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Development of an oxazolopyridine series of dual thrombin/factor Xa inhibitors via structure-guided lead optimization

James Z. Deng,[a] Daniel R. McMasters,[b] Philippe M. A. Rabbat,[a] Peter D. Williams,[a] Craig A. Coburn,[a] Youwei Yan,[c] Lawrence C. Kuo,[c] S. Dale Lewis,[d] Bobby J. Lucas,[d] Julie A. Krueger,[d] Berta Strulovici,[e] Joseph P. Vacca,[a] Terry A. Lyle[a] and Christopher S. Burgey[a,*]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Molecular Systems, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Structural Biology, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[e]*Department of Automated Biotechnology, Merck Research Laboratories, West Point, PA 19486, USA*

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Abstract—Thrombin-inhibitor X-ray crystal structures, in combination with the installation of binding elements optimized within the pyrazinone series of thrombin inhibitors, were utilized to transform a weak triazolopyrimidine lead into a series of potent oxazolopyridines. A modification intended to attenuate plasma protein binding (i.e., conversion of the P3 pyridine to a piperidine) conferred significant factor Xa activity to this series. Ultimately, these dual thrombin/factor Xa inhibitors demonstrated excellent in vitro and in vivo anticoagulant efficacy.

In an attempt to overcome the monitoring and safety liabilities associated with current anticoagulation therapies, an intensive effort to develop orally bioavailable inhibitors of critical coagulation enzymes has been undertaken. Among the potential targets, thrombin (factor IIa) and factor Xa have received the most attention. A recent disclosure on the clinical efficacy of a small-molecule thrombin inhibitor, ximelagatran, in the prevention of stroke in patients with atrial fibrillation has helped validate this strategy.[1] Recently, there has been considerable interest in developing *dual inhibitors* of both thrombin and factor Xa that could afford highly efficacious antithrombotic agents.[2]

Previous work from our laboratories has primarily focused on the design, development, and optimization of the pyrazinone acetamide series of thrombin inhibitors (e.g., **1**).[3] In an effort to expand the structural diversity within our thrombin inhibitor program, the Merck sample repository was screened for activity versus thrombin; this survey revealed the triazolopyrimidine **2a** to be a weak inhibitor ($IC_{50} \sim 1$ μM, Fig. 1).[4] Herein, we detail an optimization process in which inhibitor-enzyme X-ray crystal structures were utilized to convert this lead into a series of potent dual thrombin/factor Xa inhibitors.

Determination of the X-ray crystal structure of **2a** complexed to thrombin helped elucidate the following general binding features (Fig. 2): the 5-chloro-2-methylaniline occupies the S1 specificity pocket, the methyl of the triazolopyrimidine fills the S2 insertion loop, and the butyl group binds to the distal hydrophobic pocket. The antiparallel β-sheet hydrogen bonding motif, common to many thrombin inhibitors,[5] is maintained between the triazolopyrimidine and Gly-216: the substrate is strongly hydrogen bonded to the C=O ($d_{N-O} = 2.26$ Å) and NH ($d_{N-N} = 2.72$ Å) of Gly-216, although the acceptor angles are not optimal.[6] The inhibitor aniline-NH is possibly engaged in a weak H-bond with Ser-195 ($d_{N-O} = 3.45$ Å). Another notable feature is that the P3 butyl group does not take advantage of the

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* Corresponding author. Tel.: +1 215 652 2382; fax: +1 215 652 7310; e-mail: christopher_burgey@merck.com

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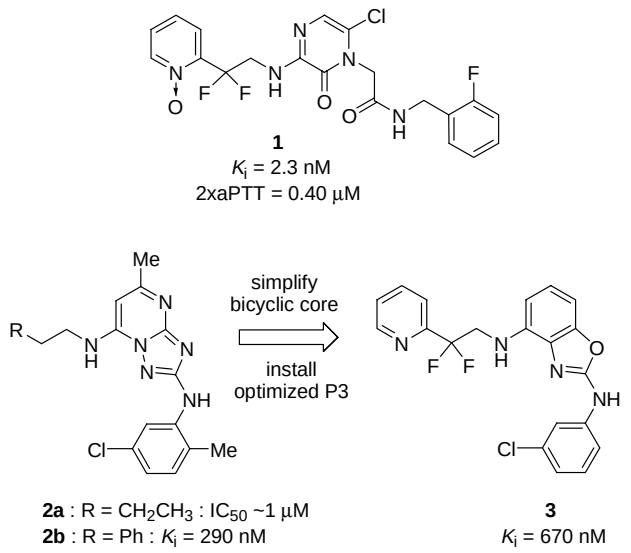


Figure 1.

