Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 723–728

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Design, Synthesis, and Structure–Activity Relationships of Unsubstituted Piperazinone-Based Transition State Factor Xa Inhibitors

Wenrong Huang,[a,*] Mary Ann Naughton,[a] Hua Yang,[a] Ting Su,[a] Suiko Dam,[b] Paul W. Wong,[b] Ann Arfsten,[b] Susan Edwards,[b] Uma Sinha,[b] Stanley Hollenbach,[c] Robert M. Scarborough[a] and Bing-Yan Zhu[a,*]

[a]*Department of Medicinal Chemistry, Millennium Pharmaceuticals Inc., 256 East Grand Ave., South San Francisco, CA 94080, USA*
[b]*Department of Biology, Millennium Pharmaceuticals Inc., 256 East Grand Ave., South San Francisco, CA 94080, USA*
[c]*Department of In Vivo Science, Millennium Pharmaceuticals Inc., 256 East Grand Ave., South San Francisco, CA 94080, USA*

Received 12 February 2002; accepted 1 November 2002

Abstract—A series of novel transition state factor Xa inhibitors containing a variety of lactam ring systems as central templates was synthesized in an expedient manner and allowed for a great deal of structural variability. Among them, the piperazinone-based inhibitors were found to be not only active against factor Xa but also selective over thrombin. Optimization of the P4 moiety yielded several potent compounds with IC_{50} below 1 nM against factor Xa.

Factor Xa is a trypsin-like serine protease positioned at the convergence point of both intrinsic and extrinsic coagulation pathways. It plays a pivotal role in the blood coagulation cascade and in maintaining homeostasis.[1] Factor Xa forms a prothrombinase complex with factor Va, Ca^{2+} and phospholipids. It is the active enzyme in this complex that catalyzes the conversion of inactive prothrombin to active thrombin. Thrombin is the final serine protease in the coagulation pathway that ultimately leads to blood clotting. Factor Xa has recently emerged as an attractive pharmacological target for the development of improved antithrombotic agents.[2–9] Highly potent and specific factor Xa inhibitors have been shown to be efficacious in several animal thrombosis models.[10] They can effectively block both venous and arterial thrombosis formation and may have a much wider therapeutic window than direct thrombin inhibitors, heparin and LMWH, and warfarin.

Previously, we reported a series of tripeptide transition state factor Xa inhibitors, R-SO_2-(D)-Arg-Gly-Arg-Thiazole.[2,11] This class of compounds is highly potent and selective (against thrombin) inhibitors for factor Xa. For example, compound **1** has a K_i value of 13 pM and an IC_{50} value of 10,000 nM against factor Xa and thrombin, respectively. However, concerns with its peptidic features and highly basic character of the two guanidinium groups led us to design compounds with better physiochemical properties. In this letter, the design, synthesis, and SAR of a series of novel lactam based transition state factor Xa inhibitors will be presented.

Although the X-ray structure of **1** with factor Xa has not been determined, we believe there are many interactions that lead to the high inhibitory activity. It is likely that the ketone carbonyl group forms a reversible covalent bond with the hydroxyl group of Ser-195 of factor Xa. The thiazole group may also form a hydrogen bond with the imidazole ring of His-57. The P1 Arg side chain would insert into the S1 specific pocket and form ionic interactions with the carboxylic acid side chain of Asp-189. Both the P3-(D)-Arg side chain and the P4 sulfonamide could occupy the S4 aryl-binding pocket of factor Xa through hydrophobic interactions and the guanidinium group of (D)-Arg might also form ionic interactions with the S4′cation hole of factor Xa. This hypothesis led us to believe that the highly positively charged P3-(D)-Arg could be replaced by hydrophobic or

