P_1-arginine mimics **1a**–**w**.[6]

We recently described new classes of peptidomimetic P_1-argininals as thrombin[7] and factor Xa[8] inhibitors that incorporated lactam and heterocyclic scaffolds at the P_3-position. Several potent, selective, and orally bioavailable transition-state inhibitors emerged from this work. The prototypical 7-membered lactams **CVS 1778** and **CVS 2097** (Fig. 1) showed superior in vitro potency against thrombin, selectivity towards other important serine proteases, and demonstrated 66 and 67% oral bioavailability in fasted dogs, respectively.[7c,9] Although these candidates showed interesting biological profiles, the presence of the P_1-argininal moiety posed problems with regard to scale-up, purification, and long-term configurational stability. Furthermore, the high basicity of the guanidine function (pK_a ~12.5) negatively impacted the pharmacokinetic (PK) profiles of some of these inhibitors by making them susceptible to active or 'facilitated' intestinal transport mechanisms.[10] This mode of drug transport may lead to undesirable food effects and rapid excretion, often resulting in sub-optimal drug plasma levels and relatively short half-lives (typically 1 to 4 h for P_1-argininals).[11]

SAR, modeling, and topographic considerations of our lead series led us to design and prepare the non-covalent P_3-lactam inhibitor prototypes **1a**–**w**. As summarized in Figure 1, our approach was to judiciously combine intrinsically potent P_4-sulfonamido-P_3-lactam arrays with rigidified P_1-mono- and bicyclic arginine surrogates[12] possessing a wide range of basicity (calcd pK_a's ~neutral–14). Arginine mimics investigated are listed in Figure 2 in order of decreasing basicity and are identified by the indicated acronyms (see SAR Table 1).

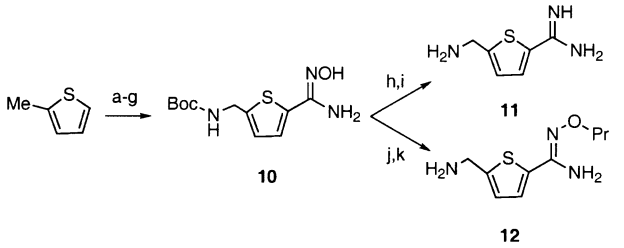
The calculated pK_a values[13] for several prototypical P_1 arginine surrogates are listed and range from the highly basic cyclic guanidine (GuanPip) through the essentially non-basic indazole (H-bond donor). Novel peptide mimics that probe the S_1, S_2, and S_3 specificity pockets of thrombin comprise the resultant targets. Several potent and selective thrombin inhibitors resulted from this exercise.

Synthetic routes to the rigid P_1-arginine mimic precursors are outlined in Schemes 1 and 2.[14] 4-Amidinobenzyl intermediates **2**, **3**, and **4** were prepared from *p*-cyanobenzyl bromide by straightforward, high-yielding methods. 2-Fluoro-4-amidinobenzylamine intermediate **6** was assembled in six steps in satisfactory overall yield from commercial 4-bromo-2-fluoro-toluene via benzyl azide **5**. *N*-Boc-protected aminopyridine **7**[4c] and cyclohexylamine **8**[15] were prepared in three steps and five steps, respectively, following literature protocols. Guanidine **9** was commercially available from AstaTech, Inc.



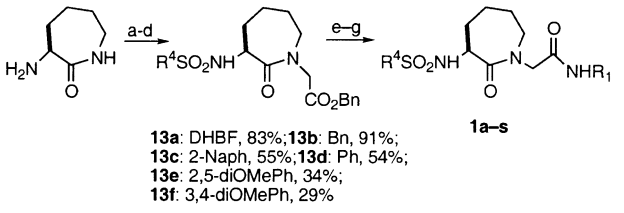
Scheme 1. Reagents and conditions: (a) NaN_3, DMF, rt, 5 h, 96%; (b) H_2, Pd/C, EtOAc, 45 psi, 11 h, 93%; (c) $NH_2OH \cdot HCl$, NMM, MeOH, rt, 3 days, 89%; (d) H_2, Pd/C, MeOH, 45 psi, 11 h, 99%; (e) CuCN, DMF, reflux, 11 h, 58%; (f) NBS, $(PhCOO)_2$, CCl_4, reflux, 14 h, 42%; (g) NaN_3, DMF, rt, 20 h, 86–90%; (h) $NH_2OH \cdot HCl$, NMM, MeOH, rt, 3 days, 82%; (i) *n*-PrI, Cs_2CO_3, DMF, 50 °C, 20 h, 62%; (j) Ph_3P, THF, rt, 20 h, 77–89% (k) 3 steps, see ref 4c; (l) 5 steps, see ref 15.

