Bioorganic & Medicinal Chemistry Letters 25 (2015) 5437–5443

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Development of a novel tricyclic class of potent and selective FIXa inhibitors

Dongfang Meng [a,*], Patrick Andre [b], Thomas J. Bateman [c], Richard Berger [a], Yi-Heng Chen [a], Kunal Desai [b], Sunita Dewnani [a], Kenneth Ellsworth [d], Daming Feng [a], Wayne M. Geissler [d], Liangqin Guo [a], Alan Hruza [e], Tianying Jian [a], Hong Li [a], Joe Metzger [b], Dann L. Parker [a], Paul Reichert [e], Edward C. Sherer [f], Cameron J. Smith [a], Lisa M. Sonatore [d], Richard Tschirret-Guth [c], Jane Wu [a], Jiayi Xu [a], Ting Zhang [a], Louis-Charles Campeau [g], Robert Orr [g], Marc Poirier [g], Jamie McCabe-Dunn [g], Kazuto Araki [h], Teruyuki Nishimura [h], Isao Sakurada [h], Tomokazu Hirabayashi [h], Harold B. Wood [a]

[a] Department of Discovery Chemistry, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[b] Department of Cardiometabolic Disease, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[c] Department of Pharmacokinetics, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[d] Department of Pharmacology, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[e] Department of Structural Chemistry, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[f] Department of Chemistry Modeling and Informatics, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[g] Department of Process Chemistry, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA
[h] Discovery Research, Mochida Pharmaceutical Co., LTD, 7, Yotsuya 1-Chome, Shinjuku-ku, Tokyo 160-8515, Japan

ARTICLE INFO

Article history:
Received 21 May 2015
Revised 20 July 2015
Accepted 23 July 2015
Available online 31 July 2015

Keywords:
Benzimidazole
Quninazolinone
FIXa inhibitor
TGA
Structure based drug design

ABSTRACT

Using structure based drug design, a novel class of potent coagulation factor IXa (FIXa) inhibitors was designed and synthesized. High selectivity over FXa inhibition was achieved. Selected compounds were evaluated in rat IV/PO pharmacokinetic (PK) studies and demonstrated desirable oral PK profiles. Finally, the pharmacodynamics (PD) of this class of molecules were evaluated in thrombin generation assay (TGA) in Corn Trypsin Inhibitor (CTI) citrated human plasma and demonstrated characteristics of a FIXa inhibitor.

Recently, apixiban[1] and rivaroxiban[2] (Factor Xa inhibitors) and dabigatran[3] (direct thrombin (factor IIa) inhibitor) have been introduced to the market as novel anticoagulant therapies for stroke prevention in atrial fibrillation (SPAF). Inhibition of Factors which resides on the intrinsic pathway is hypothesized to be an attractive target for SPAF with a potentially diminished bleeding risk.[4] Inhibition of FIXa, right above Factor Xa on the 'intrinsic' pathway of the coagulation propagation cascade, may lead to better safety margin clinically with similar efficacy.[5–7]

Several groups published their finding on potent and selective FIXa inhibitors.[8] Previously, we have reported our early hit-to-lead efforts leading to 2 classes of FIXa inhibitors (**1** and **2** in Fig. 1) with moderate potency and selectivity over the FXa,[9] as well as the SAR of the acyclic lead series (**1**).[10]

Herein, we continue the discussion on further SAR studies on the cyclic series, leading to potent and selective FIXa inhibitors with desirable PK profiles and demonstrated efficacy in PD assay. While we will discuss SAR to achieve selectivity over FXa, it should be noted these cyclic analogs were essentially devoid of activity against the other enzymes in the coagulation cascade.

The final steps of general syntheses of analogs of compound **1** are described in Scheme 1. Starting from acid **3**, Curtius rearrangement and deprotection gave amine **4**. Amide coupling with tail piece **5** afforded amide **6**, which was subjected to chiral separation to give enantiomerically pure FIXa inhibitor **7**. Analogs shown in Tables 1–4 were synthesized using similar approaches described above.[9,10]

One of the distinguishing features of the cyclic series is the novel pyrazolopyridine moiety. To explore the SAR at P1, the syntheses of different P1 moieties are shown in Schemes 2–4.

* Corresponding author. Tel.: +1 732 594 3169; fax: +1 732 594 2840.
E-mail address: dongfang-meng@merck.com (D. Meng).