*Corresponding author. Fax: +1-650-244-9287; e-mail: bingyan.zhu@mpi.com

0960-894X/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0960-894X(02)01037-5

polar amino acids such as (D)-Phe, (D)-Cha, and (D)-Trp. These compounds retained the potency against factor Xa, but they are significantly less selective over thrombin.[2,12] For example, compound **2** has IC_{50} values of 2 and 870 nM for factor Xa and thrombin, respectively. Nevertheless, these results indicated that the S4 pocket of factor Xa could accommodate a variety of motifs, thus, the P3-P4 part of a factor Xa inhibitor could be readily manipulated without sacrificing the potency. Inspired by the pioneering work in the elastase and thrombin inhibitors areas,[13–15] we introduced the structural constraints into the molecules. Utilizing different cyclization approaches, we designed several substituted lactam ring systems as the templates to mimic the P2–P3–P4 region of our tripeptide transition state inhibitors (Fig. 1). By cyclizing the P3-(D)-Arg side chain and P2–P3 back bone amide nitrogen, compounds with the α-amino lactam, such as compound **3a**, were obtained. Similarly, cyclization of the sulfonamide nitrogen with the P2–P3 back bone amide nitrogen produced the piperazinone based transition state inhibitors (**3b**). The subsequent article[16] explored this approach further and identified a series of substituted piperazinone transition state factor Xa inhibitors.

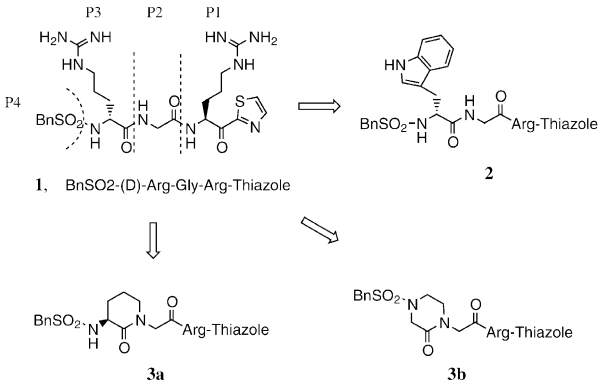
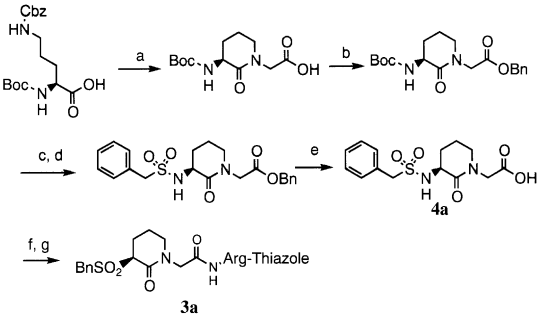
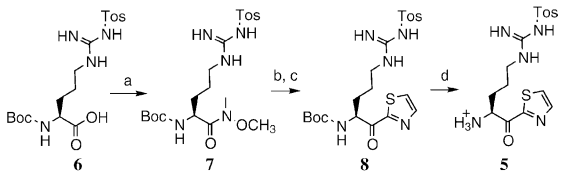


Figure 1. Design of novel factor Xa inhibitors featuring lactam ring systems as P2–P3 mimetic.

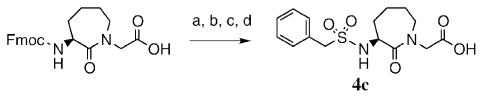
Two general strategies were used to prepare the inhibitors reported in this communication. Our initial approach utilized synthetic methods to construct the P2–P3–P4 segment containing a variety of lactams before they were connected to the P1 segment. For



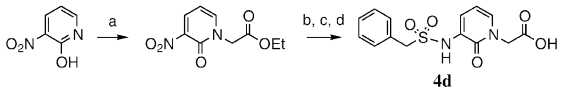
Scheme 1. (a)[13] (i) H_2 (45 psi), 10% Pd/C, MeOH/H_2O/AcOH (10/6/1), $OHCCO_2H$; (ii) MeOH, 60 °C; (b) BnBr, DIEA, DMF; (c) TFA, CH_2Cl_2; (d) $BnSO_2Cl$, DIEA, CH_2Cl_2, −78 °C; (e) H_2, 10% Pd/C, EtOH; (f) **5**, BOP, DIEA, DMF; (g) HF.