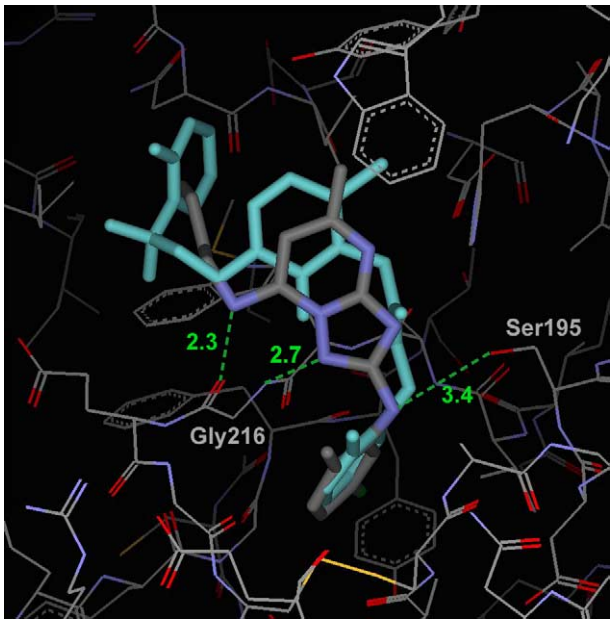


Figure 2. X-ray crystal structures of **1** (blue) and **2a** bound to the thrombin active site.

potential π-interactions (with Trp-215) available within the S3 pocket. Replacement of the P3 butyl with a phenethyl group exploits these interactions to bring about a 3-fold improvement in potency (**2b**, K_i = 290 nM, Fig. 1).[7]

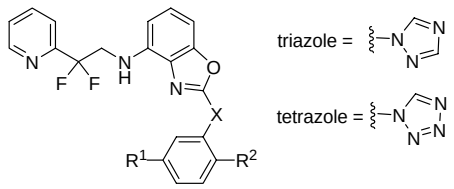
Further analysis of this X-ray structure (Fig. 2; PDB numbers: 1MUE and 1ZGV for **1** and **2a**, respectively) has indicated that the majority of heteroatoms within the triazolopyrimidine ring system are not engaged in specific, constructive interactions with the enzyme. As a result, an alternative and structurally more simple core was sought in which a modular synthesis (vide infra) would facilitate optimization of this series. A basic criterion in this analysis was the preservation of crucial inhibitor H-bonding interactions with Gly-216. These considerations led to the design and preparation of benzoxazole **3** (Fig. 1), in which the additional modifications of P3 2,2-difluoro-2-(2-pyridyl)ethyl ligand[3] incorporation, and P1 and P2 methyl group deletion have been made. These extensive structural changes yielded a moderately potent thrombin inhibitor, **3** (K_i = 670 nM), from which optimization studies could be readily developed.

Guided by the X-ray structure (Fig. 2), efforts to explore the nature of a P1–P2 linker were initiated. Molecular modeling studies have revealed that, to achieve the conformation necessary for thrombin binding, the aniline P1 phenyl and P2 triazole rings must break away from the coplanar arrangement that is favored in the unbound state of this extended conjugated system ($\Delta E_{(\text{bound–unbound})}$ = 7.3 kcal/mol). Elimination of this preference for coplanarity by insertion of a methylene group between the NH and the 3-chlorophenyl group resulted in a significant improvement in potency (Table 1, **4**). This is presumably due, at least in part, to a smaller energy difference between the bound and unbound states ($\Delta E_{(\text{bound–unbound})}$ = 4.7 kcal/mol). Alternatively, replacement of the aniline NH with a CH_2 afforded a 27-fold improvement in potency (**5**, K_i = 25 nM); this analog combines both the correct linker length (compare **6**: K_i = 16 μM) and angle (i.e., sp^3 hybridization) required to access the S1 subsite via a low-energy conformer ($\Delta E_{(\text{bound–unbound})}$ = 3.5 kcal/mol).