http://dx.doi.org/10.1016/j.bmcl.2015.07.078
0960-894X/

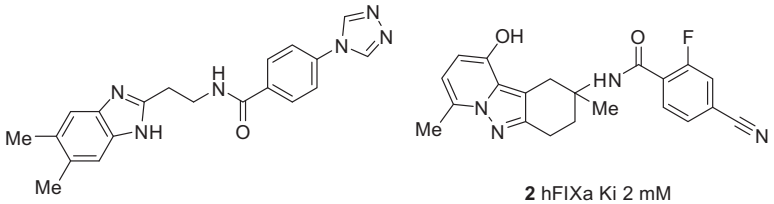
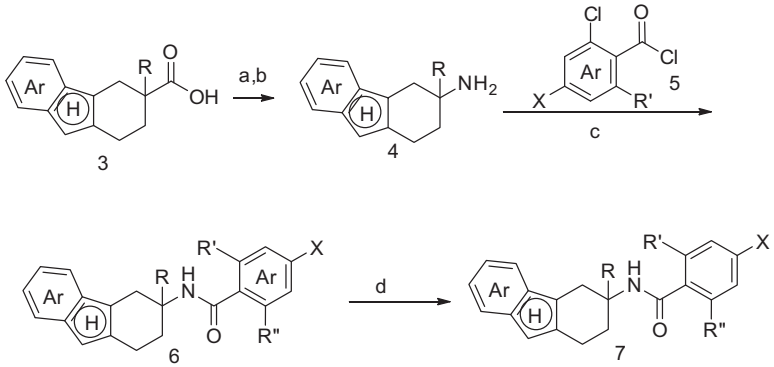
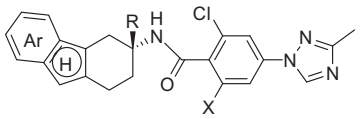


Figure 1. Hits of interest from high throughput screening campaign, acyclic **1** and cyclic **2**.



Scheme 1. Reagents and conditions: (a) DPPA, TEA, Toluene, BnOH or *t*-BuOH; (b) Pd/C or TFA; (c) HOBT, EDC, DMF, rt; (d) Chiral separation on.

Table 1



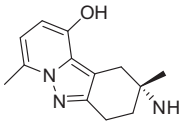
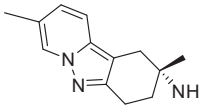
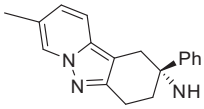
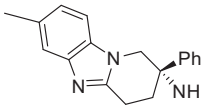
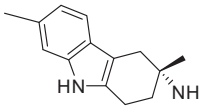
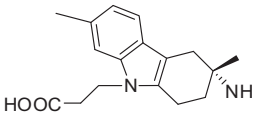
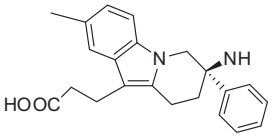
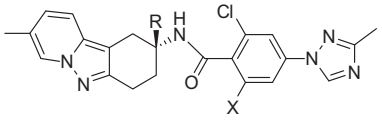
Tricyclic	X	Compd	hFIXa K_i (nM)	hFXa K_i (nM)
	**Cl**	**52**	12.1	2259
	**Cl**	**53**	10.2	2145
	**H**	**54**	6.9	662
	**H**	**55**	5.9	2036
	**Cl**	**56**	267.6	28890
	**Cl**	**57**	11.7	10710
	**H**	**58**	2.7	4227

Table 2



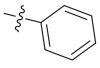
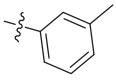
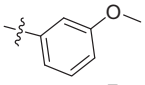
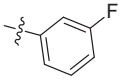
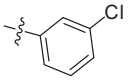
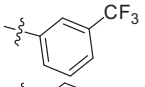
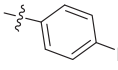
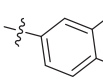
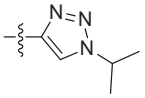
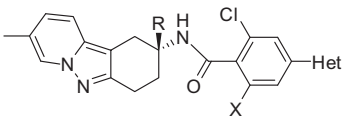
R	X	Compd	hFIXa K_i (nM)	hFXa K_i (nM)
	**Cl**	**53**	10.2	2145
	**Cl**	**59**	13.8	1006
	**Cl**	**60**	12.5	258
	**H**	**61**	6.9	662
	**H**	**62**	2.1	605
	**H**	**63**	3.0	378
	**Cl**	**64**	6.6	246
	**Cl**	**65**	3.1	1682
	**Cl**	**66**	4.5	1553
	**Cl**	**67**	4.2	1110
	**Cl**	**68**	10.5	1540
	**Cl**	**69**	5.0	743

Table 3



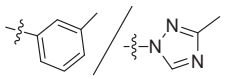
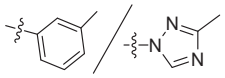
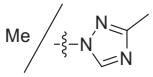
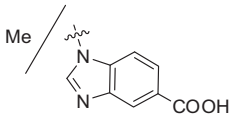
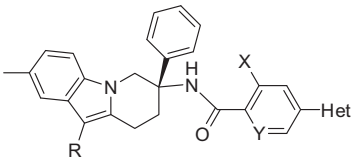
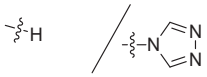
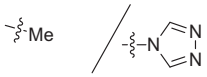
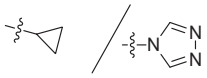
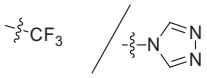
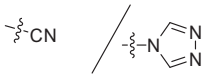
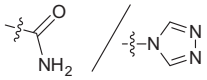
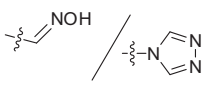
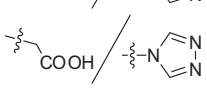
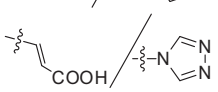
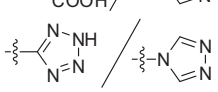
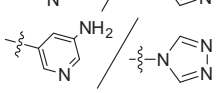
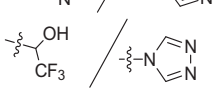
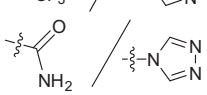
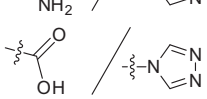
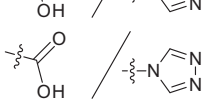
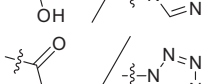
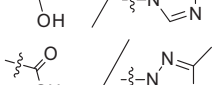
R/Het	X	Compd	hFIXa K_i (nM)	hFXa K_i (nM)
	**H**	**62**	2.1	605
	**Cl**	**70**	1.8	590
	**Cl**	**71**	10.2	2145
	**H**	**72**	10.5	518