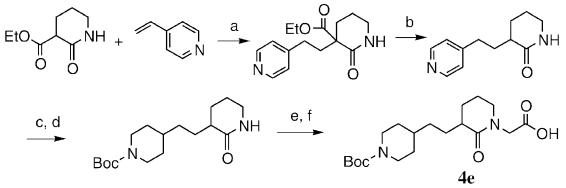
Scheme 2. (a) $HN(OCH_3)(CH_3)$, BOP, DIEA, CH_2Cl_2; (b) thiazole, *n*-BuLi, THF, −78 °C; (c) THF; (d) TFA, CH_2Cl_2.



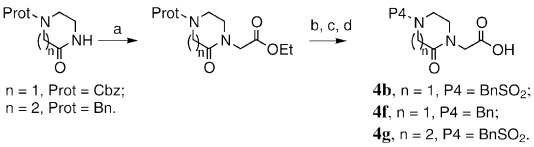
Scheme 3. (a) BnBr, DIEA, DMF; (b) piperidine, DMF; (c) $BnSO_2Cl$, DIEA, CH_2Cl_2, −78 °C; (d) H_2, 10% Pd/C, EtOH.



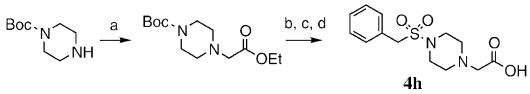
Scheme 4. (a) (i) NaH, THF, −78 °C; (ii) ICH_2CO_2Et; (b) H_2 (40 psi), Pd/C, MeOH; (c) $BnSO_2Cl$, Et_3N, DMF, 0 °C; (d) 0.2 N LiOH, H_2O, dioxane.



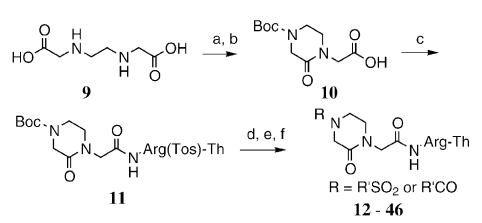
Scheme 5.[17] (a) EtONa, EtOH, 75 °C; (b) (i) aq NaOH; (ii) concd HCl; (iii) CH_3CN, reflux; (c) H_2 (40 psi), PtO_2, MeOH, H_2O; (d) Boc_2O, Et_3N, CH_2Cl_2; (e) (i) $LiN(TMS)_2$, THF, −78 °C; (ii) ICH_2CO_2Et; (f) LiOH, EtOH.



Scheme 6. (a) (i) $LiN(TMS)_2$, THF, −78 °C; (ii) ICH_2CO_2Et; (b) H_2, Pd/C, MeOH; (c) $BnSO_2Cl$, DIEA, CH_2Cl_2, −78 °C (**4b** and **4g**), or BnBr, Et_3N, THF (**4f**); (d) LiOH, EtOH.



Scheme 7. (a) ICH_2CO_2Et, DIEA, DMF, 60 °C; (b) TFA, CH_2Cl_2; (c) $BnSO_2Cl$, DIEA, CH_2Cl_2, −78 °C; (d) LiOH, EtOH.