The P_1-amidinothiophene precursors **11** and **12** were constructed by a nine-step sequence as outlined in Scheme 2. Using conventional methodology, 2-methylthiophene was elaborated over 7 steps to provide multigram lots of the P_1-hydroxyamidine intermediate **10**. Direct catalytic reduction of **10** and *N*-deprotection led to the parent amidinothiophene P_1-intermediate **11**. Alternatively, **10** was cleanly *O*-alkylated and *N*-deprotected to afford the convenient precursor **12** in high yield.



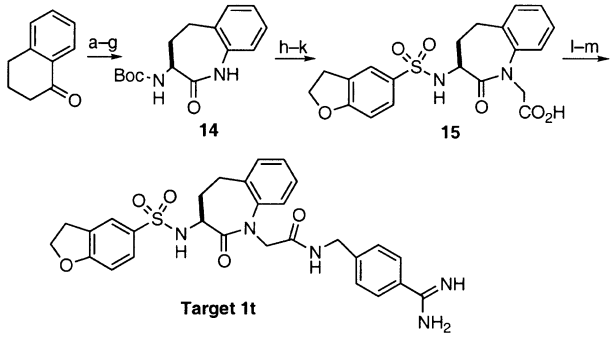
Scheme 2. Reagents and conditions: (a) NBS, CCl_4, $HClO_4$, 84%; (b) CuCN, DMF, reflux, 4 h, 87%; (c) NBS, AIBN, CCl_4, reflux, 5 h, 91%–quant; (d) NaN_3, DMF, rt, 10 h, 83%–quant.; (e) Ph_3P, THF, H_2O, 0 °C to rt, 94%; (f) Boc_2O, K_2CO_3, dioxane, H_2O, rt, 12 h, 56%; (g) $NH_2OH{\cdot}HCl$, NMM, MeOH, rt, 12 h, 86%; (h) H_2, Pd/C, MeOH, 45 psi, 10 h, 94%; (i) 4 M HCl, dioxane, 0 °C to rt, 3 h, 84%; (j) *n*-PrI, Cs_2CO_3, DMF, rt, 10 h; (k) 4 M HCl, dioxane, 0 °C to rt, 3 h, 81% overall.

Assembly of the P_3-azepinonecarboxylic acid intermediates **13a**–**f** and elaboration to targets **1a**–**s** is summarized in Scheme 3 (note: DHBF = 2,3-dihydrobenzofuran-5-yl). Following a variation of our published protocol,[7,9] ε-aminocaprolactam was converted in 4 steps and in satisfactory overall yield to benzyl esters **13a**–**f**. Ester hydrogenolysis delivered the corresponding carboxylic acids, which were coupled with the appropriate P_1-arginine precursors **2**–**12** and the resultant penultimate intermediates were either *N*-deprotected or reduced to provide the desired final targets **1a**–**s**. Representative deprotection conditions are summarized in Scheme 3 and illustrate the breadth of chemistry used for completion of the targets **1c**,**e**,**i**,**k**,**p**,**r**,**s**.