Table 4



R/Het	X/Y	Compd	hFIXa K_i (nM)	hFXa K_i (nM)
	**Cl/C**	**73**	34.8	–
	**Cl/C**	**74**	6.3	1748
	**Cl/C**	**75**	8.0	1416
	**Cl/C**	**76**	8.4	3283
	**Cl/C**	**77**	5.1	1082
	**Cl/C**	**78**	1.2	193
	**Cl/C**	**79**	2.4	397
	**Cl/C**	**80**	2.9	>5,000
	**Cl/C**	**81**	0.8	337
	**Cl/C**	**82**	2.4	507
	**Cl/C**	**83**	1.6	257
	**Cl/C**	**84**	5.5	5315
	**H/C**	**85**	2.6	1035
	**H/C**	**86**	0.6	234
	**H/N**	**87**	2.5	–
	**Cl/C**	**88**	8.6	1053
	**Cl/C**	**89**	0.6	409

In Scheme 2, the pyrazolopyridine synthesis is described. Starting from ketone **8**, Pd-catalyzed α-arylation with pyridine halide **9** led to **10**. Compound **10** was first condensed with hydroxylamine to form oxime **11**, which was then converted to **12** following known procedure.[11] The unmasked ketone **13** was treated with desired Grignard reagent to form alcohol **14**, then further converted to amide **15** through a Ritter reaction. Hydrolysis of **15** gave amine **16**.

In Scheme 3, a tricyclic imidazole synthesis is described. Condensation of cyanoester **17** and chloride **18** gave nitrile **19**, which was reduced to an amine and cyclized in situ to form lactam **20**. A routine saponification and Curtis rearrangement generated **22**, which was coupled with aryl bromide **23**, to give intermediate **24**. Reduction of nitro group under acidic conditions yielded imidazole **25**, which after deprotection, gave amine **26**.

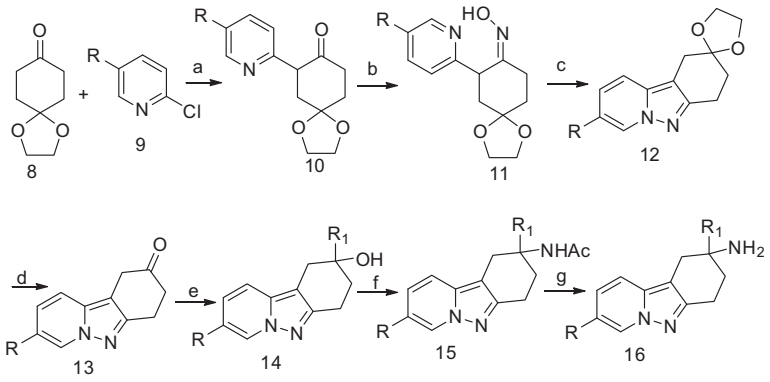
In Scheme 4, a tricyclic indole synthesis is described. A modified Fisher indole synthesis was employed to condense ketone **27** and hydrazine **28**, to give intermediate **29**, which was converted to **an** amine through either deprotection or Curtius rearrangement. Alkylation and deprotection gave substituted indole amine **30**.

In Scheme 5, a reversed indole core synthesis is described. Condensation of **31** and ethyl acrylate gave **33**, which was converted to lactam with formalin and ammonium acetate, then the nitro group reduced to an amine and cyclized in situ to form lactam **34**. A N–C coupling with aryl iodide **35** generated **36**, which was converted to bromide **37**. The bromide can be converted to phosphonium salt **38** or nitrile **41**, then cyclized with the lactam to form indoles **39** or **42** (X = CN). C3 activation of the indole can be done with electrophiles at this stage to, for example, generate an amide or ester **42**. Reduction of nitro group under acidic condition yields amine **43**.

