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Discovery of potent, efficacious, and orally bioavailable inhibitors of blood coagulation factor Xa with neutral P1 moieties

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Abstract—The bicyclic dihydropyrazolopyridinone scaffold allowed for incorporation of multiple P1 moieties with subnanomolar binding affinities for blood coagulation factor Xa. The compound 3-[6-(2′-dimethylaminomethyl-biphenyl-4-yl)-7-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-pyrazolo[3,4-*c*]pyridine-l-yl]-benzamide **6d** shows good fXa potency, selectivity, in vivo efficacy and oral bioavailability. Compound **6d** was selected for further pre-clinical evaluations.

Thrombosis is initiated by the rupture of an atherosclerotic plaque in arteries and subsequently leads to clot formation and sets in motion disease states such as thromboembolism, myocardial infarction, and stroke. Despite the advances in identifying novel anticoagulants, warfarin (Coumadin®)[1a–c] remains the only approved oral anticoagulant in the United States. Other parenteral treatments are also available such as heparin, low molecular weight heparins (LMWH), and fondaparinux.[2,3,4a–c] Blood coagulation factor Xa (fXa), a key enzyme in the coagulation cascade, catalyzes the conversion of prothrombin to thrombin, the final enzyme that triggers clot formation.[5a–g] Pre-clinical animal models have suggested that inhibiting fXa has the potential for providing excellent antithrombotic efficacy with minimal risk of bleeding.[5f,g]

Recently, in a phase II study we have shown that a small molecule fXa inhibitor razaxaban (BMS-561389 fXa $K_i = 0.19$ nM, trypsin $K_i > 10{,}000$ nM) demonstrated good antithrombotic efficacy and minimal bleeding in humans.[6a,b] Razaxaban, a pyrazole-based aminobenzisoxazole fXa inhibitor with good potency, selectivity, and oral bioavailability, was a follow-on candidate to an earlier compound from the pyrazole class, that is, DPC423.[7] As part of a strategy to mask the arylaniline P4 moiety, we recently described an optimization strategy that led to the discovery of a highly potent and orally bioavailable bicyclic pyrazole compound BMS-740808 (Fig. 1).[8] In this report, we wish to describe further efforts to optimize the bicyclic dihydropyrazolopyridinone series by replacing the aminobenzisoxazole with other P1 moieties.

The bicyclic dihydropyrazolopyridinone scaffold was prepared as outlined in Scheme 1. The starting material

Keywords: Blood coagulation; Factor Xa; Thrombin, trypsin; Selectivity; BMS-740808; Aminobenzisoxazole; P-methoxyphenyl and 3-phenylcarboxamido P1; Dog 'N-in-one' pharmacokinetics; Oral bioavailability; Clearance; V_{dss}; Half-life; Rabbit AV Shunt efficacy.
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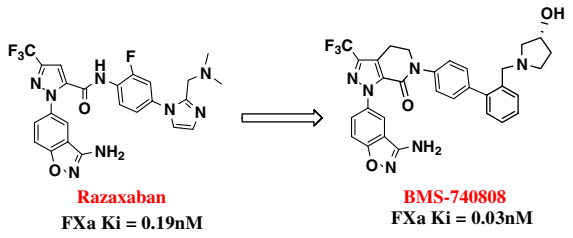