Having established the preferred P1–P2 linker,[8] the P1 aryl group SAR was investigated next (Table 1). As anticipated, installation of the 2,5-dichlorophenyl P1 ligand afforded a substantial improvement in potency (Table 1, **7**).[3] Incorporation of the 1-phenyl-1,2,4-triazoles and tetrazoles, P1 binding elements that afforded extremely potent pyrazinone thrombin inhibitors,[9] brought about an improvement in potency (**8**–**9**). The triazole and *m*-chloro substituents were combined to afford **10**, an 80 pM thrombin inhibitor.

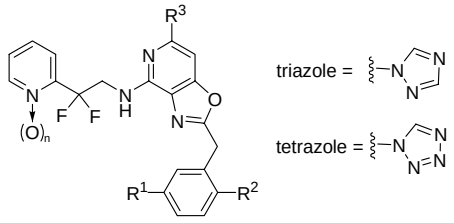
The preceding studies afforded a series of potent thrombin inhibitors; however, the enzyme potency did not translate into good in vitro anticoagulant efficacy, as measured by the 2xaPTT assay in human plasma.[7] For example, inhibitor **8** exhibited a good binding potency of 2.1 nM but a weak functional potency (2xaPTT) of 3.2 μM. This discrepancy between binding and clotting potency is presumably due to the high lipophilicity and protein binding of this series of benzoxazole inhibitors (e.g., **8**: $c\log P$ = 3.0).[10] In an effort to reduce the overall lipophilicity, the analogous *oxazolopyridine* series was prepared (Table 2). Although compounds within this series generally exhibited a slightly diminished inherent potency, the shift in anticoagulant efficacy (2xaPTT assay) was reduced in comparison to the benzoxazoles. For example, **8** and **11** possess the same anticoagulant potency, even though **8** is an 8-fold more potent thrombin inhibitor. In accord with the pyrazinone series of thrombin inhibitors, conversion of the P3 pyridine to its *N*-oxide confers an improvement in

Table 1. SAR of P1–P2 linker and P1 phenyl ring



Compound	X	R^1	R^2	IIa K_i (nM)	2xaPTT (μM)
3	NH	Cl	H	670	—
4	$NHCH_2$	Cl	H	150	—
5	CH_2	Cl	H	25	—
6	CH_2CH_2	Cl	H	16,000	—
7	CH_2	Cl	Cl	3.4	>8.2
8	CH_2	H	Tetrazole	2.1	3.2
9	CH_2	H	Triazole	10.0	5.2
10	CH_2	Cl	Triazole	0.08	0.81

Table 2. SAR of P2 oxazolopyridines



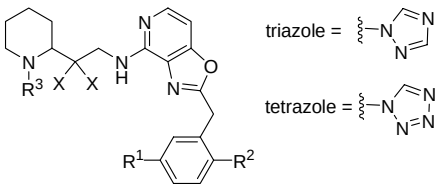
Compound	*n*	R^1	R^2	R^3	IIa K_i (nM)	2xaPTT (μM)	Xa K_i (μM)
11	0	H	Triazole	H	16	3.0	47
12	0	Cl	Triazole	H	0.31	0.40	0.77
13	0	Cl	Triazole	Me	0.04	0.41	0.75
14	0	Cl	H	Me	7.8	>8.2	>20
15	1	Cl	H	H	15	>8.2	3
16	1	Cl	H	Me	2.3	3.0	6
17	1	H	Triazole	H	9.4	1.4	14
18	1	H	Triazole	Me	1.5	0.49	7.2
19	1	H	Tetrazole	H	2.0	0.38	2.7

both enzyme and functional potency (**15**–**19**, Table 2).[3] For instance, triazole analog **17** containing the *N*-oxide was 2-fold more potent in the clotting assay (2xaPTT) than its pyridine version **11**. Reintroduction of the insertion loop substituent (i.e., 6-methyl group) affords a 6-fold potency improvement (**13**–**14**, **16**, and **18**). Notably, this series of thrombin inhibitors exhibits an excellent selectivity profile against the homologous proteases trypsin (>20,000-fold) and factor Xa (>200-fold).