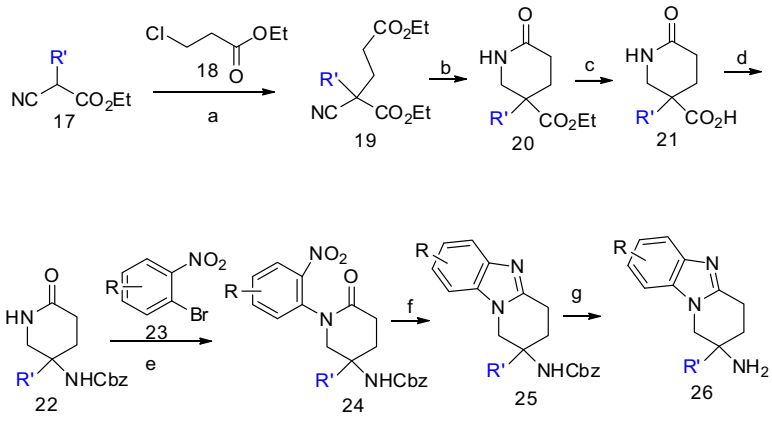
In Scheme 6, derivitization of the reversed indole C-3 position is described with a fully functionalized quaternary amine. Iodonization gave a handle for multiple couplings, especially Suzuki. Some heteryl cycles, for example tetrazole **47**, can be made from **46** (R = CN). Electrophilic reactions also work on **44** to form aldehyde or ketones **48**, which can be either reduced to alcohol **49** or converted to oxime **50**. A trifluoromethyl group can also be introduced through a novel photo reaction to form **51**.

FIXa and FXa inhibitory activities (IC_{50}) were measured by the cleavage of a fluorescent peptide. The cleaved fluorophore was detected with a fluorescence detector.[12] As competitive inhibitors, their apparent Kis were derived from measured IC50s taking into account the assay conditions. The apparent K_i in each case was used to compare FIXa and FXa for selectivity.

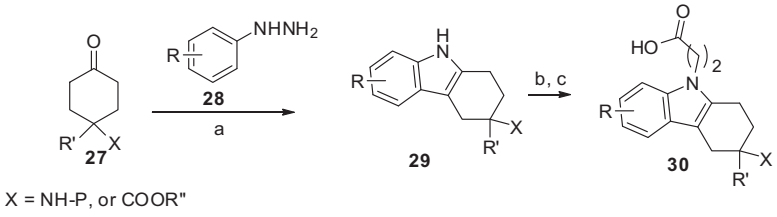
Previously, we reported the X-ray crystal structure of a pyrazolopyridine compound with human Factor IXa,[9] this result and all the following X-rays proved the absolute stereo chemistry at the quaternary center is as drown.



Scheme 2. Reagents and conditions: (a) $Pd(OAc)_2$, 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, NaHMDS in THF, dioxane, 100 °C, 3 h; (b) $HONH_2$, KOAc, MeOH, 70 °C; (c) *p*-toluenesulfonyl chloride, TEA, DCM, rt; (d) HCl, rt, overnight; (e) RMgBr, THF; (f) MeCN, H_2SO_4; (g) HCl, 95 °C.



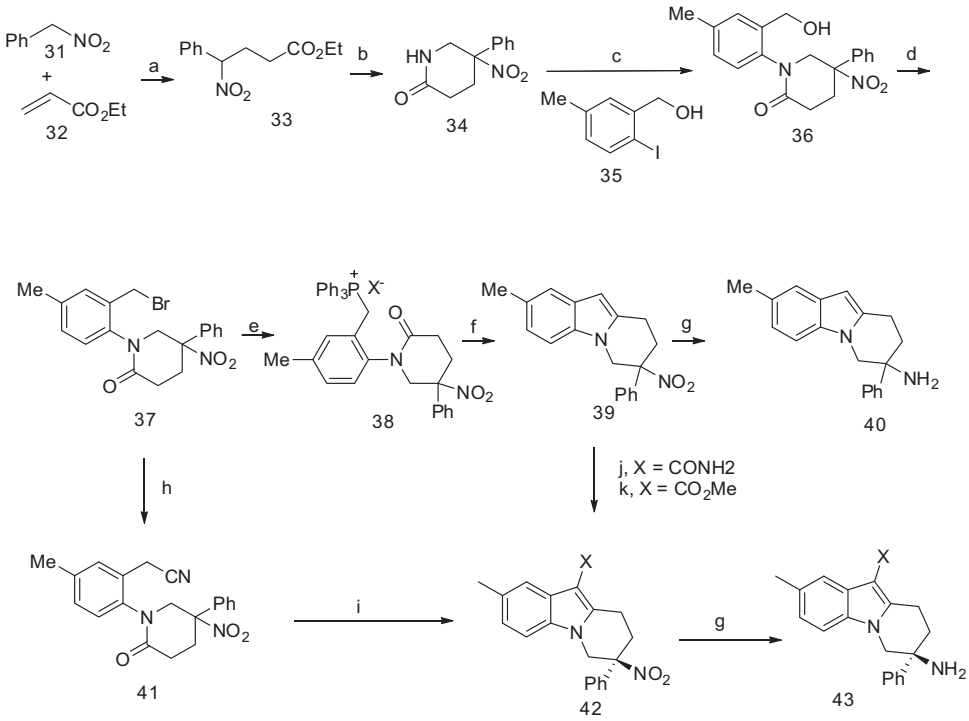
Scheme 3. Reagents and conditions: (a) NaOEt, EtOH; (b) PtO_2, H_2, MeOH/AcOH; (c) LiOH; (d) DPPA, DIEA, BnOH; (e) Xantphos, $Pd_2(dba)_2$, Cs_2CO_3, toluene, 85 °C; (f) AcOH, Fe; (g) $Pd(OH)_2/C$, H_2, EtOH, rt, 97%.