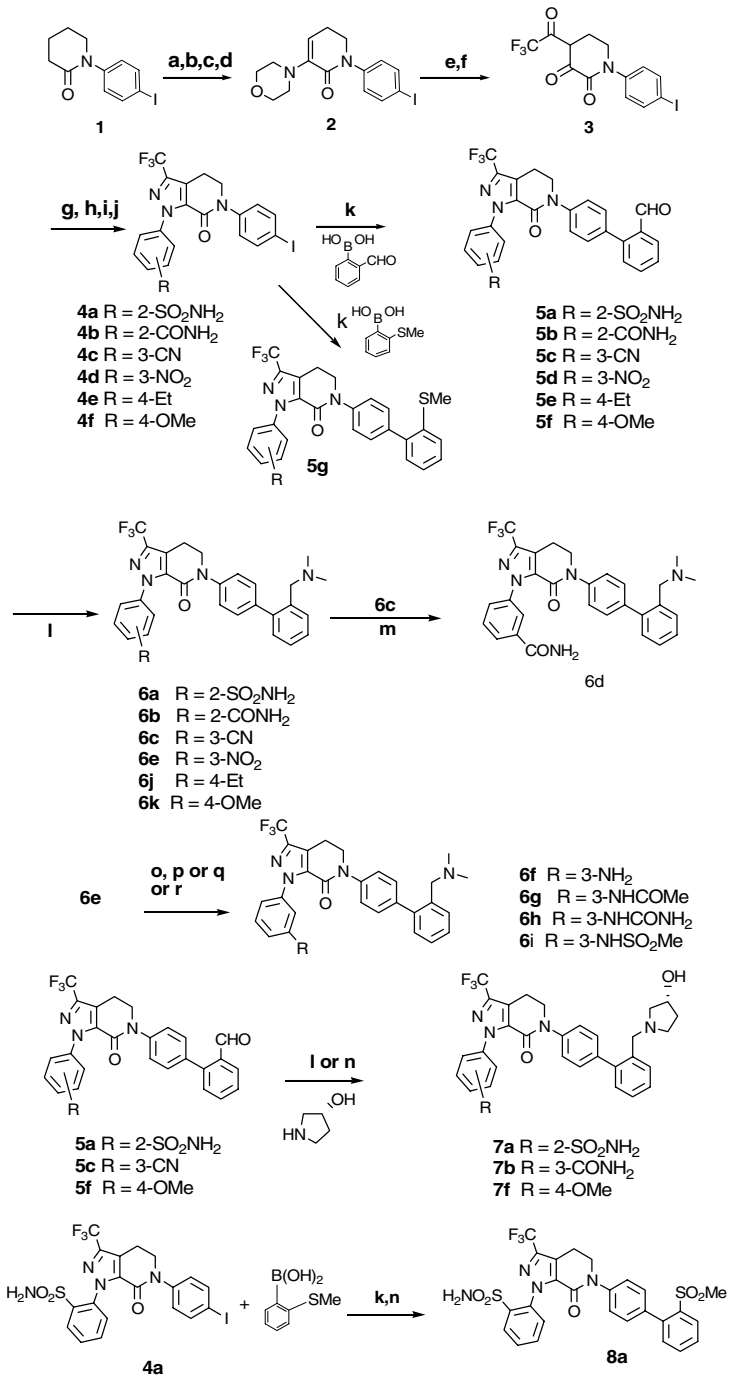
Figure 1.

1 was readily prepared in excellent yield following a two-step sequence from 4- iodoaniline and 5-bromovaleryl chloride [10% NaOH, DCM followed by treatment with potassium *tert*-butoxide]. Chlorination of **1** with phosphorus pentachloride in chloroform at reflux afforded α,α-dichloro-piperidinone intermediate which on heating with excess morpholine provided the morpholine-enamine **2** in 70% yield. Treatment of enamine **2** with trifluoroacetic anhydride in the presence of DMAP, followed by acid hydrolysis, gave the trifluoroacetyl-piperidine-2,3-dione intermediate **3** in high yield (>90%). Condensation of intermediate **3** with commercially available 3-CN, 3-NO_2, 4-Et, and 4-OMe phenylhydrazines afforded the requisite bicyclic pyrazole scaffolds **4c**–**f** in good yield. The coupling of the 2-aminosulfonyl-phenylhydrazine (prepared in situ by diazotization of 2-amino-phenylsulfonamide and subsequent reduction with tin chloride in HCl) afforded the 2-aminosulfonyl-phenyl bicyclic pyrazole intermediate **4a** (R = 2-SO_2NH_2). In a similar manner, intermediate **4b** (R = 2-$CONH_2$) was obtained by condensation of the 2-amidophenyl P1-phenylhydrazine (prepared in situ from 2-aminobenzamide as described above) with the tricarbonyl intermediate **3**. Suzuki cross-coupling of bicyclic pyrazole intermediates **4a**–**f** with 2-formyl-phenylboronic acid or 2-methylthiophenylboronic acid afforded the corresponding 2′-formyl-biaryl **5a**–**f** or the 2′-methylthio-biaryl intermediate **5g** in good yields. Reductive amination of intermediates **5a**–**c**, **5d**, and **5e**,**f** with dimethylamine and sodium cyanoborohydride in methanol provided the desired dimethylaminomethyl biaryl P4 compounds **6a**–**c**, **6e** and **6j k**.[7a,8] The 3-carboxamidophenyl P1 compound **6d** was obtained from the 3-cyanophenyl compound **6c** by treatment with hydrogen peroxide in the presence of aqueous sodium hydroxide. The reduction of the 3-nitrophenyl intermediate **6e** with tin chloride in ethylacetate and concd hydrochloric acid provided the 3-amino compound **6f**. Treatment of **6f** with acetic anhydride and triethylamine in dichloromethane gave the acetamide compound **6g**. Likewise, treatment of **6f** with excess NaOCN in dioxane at 100 °C gave the urea compound **6h**. The phenylsulfonamide P1 compound **6i** was obtained from the 3-aminophenyl compound **6f** by treatment with methanesulfonyl chloride in pyridine. The reductive amination of the carboxaldyhyde intermediates **5a**, **5c** and **5f** with 3-(*R*)-hydroxy-pyrrolidine and $NaBH_3CN$ in methanol afforded the 3-(*R*)-hydroxy-pyrrolidinomethyl biaryl P4 compounds **7a**, **7c** and **7f**. The methylsulfonyl biaryl P4 compound **8a** was prepared by oxidation of the corresponding 2′-methylthio-biaryl intermediate **5g** with MCPBA. In a similar fashion, other P1 phenyl-substituted compounds **8b**–**f** (not shown in Scheme 1) were also prepared. The aminobenzisoxazole pyrazole derivative **9** was prepared according to the methodology previously reported.[8]