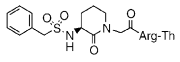
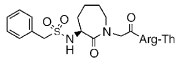
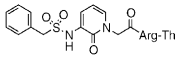
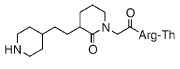
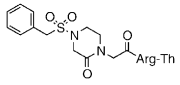
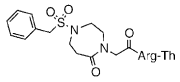
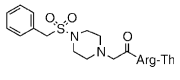
Scheme 8. (a) 1.6 N aq HCl, reflux, 4 h; (b) Boc_2O, Na_2CO_3, dioxane/H_2O; (c) **5**, BOP, DIEA, DMF; (d) TFA, CH_2Cl_2; (e) $R'SO_2Cl$, DIEA, DMF, −78 to 0 °C or R′COCl, DIEA, CH_2Cl_2, 0 °C; (f) HF.

example, to make compound **3a** (Scheme 1), the key intermediate (2-oxo-3-phenylmethanesulfonyl-piperidin-1-yl)-acetic acid (**4a**) was formed through a five-step sequence from α-Boc-ω-Cbz-L-Orn. It was then assembled with NH_2-Arg(Tos)-thiazole (**5**) through BOP coupling, followed by HF deprotection to remove the tosyl group giving the desired inhibitor **3a**. Compound **5** was obtained from the TFA treatment of Boc-NH-Arg(Tos)-thiazole (**8**), which was obtained through reaction of 2-lithiothiazole and the Weinreb amide **7** (Scheme 2). Compounds **3b**–**3h** were prepared in a similar fashion from the corresponding acids **4b**–**4h**, which were synthesized according to Schemes 3–7.

The second synthetic approach was developed for making a large number of piperazinone compounds containing a variety of P4 moieties. As shown in Scheme 8, the readily available diacid **9** was cyclized under acidic conditions.[18] After neutralization of the reaction solution, the Boc group was installed to give the acid **10**. BOP coupling of **10** with **5** led to the key intermediate **11**. Compound **11** was subjected to TFA treatment, followed by *N*-acylation or *N*-sulfonylation and subsequent HF deprotection to give the desired inhibitors **12**–**46**. This process allowed us to produce many analogues rapidly by using commercially available acid chlorides and sulfonyl chlorides.

Table 1 summarizes the in vitro IC_{50} data[11,19] of the compounds containing different lactams. The α-amino-lactam compounds containing a nonbasic P4 moiety ($BnSO_2$), **3a**, **3c**, and **3d**, are potent against factor Xa but have little selectivity over thrombin. Interestingly, compound **3e**, which has a basic group installed at the α-position of the lactam, showed modest potency for factor Xa but excellent selectivity between factor Xa and thrombin. To our delight, when the neutral P4 moiety was moved into the β-position of the lactam, the resulting compounds, **3b** and **3g**, displayed the desired potency against factor Xa as well as the selectivity over thrombin. Although compound **3g** is more selective than **3b**, compound **3b** was chosen as the lead for further structure modifications and SAR studies due to the relative synthetic accessibility of the piperazinone template. Compound **3h** demonstrated the importance of the ring carbonyl group towards activity. The carbonyl group presumably acts in the following two ways: to eliminate the positive charge of the nitrogen and to provide hydrogen bonding with factor Xa.

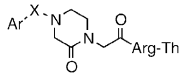
Table 1. Inhibitory activities for compounds with different central templates

Compd	Structure	IC_{50} (nM)	
		Factor Xa	Thrombin
3a		29	138
3c		3	38
3d		3	8
3e		65	12,000
3b		4	390
3g		5	2000
3h		24,000	> 500,000

The SAR of the piperazinone-based inhibitors with modified P4 will be the focus of the remainder of this report. First, the effect of different P4 linkers on inhibitory activities was examined (Table 2). Unsubstituted amine **12** is 500 times less potent than **3b** indicating that the P4 moiety provides crucial binding for the inhibitory activity. We compared carboxamide, sulfonamide and methylene moiety as linkers, and discovered that the sulfonamide linkage generally led to more potent factor Xa inhibitors. For example, sulfonamide **14** is nearly 100 and 40 times more potent than compounds **3f** and **13**, respectively. In the sulfonamide series, extending the length of the P4 moiety only slightly increases the potency for factor Xa (**3b** vs **14**). By contrast, this has a more positive influence on the inhibitory activity for the carboxamide series. Compound **17** is about 15 times more active than **13**, and **18** is 7 times more active than **15** against factor Xa.