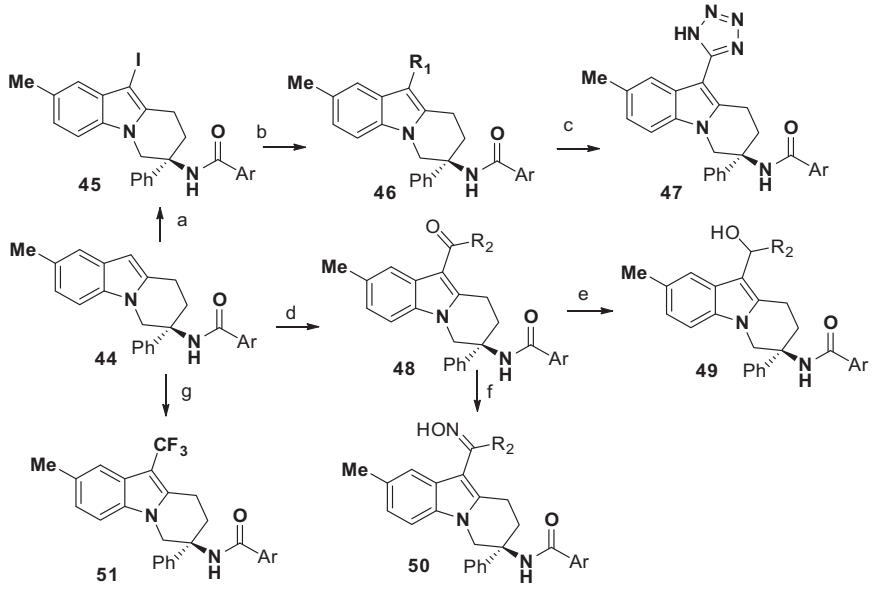
Scheme 4. Reagents and conditions: (a) $Zn(OTf)_2$, EtOH, 50 °C; (b) *tert*-butyl acrylate, Cs_2CO_3; (c) TFA, DCM.

Firstly, as shown in Table 1, we conducted SAR studies on the S1 moiety of the molecule. The P1 site of FIXa protein structure is a narrow pocket that has several polar groups in the backbone. In general, fused aromatic rings were preferred binders to this region. Heteroaryls with hydrogen bond donors (HBDs) or hydrogen bond acceptors (HBAs) were investigated to pick up polar interactions with the P1 backbone. Results are shown in Table 1. Investigation of the substitution pattern on the pyrazolopyridines revealed that the phenol is not critical for FIXa potency and FXa selectivity, especially when the methyl group is moved from the 7- to 6-position (Table 1, compounds **52** and **53**). In addition, changing the quaternary methyl to other alkyl and aromatic rings is also tolerated (Table 1, compounds **54**), and will be discussed further. Borrowing from our knowledge of the S1 SAR in the acyclic series (**1**), resulted in cyclic benzimidazoles with comparable potency, but improved selectivity (Table 1, compound **55**). Generally, replacement with an indole without substitution on the nitrogen afforded analogs with modest activity, but substitutions, especially with HBDs and HBAs, significantly improve potency (Table 1, compounds **56**–**58**), and will be discussed later.

Table 2 shows a selected list of tolerated groups at the quaternary center after a thorough investigation of both alkyl and aryl substituents. Small alcohols gave essentially the same potency and selectivity as a methyl group (Table 2, compounds **53**, **59** and **60**). Introducing larger alkyl groups resulted in a loss of activity. Aromatic rings can be introduced at the quaternary position to improve both potency and selectivity. *Meta*-substituted phenyl groups are tolerated and usually improve selectivity over Factor Xa (Table 2, compounds **61**–**66**). The *para*-position tolerated only small groups. A 4,5-disubstituted benzene offers no potency



Scheme 5. Reagents and conditions: (a) Et_3N, MeCN; (b) formalin, NH_4OAc, EtOH/H_2O, 70 °C; (c) CuI, diamine, Cs_2CO_3, dioxane; (d) CBr_4, PPh_3, DCM; (e) PPh_3, PhMe, 100 °C; (f) LDA, PhMe; (g) Zn, AcOH; (h) KCN, 19-c-6, MeCN; (i) LDA, THF, −10–50 °C; (j) chlorosulfonyl isocyanate, CH_2Cl_2; (k) phosgene, CH_2Cl_2, then MeOH, TEA.



Scheme 6. Reagents and conditions: (a) NIS, DCM, −10 °C; (b) boronic acid/ester, chloro[(tri-*tert*-butylphosphine)-2-(2-aminobiphenyl)] palladium(II), tripotassium phosphate, THF, 50 °C; (c) $(CH_3)_3SiN_3$, dibutyltin (IV) oxide, toluene; (d) $POCl_3$, DMF/DMA/TFA; (e) $NaBH_4$, MeOH; (f) $HONH_2$, pyridine; (g) CF_3I, Tris[2-(4,6-difluorophenyl)pyridinato-C^2,*N*]iridium(III), K_2CO_3, light.

advantage (Table 2, compounds **67**–**68**). Quite a few hetero cycles (pyrido, thophino, oxadiazolo, etc.) can be used to replace phenyl, exemplified as triazolo compound **69** in Table 2.