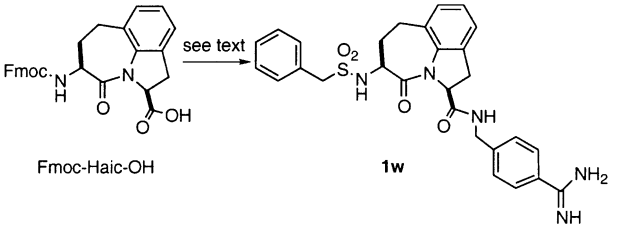
Scheme 3. Reagents and conditions: (a) Boc_2O, K_2CO_3, THF, rt, 18 h, 99%; (b) LiHMDS, THF, 35 °C; $BrCH_2CO_2Bn$, 0 °C to rt, 15 h, 97%; (c) 5 M HCl, EtOAc, 0 °C to rt, ~quant.; (d) R^4SO_2Cl, Et_3N or NMM, CH_3CN, 0 °C to rt, 29–83%; (e) H_2, Pd/C, MeOH:toluene (3:1), 45 psi, 12–24 h, 62% to ~quant.; (f) couple P_1-amine: NMM, DMF, rt, 7–14 h, BOP or EDC/HOBt, 45–99%; (g) deprotect P_1-group: for **1c**: H_2, Pd/C, MeOH, 45 psi, 13 h, RP-HPLC, 65%; for **1e**: Zn, HOAc, rt, 2 h; RP-HPLC, 44% overall; for **1i**: Zn, HOAc, rt, 2 h; RP-HPLC, 70%; for **1p**: TFA, CH_2Cl_2, 50 °C, 30 min, RP-HPLC, 59% overall; for **1r**: 5 M HCl, EtOAc, rt, 2 h, RP-HPLC, 77% overall; for **1s**: 4 M HCl, dioxane, rt 2 h, RP-HPLC, 26%.

Synthesis of the benzolactam target **1t** is outlined in Scheme 4. α-Tetralone was converted to **14** via the following 7-step protocol. Beckmann rearrangement of the requisite oxime intermediate,[16] three-step elaboration to racemic 3-aminobenzolactam, classical resolution or 'racemization-resolution' (preferred),[8d,17] followed by protection of the resultant chiral amine intermediate delivered optically pure **14** in multigram lots. Employing similar methodology as described above, intermediate **14** was elaborated over four steps to carboxylic acid **15**. Standard EDC-HOBt mediated coupling of **15** with amine **2**, reaction of the resultant P_1-nitrile with hydroxylamine to provide P_1-hydroxyamidine **1u** (Table 1), and catalytic reduction afforded the target **1t**.



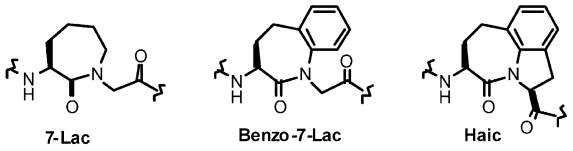
Scheme 4. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, rt to reflux, 95%; (b) PPA, 115 °C, 5 min, 50–70%; (c) TMSCl, TMEDA, NaI, CH_3CN, −5 °C; (d) I_2, −5 °C to rt, 95%; (e) NH_3, aq EtOH, 0 °C to rt, 70–80%; (f) L-Pyroglutamic acid, 95% aq *i*-PrOH, reflux; concd NH_4OH, 40–45%, or via racemization-resolution: L-Pyroglutamic acid, 95% aq *i*-PrOH, 5-NO_2-salicylaldehyde, 70 °C, 2 days, 80–85% (~98% ee); (g) Boc_2O, Na_2CO_3, dioxane, H_2O, rt, 18 h, 99%; (h) LiHMDS, THF, 0 °C, $BrCH_2CO_2Bn$, 0 °C to rt, 92%; (i) 5 M HCl, EtOAc, 0 °C to rt, ~quant.; (j) 2,3-dihydrobenzofuran-5-sulfonyl chloride, NMM, DMF, rt, 57%; (k) H_2, Pd/C, MeOH, 45 psi, 3 h, 97%; (l) 4-cyanobenzylamine, EDC, HOBt, NMM, DMF, 83%; (m) $NH_2OH{\cdot}HCl$, NMM, MeOH, rt, 10 h, 51% (**1u**); (n) H_2, Pd/C, MeOH, 45 psi, 2 days; RP-HPLC purification, 49%.