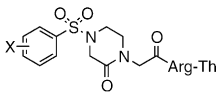
We noticed that a chloro substituent on the phenyl ring improved the potency in the sulfonamide series (**14** versus **16**). This prompted further investigation into the effect of substituents on the in vitro activities (Table 3). When a halogen substituent is placed at the 4-position of the phenyl ring (**19**, **16**, and **20**), a modest increase in both potency and selectivity is observed relative to the unsubstituted phenylsulfonamide **14**. The 4-bromo compound **20** displayed a significant 10- and 20-fold increase in activity for factor Xa and selectivity against

Table 2. Effect of linkers on the inhibitory activities for piperazinone-based inhibitors



Compd	Ar	X	IC_{50} (nM)	
			Factor Xa	Thrombin
12	—	H	22,000	220,000
3f	Phenyl	CH_2	771	14,000
13	Phenyl	CO	320	7000
14	Phenyl	SO_2	8	417
15	4-Cl-phenyl	CO	118	5000
16	4-Cl-phenyl	SO_2	2	1000
17	Benzyl	CO	21	2000
18	4-Cl-benzyl	CO	17	11,000
3b	Benzyl	SO_2	4	390

Table 3. Effect of substituents on the P4 phenyl sulfonamide on inhibitory activities for piperazinone-based inhibitors

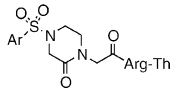


Compd	X	IC_{50} (nM)	
		Factor Xa	Thrombin
14	H	8	417
19	4-F	2	751
16	4-Cl	2	1000
20	4-Br	0.7	809
21	3-Cl	5	134
22	3,4-diCl	1	1000
23	2,4,5-triCl	1	573
24	4-OMe	0.89	792
25	4-CF_3	10	6000
26	4-NO_2	6	3000
27	4-NH_2	6	5000
28	4-NHOH	10	7000
29	4-$NHCOCH_3$	116	5000
30	4-CN	32	3000
31	4-SO_2Me	85	4000
32	4-O(3-Cl-2-CN)Ph	38	4000
33	4-CO_2H	510	17,000

thrombin, respectively. A 3-chloro substituent at the phenyl ring (**21**) has little effect on the potency but significantly reduces the selectivity. Multiple chloro substituents (**22** and **23**) do not further enhance the inhibitory activities.

Non-halogen substituents also have a noticeable influence on the in vitro activities. The 4-OMe group (**24**) increases the inhibitory activity for factor Xa by 10 fold when compared to **14**. Compounds **25**–**28** containing 4-CF_3, 4-NO_2, 4-NH_2, or 4-NHOH phenyl sulfonamide, displayed comparable inhibitory activities for factor Xa with much improved selectivity over thrombin. Interestingly, acylating the amino group of **27** afforded **29**, which is 20 times less active and selective than **27**.

Table 4. Inhibitory activities for piperazinone-based inhibitors with other P4 moieties



Compd	Ar	IC_{50} (nM)	
		Factor Xa	Thrombin
34	2-Naphthyl	8	6000
35	5-Chloro-naphthalen-2-yl	0.79	2000
36	1-Naphthyl	2	118
37	5-Chloro-naphthalen-1-yl	0.62	185
38	2-Naphthalen-1-yl-ethyl	3	375
39	5-Isoquinolinyl	1	267
40	8-Quinolinyl	2	569
41	Benzo[2,1,3]oxadiazol-4-yl	2	719
42	5-Chloro-3-methyl-benzo[*b*]thiophen-2-yl	0.51	751
43	5-Pyridin-2-yl-thiophen-2-yl	4	4000
44	*trans*-1-Styryl	13	7000
45	2-Acetylamino-4-methyl-thiazol-5-yl	58	4000
46	3,5-Dimethyl-isoxazol-4-yl	69	669

Moderate loss of activity was observed for compounds **30**, **31**, and **32** containing 4-CN, 4-SO_2Me and a substituted phenoxyl phenylsulfonamide, respectively. A 4-CO_2H (**33**) substituent at the phenyl ring dramatically reduces the inhibitory activity towards both enzymes, indicating that an acidic group is not well tolerated in the S4 binding pocket.