In general the S2–S4 SAR trends identified in the acyclic series transferred to the tricyclic series with the following noted exceptions. In the acyclic series, the second chlorine on the aromatic ring boosts potency by about fivefold, but does not have that effect in the tricyclic series (Table 3, compounds **62**–**70**). Also, benzimidazoles were found to be a replacement for triazoles, but resulted in a loss of selectivity over FXa (Table 3, compounds **72**).

Previously, we reported the X-ray crystal structure of a pyrazolopyridine compound with human Factor IXa.[9] There is a water molecule between N1 and the backbone of the protein. Introducing a small group, capable of forming a hydrogen bond with the protein, to the tricycles could replace the water and benefit from entropy and enthalpy effects. Modifications to the 3-position of the reverse indole supplies a perfect platform to test this assumption. Parent indole **73** shows only about 35 nM affinity. Adding a small alkyl group (Table 4, compounds **74**–**77**), which may only replace the water molecule without hydrogen bonding to the pro-

tein, improves the affinity by fivefold. Groups with hydrogen bonding capability further improve affinity by another 5–10 fold (Table 4, compounds **78**–**83**). The X-ray crystal structure of **82** supported this hypothesis (see Fig. 2). The tetrazolo group occupied the water position, and forms a hydrogen bond with serine 195. Alcohols without a neighboring electron withdrawing group are not very stable, trifluoro ethyl alcohols, for example compound **84**, are stable and maintain good potency. With these extremely potent P1s, the Cl on the phenyl of S2–S4 unit is not required to achieve desired affinity (Table 4, compounds **85**, **86**), even the phenyl group itself can be replaced with a pyridine (Table 4, compounds **87**). The 1,3,4-triazole can also be replaced with other triazole or triazolone, even a tetrazole (Table 4, compounds **88**–**89**). All compounds in this class maintain at least 200 fold selectivity over human Factor Xa enzyme, some even show thousand fold selectivity. This increased selectivity was not observed in other sub-classes with 1,3,4 triazole unit.

Based upon an understanding of the basal SAR of the cyclic lead series, several analogs were selected to address the pharmacokinetic parameters. Compounds with S2–S4 1,3,4 triazole unit generally are not orally available, some bioavailable methyl 1,2,4 triazole analogues are shown in Table 5. Compound **55** showed moderate half-life in both rat and dog with a relatively high clearance, but good bioavailability (Table 5). Compound **89** has lower clearance and longer half-life (Table 5, entry 3, 4), but slightly lower bioavailability.

Having demonstrated reasonable overall oral PK for this class of molecules, we evaluated the FIXa inhibitory efficacy in TGA assay, APTT/PT and in a rat AV shunt/cuticle bleeding model, and compared with the Factor Xa inhibitor apixaban.

In TGA assay as previously described,[10] see Figure 3, compound **55** behaves very similar to the acyclic analogues, and showed limited activity when compared with apixaban upon increasing concentration of Tissue Factor.

As shown in Figure 4,[14] compound **55** increased APTT, which proved their efficacy through the intrinsic pathway. At the same time, it did not change PT at all even at high dose, which denies any big role of extrinsic pathway. Furthermore, it decreased clot weight effectively in a dose dependent manor in rat AV shunt assay, just like apixaban. At the same time, it has little effect on bleeding time, at the doses tested. It was not possible to dose **55** higher due to solubility limitations.

In conclusion, we have discovered a new class of tricyclic FIXa inhibitors occupying the S1–S4 pockets of the FIXa active binding

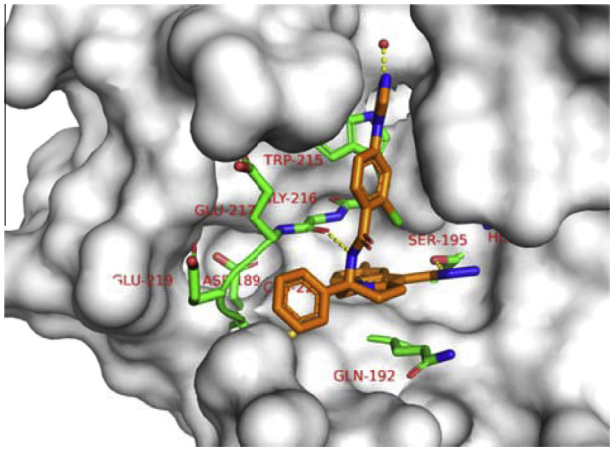


Figure 2. Representation of the X-Ray crystal structures of compounds **86** with human Factor IXa.