Fmoc-aminohexahydroazepinoindole-4-one-2-carboxylic acid, (Fmoc-Haic-OH)[18] serving as the starting material for the P_2-P_3-tricyclic 'Haic' target **1w**, was purchased from Neosystem Laboratories, Strasbourg, France. This material was elaborated via similar approaches (esterification, *N*-deprotection, sulfonylation, hydrolysis, coupling with **2**, reaction with $HONH_2$, hydrogenolysis, RP-HPLC purification) to the target **1w** in satisfactory overall yield.



The in vitro biological activity of 23 non-covalent targets **1a**–**w** along with the argininal standards **CVS 1778** and **CVS 2097**[7c,9] is summarized in Table 1. All targets were inactive on the thrombolytic enzymes plasmin, tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) as well as activated protein C (PCa). **CVS 1778** and **CVS 2097** were potent inhibitors of thrombin in vitro, exhibiting good selectivity against factor Xa and moderate selectivity against trypsin (trypn). Moderate to excellent levels of thrombin inhibitory potency were observed for several new targets, with K_i's = 0.6–61 nM for our leading candidates. Targets of greatest interest in terms of activity and/or selectivity profiles include **1b**, **1c**, **1f**, **1i** (most potent), **1k** (good potency, high trypsin selectivity), **1p** (moderate potency, highest trypsin selectivity), **1v**, and **1w**.

Table 1. In vitro activity of non-covalent P_3-lactam thrombin inhibitors **1a**–**w** (R_4SO_2-P_3-P_2-P_1)



Compd	R_4SO_{2-}	P_3-P_2	P_1	K_i Values (nM)[a]			
				FIIa	FXa	Trypn	Trypn/FIIa
Reference Covalent Inhibitors							
CVS 1778	$BnSO_2$	7-Lac	Arg-al	0.54	40	18.0	33.3
CVS 2097	(2-CO_2Me)-$BnSO_2$	7-Lac	Arg-al	0.95	93	16.0	16.8
Non-Covalent Targets							
1a	$PhSO_2$	7-Lac	AmdnBnAm	19.4	> 338	8.3	0.4
1b	$BnSO_2$	7-Lac	AmdnBnAm	19.4	315.0	84.6	4.4
1c	5-(2,3-DH Benzofuran)SO_2	7-Lac	AmdnBnAm	6.2	> 338	3.2	0.5
1d	5-(2,3-DH Benzofuran)SO_2	7-Lac	OHAmdnBnAm	239.7	Inact.	80.5	0.3
1e	5-(2,3-DH Benzofuran)SO_2	7-Lac	FAmdnBnAm	29.8	> 338	7.6	0.3
1f	2,5-diOMePhSO_2	7-Lac	AmdnBnAm	9.0	> 338	35.2	3.9
1g	3,4-diOMePhSO_2	7-Lac	AmdnBnAm	13.3	> 338	11.6	0.9
1h	2-NaphSO_2	7-Lac	AmdnBnAm	163.5	> 338	12.3	0.1
1i	5-(2,3-DHBenzofuran)SO_2	7-Lac	AmdnTpn	0.6	52.7	5.9	10.7
1j	$PhSO_2$	7-Lac	GuanPip	71.4	> 338	1678.0	23.5
1k	5-(2,3-DHBenzofuran)SO_2	7-Lac	GuanPip	23.8	Inact.	872.5	36.7
11	3,4-diOMePhSO_2	7-Lac	GuanPip	85.7	> 338	> 1678	> 19.6
1m	2,5-diOMePhSO_2	7-Lac	GuanPip	166.7	Inact.	Inact.	
1n	$BnSO_2$	6-Lac	AmMePyr	> 397	Inact.	> 1678	~4.2
1o	$BnSO_2$	7-Lac	AmMePyr	92.9	Inact.	1678.0	18.0
1p	5-(2,3-DH Benzofuran)SO_2	7-Lac	AmMePyr	39.5	> 338	1678.0	42.5
1q	$BnSO_2$	7-Lac	AmChx	195.2	Inact.	Inact.	
1r	5-(2,3-DH Benzofuran)SO_2	7-Lac	ArnChx	53.2	Inact.	> 1678	> 31.5
1s	5-(2,3-DH Benzofuran)SO_2	7-Lac	Indazole	282.5	Inact.	Inact.	
1t	5-(2,3-DH Benzofuran)SO_2	Benzo-7-Lac	AmdnBnAm	14.4	> 338	19.5	1.4
1u	5-(2,3-DH Benzofuran)SO_2	Benzo-7-Lac	OHAmdnBn Am	> 397	Inact.	Inact.	
1v	5-(2,3-DH Benzofuran)SO_2	Benzo-7-Lac	GuanPip	61.0	Inact.	Inact.	Good
1w	5-(2,3-DH Benzofuran)SO_2	Haic	AmdnBnAm	10.8	49.2	2.5	0.2