We also investigated the structure–activity relationships of piperazinone-based factor Xa inhibitors with aromatic bicyclic and other sulfonamide derivatives at P4 position. As shown in Table 4, compounds containing a wide variety of sulfonamide at P4 are highly potent factor Xa inhibitors. This indicates that the hydrophobic S4 pocket of factor Xa can accommodate large aromatic ring systems. SAR of the regioisomers of naphthlene sulfonamide compounds indicates that the 1-naphthlene sulfonamide is slightly preferred over 2-naphthlene for potency. However, the 2-naphthlene sulfonamide leads to more selective factor Xa inhibitor. For example, compound **36** is 4 times more active than **34** for factor Xa, but about 10 times less selective between factor Xa and thrombin. Insertion of an ethyl unit between the 1-naphthlene and the sulfonyl group of **36** yielded **38** with comparable potency and selectivity. Again, a chloro substituent on the naphthlene ring enhanced the activity for factor Xa (**35** vs **34** and **37** vs **36**). Similar to **36**, 5-isoquinoline compound **39**, 8-quinoline **40** and 4-benzo[2,1,3]oxadiazole **41** displayed high potency for factor Xa but less desirable selectivity over thrombin. The benzothiophene sulfonamide **42** is the most active factor Xa inhibitor in this investigation. It is also highly selective over thrombin. High potency and selectivity was also displayed by the biaryl compound **43**. Compound **44** can be visualized as a close analogue of compound **34** that removes part of the naphthyl ring. Both compounds exhibited comparable in vitro activities. Compounds **45** and **46**, which contain substituted heterocyclic sulfonamides at P4, are only moderate factor Xa inhibitors.

Based on the in vitro IC_{50} data, selected compounds were profiled in a number of in vitro and in vivo studies. Table 5 summarizes the results of detailed in vitro factor Xa binding kinetic studies, enzyme selectivity data, in vitro anticoagulant activity studies, and in vivo studies of antithrombotic efficacy and pharmacokinetic properties. K_i studies[20] unveiled that these piperazinone based compounds are considerably less potent than the tripeptide compound **1**. They have comparable K_{on}'s, but the piperazinone based compounds have much faster off rates (K_{off}) than **1**. Besides the thrombin selectivity that we have already discussed in the above context, these compounds display high selectivity over activated protein C (aPC), relatively high selectivity over tissue plasminogen activator (tPA) and plasmin (except for compound **40**). Their selectivity towards plasma kallikrein is less desirable. All of these transition state factor Xa inhibitors suffer from low selectivity towards trypsin, which makes them unsuitable for oral administration.

The anticoagulant activity of these compounds were tested both in vitro in the plasma based thrombin

Table 5. In vitro and in vivo profiles for selected compounds

Compd	1	3b	16	34	35	40	42
In vitro factor Xa binding assays							
IC_{50} (nM)	0.5	4	2	8	0.8	2	0.5
K_i (nM)	0.013	1.4	2.3	2.7	1.3	4.4	0.17
K_{on} (μM^{-1} S^{-1})	6.5	2.3	3.4	6.3	NA	2.9	NA
K_{off} (S^{-1})	3.1×10^5	0.013	0.19	0.132	NA	0.107	NA
Enzyme selectivity data IC_{50} (nM)							
Thrombin	10,000	390	1000	6000	2000	569	751
Trypsin	0.8	33	10.8	39.1	20.5	2	20
tPA	329	4010	1880	1850	740	150	9960
aPC	6000	>180,000	>180,000	>180,000	170,000	>180,000	169,000
Plasmin	309	12,100	10,700	6960	1880	10	1300
Kallikrein	27	677	406	390	34	240	9.4
In vitro functional assays							
2X TG (μM)	0.18	NA	0.52	NA	NA	2.5	5.46
2X PT (μM)	6.8	11.7	11.2	14.5	12.5	10.4	14.5
2X APTT (μM)	0.5	2.8	4.2	13.5	12.5	2	15.5
Plasma protein binding (%)	43	NA	82	95	>99	NA	>99
In vivo anticoagulant efficacy in rabbits and pharmacokinetics in rats							
% inhibition	100	35	90	0	0	0	0
Plasma concentration (μM)	0.07	0.4	0.5	0.8	0.2	0.4	1.6
IV $t_{1/2}$ in rats (min)	24	10	22	15	51	29	5