Table 5
IV/PO PK for selected compounds[13]

Entry	Compd	Species	*F*%	$T_{1/2}$ (h)	CL (mL/min/kg)	V_{dss} (L/kg)
1	**55**	Rat	26	0.46	30	0.77
2	**55**	Dog	68	1.34	22	3.12
3	**89**	Rat	16	1.03	3.95	0.08
4	**89**	Dog	39	2.26	16	1.15

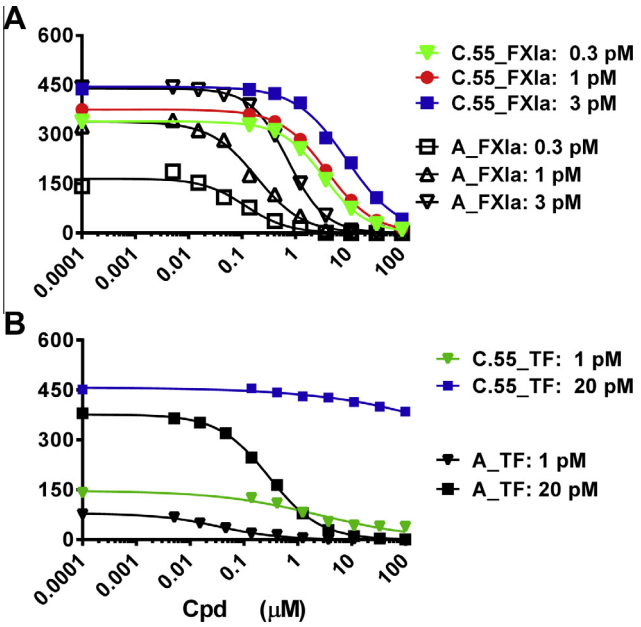


Figure 3. Compound **55** being evaluated in TGA assay. (A) Compound **55** (C.55_) and apixaban (A_) in Human CTI-citrated Plasma using FXIa as coagulation trigger; (B) Compound **55** (C.55_) and apixaban (A._) in Human CTI-citrated Plasma using tissue factor (TF) as coagulation trigger.

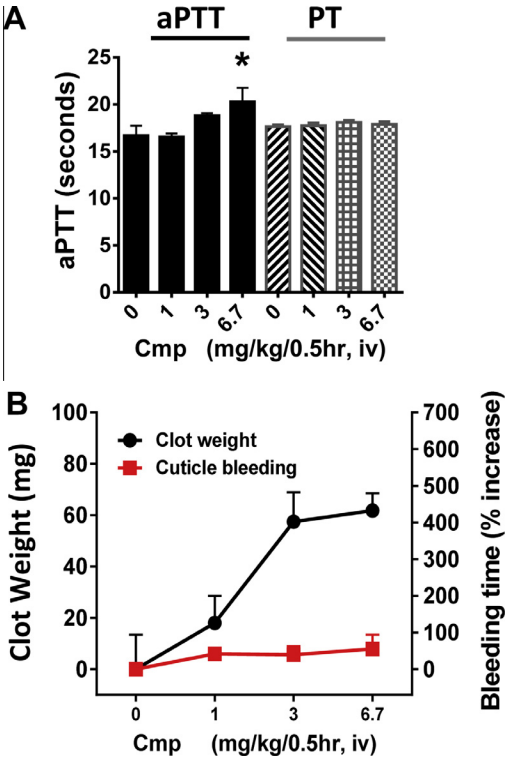


Figure 4. Compound **55** being evaluated in APTT/PT, and rat Av shunt/bleeding assay. (A) Dose dependent APTT (but not PT) increase; (B) Rat AV shunt model to check clot reduction; rat cutical bleeding assay to check bleeding liability.

site. Through structure based drug design, several highly potent and selective FIXa inhibitors were identified, and were evaluated in PK and PD assays. In vivo studies in animal models are promising. Additional studies to further define the efficacy/bleeding profiles of FIXa inhibition are on-ging and will be presented in due course.

Supplementary data

Supplementary data (the X-ray crystallization method and data and the protocol for av shunt assay) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.07.078.