Further investigation into the P3 SAR (Table 3) has revealed that reduction of the pyridine to a piperidine, a modification intended to attenuate plasma protein binding, afforded an improvement in thrombin potency (**21** vs. **11**). *Additionally, incorporation of this 2,2-difluoro-2-(2-piperidyl)ethyl P3 ligand unexpectedly conferred significantly greater factor Xa activity to this series* (**21**: K_i(Xa) = 51 nM vs. **11**: K_i(Xa) = 47,000 nM). As a result of the increased factor Xa binding and enhanced polarity of the piperidine, these derivatives exhibit a large improvement in functional potency. Significantly, introduction of this fXa activity did not compromise protease selectivity versus trypsin, chymotrypsin, activated protein C, kallikrein, and plasmin (>32 μM, >9000-fold); tPA selectivity was somewhat diminished (2.9 μM, 880-fold). The chlorotriazole P1 was also compatible with the P3 piperidine, generating the potent dual IIa/Xa inhibitor **23** with an extremely low 2xaPTT value.

The geminal fluorines of 2,2-difluoro-2-(2-pyridyl)ethyl P3 have been proposed to exert a potency enhancing effect via inductive reinforcement of the π–π interaction between the P3 pyridine ring and Trp-215 of the enzyme.[3] Since the aromatic ring (and the potential for π–π interactions) has been removed from the piperidine series, deletion of the fluorines would be expected to have minimal perturbation on thrombin binding. Indeed, this modification did not significantly impact thrombin or Xa activity (**24** vs. **22**). Resolution of the racemic piperidine revealed the differential binding of each enantiomer (**25** vs. **26**), with the same antipode being more active for both IIa and Xa. The combination of the racemic piperidine P3 and the potent

Table 3. SAR of P3 piperidines[a]

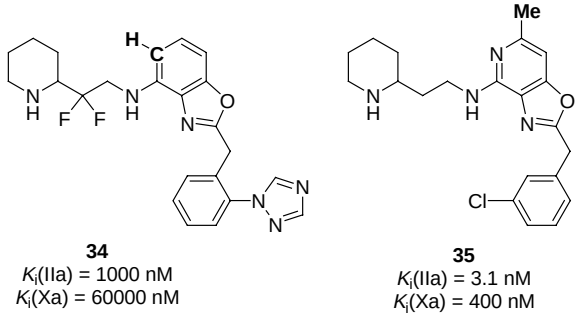


Compound	X	R^1	R^2	R^3	IIa K_i (nM)	Xa K_i (nM)	tryps K_i (μM)	tPA K_i (nM)	2xaPTT (μM)
20	F	Cl	H	H	3.3	12.0	44	2900	1.6
21	F	H	Triazole	H	4.6	50.5	86	840	0.36
22	F	H	Tetrazole	H	1.2	11.0	17	1400	0.18
23	F	Cl	Triazole	H	0.06	1.2	1.5	240	0.11
24	H	H	Tetrazole	H	1.7	7.0	23	2000	0.11
25[b]	H	Cl	H	H	1.7	12.0	16	2100	0.29
26[b]	H	Cl	H	H	100	460	342	—	—
27	H	Cl	Triazole	H	0.04	3.9	1.6	140	0.07
28	H	Cl	Triazole	Bn	0.14	3.7	1.5	100	0.13
29	H	Cl	Triazole	CH_2CO_2Et	0.07	2.2	1.3	67	0.15
30	H	Cl	Triazole	CH_2CO_2H	0.16	4.2	0.70	110	0.08
31	H	Cl	Triazole	CH_2CH_2OH	0.25	2.4	1.6	96	0.06
32	H	Cl	Triazole	CH_2CHF_2	0.52	4.7	2.9	290	0.44
33	H	Cl	Triazole	CH_2CF_3	4.6	54	6.9	3500	1.74

[a] Racemic, except where noted.
[b] Enantiomers.

chlorotriazole P1 produced **27**, a 40 pM thrombin inhibitor that demonstrated excellent in vitro anticoagulant potency (2xaPTT = 70 nM).