generation (TG),[21] prothrombin time (PT),[22] and activated partial thromboplastin time (APTT)[22] assays, and in vivo in a rabbit venous thrombosis model.[22] The tripeptide **1**, being extremely potent in binding assays and highly hydrophilic, displayed high TG and APTT activity but poor PT activity. It showed complete inhibition of thrombosis formation at a very low plasma concentration (70 nM) in vivo. The piperazinone compound **16** with a K_i of 2 nM against factor Xa and 82% plasma protein binding, displayed 90% inhibition of thrombosis formation at 500 nM plasma concentration. It is noteworthy that although compound **16** is significantly less efficacious in vivo than compound **1**, they have similar activity in the PT assay. The APTT assay did show the same degree of difference in activity between these two compounds. Compounds **34, 35,** and **40**, which have similar factor Xa binding affinity to **16**, did not display significant inhibition of thrombosis formation in vivo. Even compound **42** with a K_i of 0.17 nM does not have the desired in vivo efficacy. These compounds are highly plasma protein bound, which hampered the effectiveness of translating high factor Xa binding affinity into significant in vivo antithrombotic efficacy in the rabbit model. However, the PT and APTT data for compounds **3a**, **16**, **34**, **35**, **40**, and **42** are comparable and do not correlate to their in vivo efficacy. Thus, PT and APTT assays are not sensitive enough to differentiate and predict the in vivo antithrombotic potentials of these piperazinone based transition state factor Xa inhibitors. A similar phenomenon was observed for fondaparinux, a indirect factor Xa inhibitor.[23,24] For example, at fully efficacious doses that produce a plasma concentration of 300 nM, no PT or APTT is extended by fondaparinux. It showed a 2X APTT value of 29 μM and only extended PT by 7% at 58 μM. TG assay has been demonstrated to be more reliable in predicting the in vivo antithrombotic activity of factor Xa inhibitors. Fondaparinux displayed a 2X TG of 300 nM. Compound **16** is 5 and 10 times more active than compounds **40** and **42** in the TG assay, respectively.

The pharmacokinetic properties of this class of novel factor Xa inhibitors were evaluated in Sprague–Dawley rats. When administered by an IV bolus dose at 1 mg/kg, these compounds exhibited relatively short half life, ranging from 5 min for compound **42** to 51 min for compound **35**.

In summary, during our effort to modify compound **1** to reduce its peptidic character and high basicity, we have discovered and developed a series of novel transition state factor Xa inhibitors containing α-lactam ring system as P2–P3 mimetic. Among the lactams being studied, the piperazinone-based compounds drew the most attention with the following advantages: (1) they contain only one chiral center and one positively charged guanidinium group, (2) they can be rapidly synthesized with readily available starting materials, and (3) they displayed the desired in vitro profile in terms of inhibitory potency for factor Xa and selectivity against thrombin. Modifications of the P4 moiety led to highly potent inhibitors with IC_{50} below 1 nM for factor Xa. Some of the compounds achieved high specificity for factor Xa versus thrombin. Compound **16** also exhibited significant inhibition of thrombosis formation in a rabbit venous thrombosis model.