References and notes

1. Granger, C. B.; Alexander, J. H.; McMurray, J. J. V.; Lopes, R. D.; Hylek, E. M.; Hanna, M.; Al-Khalidi, H. R.; Ansell, J.; Atar, D.; Avezum, A.; Bahit, C.; Diaz, R.; Easton, J. D.; Ezekowitz, J. A.; Flaker, G.; Garcia, D.; Geraldes, M.; Gersh, B. J.; Golitsyn, S.; Goto, S.; Hermosillo, A. G.; Hohnloser, S. H.; Horowitz, J.; Mohan, P.; Jansky, P.; Lewis, B. S.; Lopez-Sendon, J. L.; Pais, P.; Parkhomenko, A.; Verheugt, F. W. A.; Zhu, J.; Wallentin, L. *N. Engl. J. Med* **2011**, *365*, 981.
2. Patel, M. R.; Mahaffey, K. W.; Garg, J.; Pan, G.; Singer, D. E.; Hacke, W.; Breithardt, G.; Halperin, J. L.; Hankey, G. J.; Piccini, J. P.; Becker, R. C.; Nessel, C. C.; Paolini, J. F.; Berkowitz, S. D.; Fox, K. A. A.; Califf, R. M. *N. Engl. J. Med.* **2011**, *365*, 883.
3. Connolly, S. J.; Ezekowitz, M. D.; Yusuf, S.; Eikelboom, J.; Oldgren, J.; Parekh, A.; Pogue, J.; Reilly, P. A.; Themeles, E.; Varrone, J.; Wang, S.; Alings, M.; Xavier, D.; Zhu, J.; Diaz, R.; Lewis, B. S.; Darius, H.; Diener, H.-C.; Joyner, C. D.; Wallentin, L. *N. Engl. J. Med.* **2009**, *361*, 1139.
4. a) Feuerstein, G. Z.; Stern, D. *Drug Discovery Today: Therap. Strat.* **2005**, *2*, 279.
5. Darby, S. C.; Kan, S. W.; Spooner, R. J.; Giangrande, P. L. F.; Hill, F. G. H.; Hay, C. R. M.; Lee, C. A.; Ludlam, C. A.; Williams, M. *Blood* **2007**, *110*, 815; Šrámek, A.; Kriek, M.; Rosendaal, F. R. *Lancet* **2003**, *362*, 351.
6. Weltermann, A.; Eichinger, S.; Bialonczyk, C.; Minar, E.; Hirschl, M.; Quehenberger, P.; Schönauer, V.; Kyrle, P. A. *J. Thromb. Haemost.* **2003**, *1*, 28; Heikal, N. M.; Murphy, K. K.; Crist, R. A.; Wilson, A. R.; Rodgers, G. M.; Smock, K. J. *Am. J. Clin. Pathol.* **2013**, *140*, 680.
7. Feuerstein, G. Z.; Toomey, J. R.; Valocik, R.; Koster, P.; Patel, A.; Blackburn, M. N. *Thromb. Haemost.* **1999**, *82*, 1443.
8. Vijaykumar, D.; Sprengeler, P. A.; Shaghafi, M.; Spencer, J. R.; Katz, B. A.; Yu, C.; Rai, R.; Young, W. B.; Schultz, B.; Janc, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2796; Wang, S.; Beck, R.; Blench, T.; Burd, A.; Buxton, S.; Malic, M.; Ayele, T.; Shaikh, S.; Chahwala, S.; Chander, C.; Holland, R.; Merette, S.; Zhao, L.; Blackney, M.; Watts, A. *J. Med. Chem.* **2010**, *53*, 1465; Wang, S.; Beck, R.; Burd, A.; Blench, T.; Marlin, F.; Ayele, T.; Buxton, S.; Dagostin, C.; Malic, M.; Joshi, R.; Barry, J.; Sajad, M.; Cheung, C.; Shaikh, S.; Chahwala, S.; Chander, C.; Baumgartner, C.; Holthoff, H.-P.; Murray, E.; Blackney, M.; Giddings, A. *J. Med. Chem.* **2010**, *53*, 1473.
9. Parker, D., Jr.; Walsh, S.; Li, B.; Kim, E.; Sharipour, A.; Smith, C.; Chen, Y.; Berger, R.; Harper, B.; Zhang, T.; Park, M.; Shu, M.; Wu, J.; Xu, J.; Dewnani, S.; Sherer, E.; Hruza, A.; Reichert, P.; Geissler, W.; Sonatore, L.; Ellsworth, K.; Balkovec, J.; Greenlee, W.; Wood, H. *Biorg. Med. Chem. Lett.* **2015**, *25*, 2321.
10. Zhang, T.; Andre, P.; Bateman, T.; Chen, Y.; Desai, K.; Ellsworth, K.; Geissler, W.; Guo, L.; Hruza, A.; Jian, T.; Meng, D.; Parker, D.; Qian, X.; Reichert, P.; Sherer, E.; Shu, M.; Smith, C.; Sonatore, L.; Tschirret-Guth, R.; Nolting, A.; Or, R.; Campeau, L.; Araki, K.; Nishimura, T.; Sakurada, I.; Wood, H. *Chem. Lett.* **2015**, *25*, 4945.
11. For detailed synthetic procedures for compounds found in this report please refer to our patents.
12. The activity of Factor IXa is measured by monitoring the cleavage of the fluorescent peptide, CH_3SO_2-D-CHG-Gly-Arg-AFC.AcOH. (CHG = cyclohexylGly and AFC = 7-amido-4-trifluoromethylcoumarin). 2 nM of Factor IXa is used to cleave the amide bond between Arg and AFC, thereby releasing the AFC fluorophore. The free AFC is detected with a fluorescence detector at an excitation wavelength of 405 nm and emission wavelength of 510 nm. hFIXa was assayed at substrate concentrations below K_M. IC_{50} for hFIXa was converted to K_i using the Cheng–Prusoff equation for competitive inhibition, see: Cheng, Y.; Prusoff, W. H. *Biochem Pharmacol* **1973**, *22*, 3099.
13. PK studies were conducted in fasted rats, administering a dose of 0.5 mg/kg bolus intravenously (IV) and 2 mg/kg orally (PO).
14. See the Supporting information for PT, APTT, AV shunt descriptions.