[a]Inhibition constants (K_i) of compounds **1a**–**w** are derived from the corresponding IC_{50} values necessary to inhibit human thrombin (FIIa), factor Xa (FXa), and trypsin cleavage of the chromogenic substrates described in ref 8 by 50%. Reported values for each compound are from a single IC_{50} determination that confirmed the initial range values.

In the most widely explored P_4-dihydrobenzofuran-sulfonyl-P_3-azepinone series, in vitro potency decreased as a function of the P_1 arginine surrogate in the following order: AmdnTpn (**1i**, $K_i = 0.6$ nM, $pK_a = 10.3$) > AmdnBnAm (**1c**, $K_i = 6.2$ nM, $pK_a = 10.2$) > GuanPip (**1k**, $K_i = 23.8$ nM, $pK_a = 14.1$) > FAmdnBnAm (**1e**, $K_i = 29.8$ nM, $pK_a = 9.4$) > AmMePyr (**1p**, $K_i = 39.5$ nM, $pK_a = 7.3$) > AmChx (**1r**, $K_i = 53.2$ nM, $pK_a = 10.5$) > OHAmdnBnAm (**1d**, $K_i = 239.7$ nM, $pK_a = 4.2$) > Indazole (**1s**, $K_i = 282.5$ nM, ~non-basic, H-bond donor). In this series, trypsin selectivity decreased as a function of the P_1 arginine surrogate in the following order: AmMePyr (**1p**, trypn/fIIa = 42.5) > GuanPip (**1k**, trypn/fIIa = 36.7) > AmChx (**1r**, trypn/fIIa > 31.5) > AmdnTpn (**1i**, trypn/fIIa = 10.7) > > AmdnBnAm (**1c**, trypn/fIIa = 0.5) > FAmdnBnAm (**1e**, trypn/fIIa = 0.3) > OHAmdnBnAm (**1d**, trypn/fIIa = 0.3). Indazole derivative **1s** (FIIa $K_i = 282.5$ nM) was inactive on trypsin but was excluded from the ranking due to poor inhibitor potency.

Regarding SAR of the P_2-lactam system with a fixed P_1-amidinobenzylamide residue, in vitro potency decreased in the following order: 7-Lac (**1c**, $K_i = 6.2$ nM) > Haic (**1w**, $K_i = 10.8$ nM) > Benzo-7-Lac (**1t**, $K_i = 14.4$ nM). The relative potency and selectivity profiles of **1a**–**w** may be rationalized from modeling considerations which suggest numerous energetically favorable interactions throughout the active site P_4–P_1 manifold, including β-sheet (Gly216), hydrophobic, van der Waals and aromatic edge-to-face types of interactions (S_3 pocket plus 60 loop in S_2 pocket, Fig. 1). Binding to thrombin probably occurs in a normal substrate-like mode, with the P_1-arginine surrogates participating in salt bridge and/or water-mediated hydrogen-bonding interactions with Asp189 in the S_1 pocket.[7–9] Other putative stabilizing interactions between P_1 and the S_1 specificity pocket include van der Waals interactions with Val213 and hydrogen bonds with Gly219, Gly193 and Tyr 228.[4a,c–e] Further discussions along these lines will be included in a forthcoming communication.