Solution of the X-ray structure of **21** bound to thrombin revealed a series of weak hydrogen bonding interactions (Fig. 3). The exocyclic NH and oxazole ring N are engaged in hydrogen bonds with Gly-216 (d_{N-O} = 3.3 Å, d_{N-N} = 3.6 Å). The P3 piperidinium nitrogen appears to be solvent-exposed and engaged in forming an intramolecular hydrogen bond with the aminopyridine ring nitrogen (d_{N-N} = 3.5 Å).[11] Support for the critical role that this interaction serves is provided by **34** (Chart 1), in which replacement of the pyridine nitrogen with a carbon reduces IIa and Xa activity by 218- and 1200-fold, respectively. In line with the solvent-exposed nature of the piperidine nitrogen is its tolerance to varied substitution (e.g., alkyl, carboxyalkyl, and fluoroalkyl; **28**–**33**, Table 3). The lack of a specific role for the fluorines adjacent to the P3 piperidine is also apparent from this X-ray structure. The P1 aryl ring reaches deep into the lipophilic S1 pocket and the triazole is coordinated to an ordered water molecule (d_{N-O} = 2.9 Å) and additionally engaged in a donor-atom–π interaction with the electron-rich disulfide bridge at the subsite entrance.[9] The catalytic Ser-195 lies relatively close (d_{C-O} = 3.0 Å) to the polarized methylene bridging the oxazole to the P1 aryl group and appears to be engaged in a non-classical hydrogen bonding interaction.[6]



34
K_i(IIa) = 1000 nM
K_i(Xa) = 60000 nM

35
K_i(IIa) = 3.1 nM
K_i(Xa) = 400 nM

Chart 1.

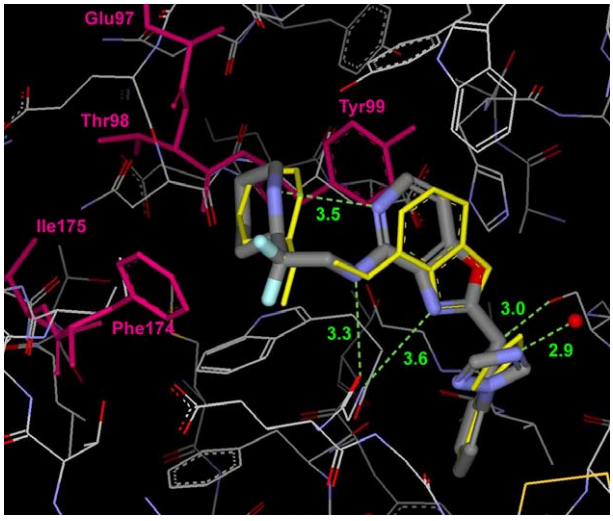


Figure 3. Overlay of **21** bound in the fIIa and fXa (yellow) active sites. Key amino acids of the fXa active site are depicted in magenta.

Based upon the structure bound to thrombin, dual inhibitor **21** was modeled into the human factor Xa active site (Fig. 3; PDB code: 1ZGI).[12] The most significant difference between the IIa and Xa active sites is the composition of the distal hydrophobic (S3/S4) and proximal (S2) binding pockets.[2] In thrombin, Ile-174

terminates the distal pocket, while the aromatic amino acid Phe-174 performs this role in fXa. In S2, there exist more dramatic differences: thrombin possesses a well-defined hydrophobic binding cleft (insertion loop) defined by the side chains of Leu-99, Tyr-60A, and Trp-60D; in comparison, Leu-99 is replaced by a more sterically demanding Tyr-99 in fXa, severely occluding this binding pocket. These differences in the enzyme structure cause the oxazolopyridine ring of **21** in the Xa structure to tilt away from the Tyr-99 (allowed to do so owing to lack of Trp-60D). This change could account for the loss of fXa binding affinity observed upon exchange of the P3 piperidine for a pyridine, as this shift of the bicyclic core would prevent the more rigid P3 pyridine from fully extending into the S3 subsite. Consistent with this restricted fit in the Xa S2 binding pocket is the 30-fold loss in potency (vs. **20**), due to the steric interaction with Tyr-99, upon introduction of a methyl group on the pyridine ring in **35** (Chart 1).