References and Notes

1. Davie, E. W.; Fujikawa, K.; Kisiel, W. *Biochemistry* **1991**, *30*, 10363.
2. Zhu, B.-Y.; Huang, W.; Su, T.; Marlowe, C.; Sinha, U.; Hollenbach, S.; Scarborough, R. M. *Curr. Top. Med. Chem.* **2001**, *1*, 101.

3. Zhu, B.-Y.; Scarborough, R. M. *Annu. Rep. Med. Chem.* **2000**, *35*, 83.
4. Scarborough, R. M. *J. Enzyme Inhib.* **1998**, *14*, 15 and references therein.
5. Kaiser, B. *Drugs Future* **1998**, *23*, 423 and references therein.
6. Kunitada, S.; Nagahara, T. *Curr. Pharm. Des.* **1996**, *2*, 531 and references therein.
7. Yamazaki, M. *Drugs Future* **1995**, *20*, 911.
8. Mao, S. S. *Perspect. Drug Discov. Des.* **1993**, *1*, 423.
9. Vlasuk, G. P. *Thromb. Haemost.* **1993**, *70*, 212 and references therein.
10. Scarborough, R. M. *Annu. Rep. Med. Chem.* **1995**, *30*, 71.
11. Zhu, B.-Y.; Yang, H.; Volkots, D. L.; Marlowe, C. K.; Gunn, A. C.; Wong, P. W.; Sinha, U.; Scarborough, R. M. 213th ACS National Meeting, San Francisco, 1997; MEDI-100.
12. Zhu, B.-Y.; Huang, W.; Martelli, A.; Gunn, A. C.; Wong, P. W.; Sinha, U.; Scarborough, R. M. 213th ACS National Meeting, San Francisco, 1997; MEDI-101.
13. Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104.
14. Bernstein, P. R.; Andisik, D.; Bradley, P. K.; Bryant, C. B.; Ceccarelli, C.; Damewood, J. R., Jr.; Earley, R.; Edwards, P. D.; Feeney, S.; Gomes, B. C.; Kosmider, B. J.; Steelman, G. B.; Thomas, R. M.; Vacek, E. P.; Veale, C. A.; Williams, J. C.; Wolanin, D. J.; Woolson, S. A. *J. Med. Chem.* **1994**, *37*, 3313.
15. Semple, J. E.; Rowley, D. C.; Brunck, T. K.; Ha-Uong, T.; 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.; Hakanson, K.; Tulinsky, A.; Nutt, R. F.; Ripka, W. C. *J. Med. Chem.* **1996**, *39*, 4531.
16. Su, T.; Yang, H.; Volkots, D.; Woolfrey, J.; Dam, S.; Wong, P.; Sinha, U.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* In press.
17. Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Mathre, D. J.; Ho, G.-J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F.-R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 215.
18. Genik-Sas-Berezowsky, R. M.; Spinner, I. H. *Can. J. Chem.* **1970**, *48*, 172.
19. Claeson, G. *Blood Coagul. Fibrinolysis* **1994**, *5*, 411.
20. Betz, A.; Wong, P. W.; Sinha, U. *Biochemistry* **1999**, *38*, 14582.
21. Hemker, H. C.; Wielders, S.; Kessels, H.; Beguin, S. *Thromb. Haemost.* **1993**, *70*, 617.
22. Hollenbach, S.; Sinha, U.; Lin, P. H.; Needham, K.; Frey, L.; Hancock, T. E.; Wong, A.; Wolf, D. L. *Thromb. Haemost.* **1994**, *71*, 357.
23. Walenga, J. M.; Jeske, W. P.; Bara, L.; Samama, M. M.; Fareed, J. *Thromb. Res.* **1997**, *86*, 1.
24. Herbert, J. M.; Petitou, M.; Lormeau, J. C.; Cariou, R.; Necciari, J.; Magnani, H. N.; Zandberg, P.; van Amsterdam, R. G. M.; van Boeckel, C. A. A.; Meuleman, D. G. *Cardiovasc. Drug Rev.* **1997**, *15*, 1.