Oral dosing of several leading non covalent inhibitor candidates at 1 mg/kg in dog cassette studies indicated generally mediocre PK profiles. Low plasma concentrations (C_{max} ~0.05–0.2 μg/mL), modest AUC values (~25–50 μg min/mL), and short half-lives ($t_{1/2}$ ~35–100 min) suggested only low levels of oral bioavailability in this series.

Starting with the reference lactam sulfonamides **CVS 1778** and **CVS 2097**, rational design strategies generated a series of 23 novel non covalent P_3-lactam-P_1-arginine surrogates **1a**–**w**. These targets probed the S_3 specificity pocket with six sulfonamide residues, the S_2 pocket with three peptidomimetic P_2–P_3 (fused) lactam moieties, and the S_1 pocket with eight rigid arginine surrogates of varying size, shape and basicity.

In vitro evaluation against serine proteases involved in the blood coagulation cascade and trypsin led to the identification of several potent and moderately selective thrombin inhibitors. The P_3-azepinone-P_1-amidinothiophene derivative **1i** (AmdnTpn, $K_i = 0.6$ nM, $pK_a = 10.3$) was the most potent candidate prepared, while the P_3-azepinone-P_1-aminomethylpyridine derivative **1p** (AmMePyr, $K_i = 39.5$ nM, trypn/fIIa = 42.5) was the most trypsin-selective. Numerous active site interactions coupled with optimal P_1-binding and presentation modes are important for conferring good thrombin inhibitory potency and trypsin selectivity in this class.