Based upon its high level of in vitro anticoagulant potency, the dual IIa/Xa inhibitor **27** was selected for in vivo characterization. Complete efficacy was observed in the rat $FeCl_3$ arterial thrombosis model (0/6 occlusions)[13] at low plasma levels (final plasma concentration = 121 nM), which significantly elevated the thrombin time (4.65-fold elevation) while producing a moderate effect upon the aPTT (ca. 1.25-fold elevation). Upon i.v. dosing of **27** (0.65 mpk) to dogs, a long plasma half-life ($t_{1/2}$ = 4.2 h; Cl_p = 26.6 mL/min/kg; V_d = 7.2 L/kg) was observed; unfortunately, this analog exhibited very low levels of oral bioavailability (Fig. 4).

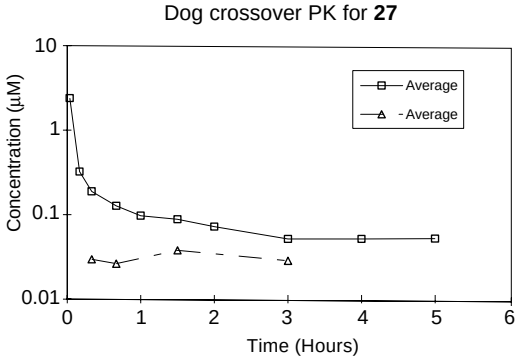
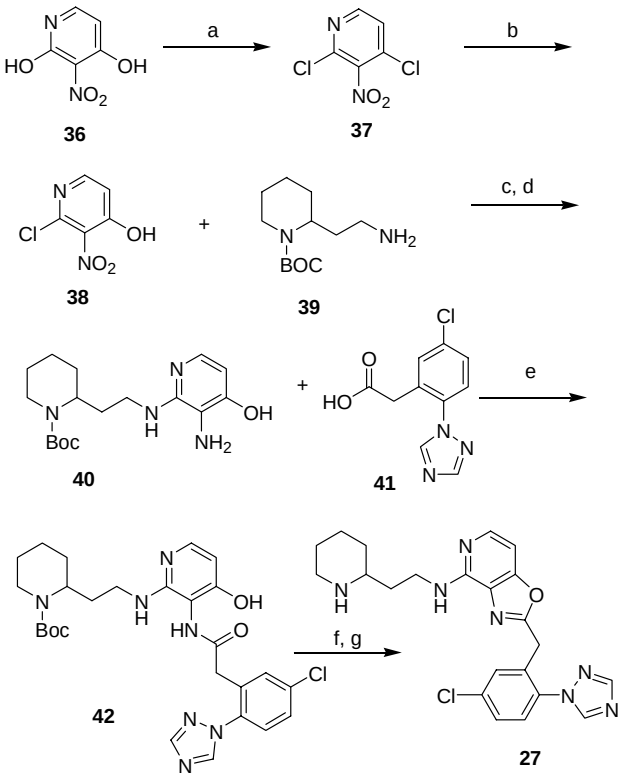


Figure 4.

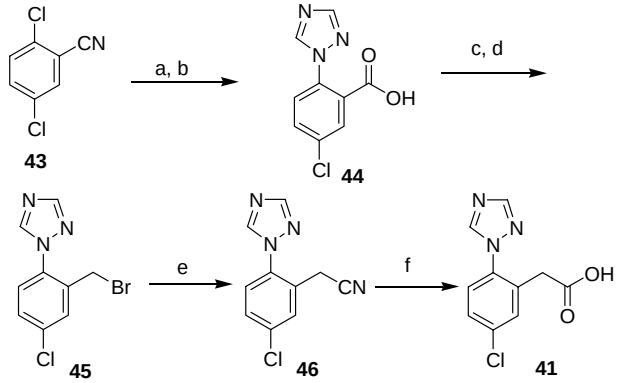
Synthesis of a representative P2 oxazolopyridine inhibitor **27** is shown in Scheme 1.[14] Conversion of 3-nitropyridine-2,4-diol **36** to its 2,4-dichloro analog **37** was completed with phosphorus oxychloride. A cesium acetate-mediated reaction, which allowed selective substitution of 4-chloro group of **37** with a hydroxyl group, afforded key intermediate **38**. Displacement of the remaining 2-chloro group with P3 amine **39**, followed by hydrogenation of the nitro group, resulted in the intermediate **40**. Aminopyridinol **40** was coupled to P1 2-triazolyl-5-chlorophenyl acetic acid **41** to give intermediate **42**. Formation of the central P2 oxazolopyridine ring was accomplished by a selective intramolecular cyclization under Mitsunobu reaction conditions.[15]



Scheme 1. Reagents and conditions: (a) $POCl_3$, $Bn(Et)_3NCl$, CH_3CN, reflux; (b) CsOAc, DMF, 80 °C; (c) $(^iPr)_2NEt$, EtOH, reflux; (d) 45 psi H_2, 10% Pd/C, EtOAc; (e) EDC, HOAt, $(^iPr)_2NEt$, DMF; (f) Ph_3P, i-$PrO_2CN{=}NCO^iPr$, DCM; (g) TFA/DCM.