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References and Notes

1. Ho, J. Z.; Gibson, T. S.; Semple, J. E. *Abstracts of Papers*, 222nd National Meeting of the American Chemical Society, Chicago, IL, August 26–31, 2001, MEDI.235.
2. (a) Coleman, R. W.; Marder, V. J.; Salzman, E. W.; Hirsch, J. In *Hemostasis and Thrombosis, Basic Principles and Clinical Practice;* 3rd ed.; Colman, R. W., Hirsch, J., Marder, V. J., Salzman, E. W., Eds.; J. B. Lippincott: Philadelphia, 1994; Chapters 1, 9, 57, and 80–86. (b) Vlasuk, G. P. *Thromb. Haemostas* **1993**, *70*, 212.
3. (a) Kaiser, B. *Drugs Fut*. **1998**, *23*, 423. (b) Vlasuk, G. P. In *New Therapeutic Agents in Thrombosis and Thrombolysis*; Sasahara, A. A, Loscalzo, J., Eds.; Marcel Dekker: New York, 1997; Chapter 15. (c) Ripka, W. C. In *Structure-Based Drug Design*; Veerapandian, P., Ed.; Marcel Dekker: New York, 1997; Chapter 11.
4. (a) Recent FIIa inhibitors: Coburn, C. A.; Rush, D. M.; Williams, P. D.; Homnick, C.; Lyle, E. A.; Lewis, C. D.; Lucas, B. J.; DiMuzio-Mower, J. M.; Juliano, M.; Kreuger, J. A.; Vastag, K.; Chen, I. W.; Vacca, J. P. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1069. (b) Narasimham, L. S.; Rubin, J. R.; Holland, D. R.; Plummer, J. S.; Rapundalo, S. T.; Edmunds, J. E.; St-Denis, Y.; Siddiqui, M. A.; Humblet, C. *J. Med. Chem*. **2000**, *43*, 361. (c) Sanderson, P. E. J.; Lyle, T. A.; Dorsey, B. D.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. *J. Med. Chem*. **1998**, *41*, 4466. (d) Brady, S. F.; Stauffer, K. J.; Lumma, W. C.; Naylor-Olsen, A. M.; Vacca, J. P. *J. Med. Chem*. **1998**, *41*, 401. (e) Feng, D. M.; Gardell, S. J.; Lewis, S. D.; Bock, M. G.; Freidinger, R. M.; Naylor-Olsen, A. M.; Lynch, J. J.; Mulichak, A. M.; Vacca, J. P. *J. Med. Chem*. **1997**, *40*, 3726. (f) Hayler, J.; Kane, P. D.; LeGrand, D.; Lugrin, F.; Menear, K.; Price, R.; Allen, M.; Cockcroft, X.; Ambler, J.; Butler, K.; Dunnet, K.; Mitchelson, A.; Talbot, M.; Tweed, M.; Wolls, N. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 567. (g) Takeuchi, K; Bastian, J. A.; Gifford-Moore, D. S.; Harper, R. W.; Miller, S. C.; Mullaney, J. T.; Sall, D. J.; Smith, G. F.; Zhang, M.; Fisher, M. J. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2347. (h) Pass, M.; Abu-Rabie, S.; Baxter, A.; Conroy, R.; Coote, S. J.; Craven, A. P.; Finch, H.; Hindley, S.; Kelly, H. A.; Lowdon, A. W.; McDonald, E.; Mitchell, W. L.; Pegg, N. A.; Procopiou, P. A.; Ramsden, N. G.; Thomas, R.; Walker, D. A.; Watson, N. S.; Jhoti, H.; Mooney, C. J.; Tang, C.-M.; Thomas, P. J.; Parry, S.; Patel, C. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1657. (i) Zhang, M.; Bailey, D. L.; Bastian, J. A.; Briggs, S. L.; Chirgadze, N. Y.; Clawson, D. K.; Denney, M. L.; Gifford-Moore, D. S.; Harper, R. W.; Johnson, L. M.; Klimkowski, V. J.; Kohn, T. J.; Lin, H.-S.; McCowan, J. R.; Rickett, M. E.; Sall, D. J.; Smith, A. J.; Smith, G. F.; Snyder, D. W.; Takeuchi, K.; Utterback, B. G.; Yan, S.-C. B. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 775. (j) Plummer, J. S.; Berryman, K. A.; Cai, C.; St-Denis, Y.; Winocour, P. D. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3409.
5. (a) Recent reviews: Coburn, C. A. *Exp. Opin. Ther. Pat*. **2001**, *11*, 721. (b) Vacca, J. P. *Curr. Opin. Chem. Biol*. **2000**, *4*, 394. (c) Fevig, J. M.; Wexler, R. R. *Annu. Rep. Med. Chem*. **1999**, *34*, 81.
6. Ho, J. Z.; Araldi, G. L.; Semple, J. E. PCT Int. Appl. WO 0179261, 2001. *Chem. Abstr*. **2001**, *135*, 318515.
7. (a) Recent Corvas FIIa inhibitors: Minami, N. K.; ; Reiner, J. E.; Semple, J. E. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2625. (b) Reiner, J. E.; Lim-Wilby, M. S.; Brunck, T. K.; Uong, T. H.; Goldman, E. A.; Abelman, M. A.; Nutt, R. F.; Semple, J. E.; Tamura, S. Y. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 895. (c) Owens, T. D.; Semple, J. E. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3683. (d) Semple, J. E.; Rowley, D. C.; Owens, T. D.; Minami, N. K.; Uong, T. H.; Brunck, T. K. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3525. (e) Semple, J. E. *Tetrahedron Lett*. **1998**, *39*, 6645. (f) Semple, J. E. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2501.
8. (a) Recent Corvas FXa Inhibitors: Semple, J. E.; Levy, O. E.; Minami, N. K.; Owens, T. D.; Siev, D. V. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2305. (b) Tamura, S. Y.; Levy, O. E.; Reiner, J. E.; Uong, T. H.; Goldman, E. A.; Brunck, T. K.; Semple, J. E. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 745. (c) Ho, J. Z.; Levy, O. E.; Gibson, T. S.; Nguyen, K.; Semple, J. E. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 3459. (d) Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2573.
9. (a) Corvas lactam prototypes: Semple, J. E.; Rowley, D. C.; Brunck, T. K.; Uong, T. H.; Minami, N. K.; Owens, T. D.; Tamura, S. Y.; Goldman, E. A.; Siev, D. V.; Ardecky, R. J.; Carpenter, S. H.; Ge, Y.; Richard, B. M.; Nolan, T. G.; Håkanson, K.; Tulinsky, A.; Nutt, R. F.; Ripka, W. C. *J. Med. Chem*. **1996**, *39*, 4531. (b) Levy, O. E.; Semple, J. E.; Lim, M. L.; Reiner, J.; Rote, W. E.; Dempsey, E.; Richard, B. M.; Zhang, E.; Tulinsky, A.; Ripka, W. C.; Nutt, R. F. *J. Med. Chem*. **1996**, *39*, 4527. (c) Krishnan, R.; Zhang, E.; Hakansson, K.; Arni, R. V.; Tulinsky, A.; Lim-Wilby, M. S. L.; Levy, O. E.; Semple, J. E.; Brunck, T. K. *Biochemistry* **1998**, *37*, 12094.
10. Ward, P. D.; Tippin, T. K.; Thakker, D. R. *Pharm. Sci. Technol. Today* **2000**, *3*, 346.
11. (a) Lee, K.; Thakker, D. R. *J. Pharm. Sci*. **1999**, *88*, 680. (b) Gan, L. S. L.; Yanni, S.; Thakker, D. R. *Pharm. Res*. **1998**, *15*, 53. (c) Gan, L. S. L.; Thakker, D. R. *Adv. Drug Delivery Rev*. **1997**, *23*, 77.
12. (a) Rigid P_1-arginine surrogates: Peterlin-Masic, L.; Kikelj, D. *Tetrahedron* **2001**, *57*, 7073. (b) Baettig, U.; Brown, L.; Brundish, D.; Dell, C.; Furzer, A.; Garman, S.; Janus, D.; Kane, P. D.; Smith, G.; Walker, C. V.; Cockcroft, X.; Ambler, J.; Mitchelson, A.; Talbot, M. D.; Tweed, M.; Wills, N. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1563. (c) Feng, D. M.;

Gardell, S. J.; Lewis, S. D.; Bock, M. G.; Chen, Z.; Freidinger, R. M.; Naylor-Olsen, A. M.; Ramjit, H. G.; Woltmann, R.; Baskin, E. P.; Lynch, J. J.; Lucas, R.; Shafer, J. A.; Dancheck, K. B.; Chen, I. W.; Mao, S. S.; Kreuger, J. A.; Hare, T. R.; Mulichak, A. M.; Vacca, J. P. *J. Med. Chem.* **1997**, *40*, 3726. (d) St Laurent, D. R.; Balasubramanian, N.; Han, W. T.; Trehan, A.; Federici, M. E.; Meanwell, N. A.; Wright, J. J.; Seiler, S. M. *Bioorg. Med. Chem.* **1995**, *3*, 1145. (e) Lee, K.; Jung, W. H.; Hwang, S. Y.; Lee, S. H. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2483. (f) Wiley, M. R.; Weir, L. C.; Briggs, S. L.; Chirgadze, N. Y.; Clawson, D.; Gifford-Moore, D. S.; Schacht, A. L.; Smith, G. F.; Vasudevan, V.; Zornes, L. L.; Klimkowski, V. J. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2767.

13. pK_a calculations were performed on model compounds of general formula Ac-NHCH$_2$-(hetero)ring-cation using ACD/ChemSketch software, version 4.55, May 2000. Advanced Chemistry Development, Inc. Toronto, Ontario, Canada.

14. All new compounds were characterized by full spectroscopic (NMR, IR, LR/HRMS) data. Yields refer to spectroscopically and chromatographically homogeneous ($\geq$95% by ^{1}H NMR, HPLC, TLC) materials.

15. Tucker, T. J.; Lumma, W. C.; Mulichak, A. M.; Chen, Z.; Naylor-Olsen, A. M.; Lewis, S. D.; Lucas, R.; Freidinger, R. M.; Kuo, L. C. *J. Med. Chem.* **1997**, *40*, 830.

16. Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511.

17. (a) Armstrong, J. D.; Eng, K. K.; Keller, J. L.; Purick, R. M.; Hartner, F. W.; Choi, W. B.; Askin, D.; Volante, R. P. *Tetrahedron Lett*. **1994**, *35*, 3239 and refs therein..

18. Robl, J. A.; Karanewsky, D. S.; Asaad, M. M. *Tetrahedron Lett*. **1995**, *36*, 1593.