Deprotection of the Boc group of the cyclized intermediate completed the synthesis of inhibitor **27**.

Synthesis of P1 2-triazolyl-5-chlorophenyl acetic acid **41** was achieved, as shown in Scheme 2. Displacement of the 2-chloro group of 2,5-dichlorobenzonitrile **43** with 1,2,4-triazole, followed by acid hydrolysis, afforded benzoic acid **44**. Reduction to the benzyl alcohol and treatment with thionyl bromide afforded benzyl bromide **45**. Bromide **45** was displaced by sodium cyanide and the



Scheme 2. Reagents and conditions: (a) 1,2,4-triazole, Cs_2CO_3, $(nBu_4)NI$, DMF, 90 °C; (b) concd HCl, reflux ; (c) BOP, $(^iPr)_2NEt$, $NaBH_4$; (d) $SOBr_2$, DCM; (e) NaCN, dioxane/H_2O, reflux; (f) concd HCl/AcOH, reflux.

resulting arylacetonitrile **46** was hydrolyzed to give the desired phenyl acetic acid **41**.

Thrombin-inhibitor X-ray crystal structures, in combination with the installation of binding elements optimized within the pyrazinone series of thrombin inhibitors, were utilized to transform a weak triazolopyrimidine lead into a series of potent oxazolopyridines. A modification intended to attenuate plasma protein binding (i.e., conversion of the P3 pyridine to a piperidine) conferred significant factor Xa activity to this series. Ultimately, these dual thrombin/factor Xa inhibitors demonstrated excellent in vitro and in vivo anticoagulant efficacy.

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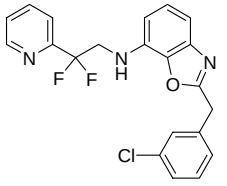
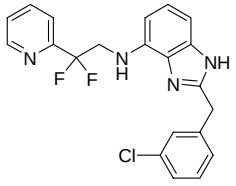
7. The inhibition constants (K_i) versus thrombin (factor IIa) and factor Xa for each compound and the concentration needed to double the activated partial thromboplastin time (2xaPTT) in human plasma (if $K_i < 15$ nM) were determined: Lewis, S. D.; Ng, A. S.; Lyle, E. A.; Mellott, M. J.; Appelby, S. D.; Brady, S. F.; Stauffer, K. S.; Sisko, J. T.; Mao, S.-S.; Veber, D. F.; Nutt, R. F.; Lynch, J. J.; Cook, J. J.; Gardell, S. J.; Shafer, J. A. *Thromb. Haemost.* **1995**, *74*, 1107.
8. The composition of the oxazole ring is also important as the isomer **i** incurs a 180-fold and the imidzaole **ii** a 12-fold potency loss versus **5**.



i
K_i = 4500 nM



ii
K_i = 290 nM

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11. The conformation of the piperidine nitrogen cannot be unequivocally assigned based upon electron density generated in this X-ray experiment. The other conformation is possible in that it could benefit from a cation–π interaction; however, this scenario is unlikely due to the argument outlined in the text.
12. To reproduce the geometries observed in the **21**-IIa crystal structure for the interactions between the P2 NH and Gly216, and between the triazole and C220, the P1 group was fixed in the S1 pocket by holding the carbon atom *para* to the triazole fixed, and the exocyclic N–O(Gly216) distance was held at 3.3 ± 0.1 Å.
13. Reported as the number of carotid artery vessels ($n = 6$) occluding after a 10 μg/kg/min 180 min infusion ($FeCl_3$ arterial injury is initiated after 120 min, followed by a 60 min observation period). Kurz, M. D.; Main, B. W.; Sandusky, G. E. *Thromb. Res.* **1990**, *60*, 269.
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