BMS-740808 (Fig. 1, fXa K_i = 0.03 nM) and several analogs within the aminobenzisoxazole P1 series demonstrated potent inhibitory activity against factor Xa.[8] Attempts to incorporate additional diversity within our factor Xa inhibitors prompted us to focus on identifying non-aminobenzisoxazole P1 moieties that shared the properties of razaxaban or BMS-740808. Table 1 lists a set of substituted 2, 3, and 4-phenyl P1 bicyclic pyrazole compounds. Several of these compounds displayed potent inhibition of factor Xa, and interestingly are considerably more potent when compared to similarly substituted analogs in the monocyclic pyrazole series.[10] These data complemented that obtained for BMS-740808, and thereby demonstrate the optimal nature of this highly constrained and rigid bicyclic pyrazolopyridinone scaffold, to maximize the inhibitor–fXa enzyme binding interactions from the S1 to the S4 regions. Although several of these inhibitors showed good fXa binding affinity, the set of neutral P1 analogs described herein are somewhat less potent when compared to similar aminobenzisoxazole P1 analogs.[8] In terms of the SAR, when compared to the corresponding 2-amidophenyl P1 analog **6b** (fXa K_i = 2.70 nM), a 3-fold improvement in binding affinity is seen for the 2-aminosulfonyl compound **6a** (fXa K_i = 0.82 nM). However, a 20-fold loss in fXa affinity is seen when compared to the aminobenzisoxazole P1 compound **9** (fXa K_i = 0.04 nM, Table 1).[8] Also noteworthy is the similarity in the anticoagulant activity (as measured by the clotting PT value) for compound **6a** and the corresponding aminobenzisoxazole P1 analog **9** (**6a** PT, EC_{2X} = 2.50 μM, **9** PT, EC_{2X} = 2.70 μM). The result suggests that in addition to protein binding differences, **6a** may have altered the overall coactivator complex.

The 3-amidophenyl compound **6d** (fXa K_i = 0.18 nM) and the 4-methoxyphenyl compound **6k** (fXa K_i = 0.35 nM) displayed sub-nanomolar fXa binding affinity with moderate clotting activity. The 3-anilino compound **6f** and the 4-ethylphenyl compound **6j** also demonstrated low nanomolar fXa activity but were weak in the clotting assay. Substituting the 3-anilino moiety (compounds **6g**–**i**) led to weaker inhibitors of fXa. It is interesting to note, however, that the pyrazole-based compounds listed in Table 1 were several fold more potent when compared to other fXa scaffolds bearing neutral P1 moieties.[11a–c] Differences in the anticoagulant activity were also seen for the 4-methoxyphenyl P1 compound **6k** (PT EC_{2X} = 6.4 μM) and the 4-ethyl compound **6j** (PT EC_{2X} > 200 μM). As indicated above, it is possible that plasma protein binding could account for these high in vitro clotting values (PTs).

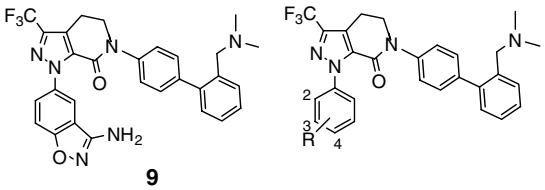
Incorporation of the 3-(*R*)-hydroxypyrrolidinomethyl biaryl P4 moiety of BMS-740808[8] led to compounds shown in Table 2. Also included in this study were compounds bearing the *o*-methylsulfonyl biaryl P4 moiety found in DPC423 (e.g., compounds **8a**–**f**) to determine



Scheme 1. General method of synthesis of the 3-trifluoromethyl-dihdropyrazolopiperidinone factor Xa compounds. Reagents and conditions: (a) 5-Br-valeryl chloride, NaOH (10%) DCM; (b) 2 equiv KO-*t*-Bu; (c) PCl_5 (3 equiv),$CHCl_3$; (d) morpholine excess 140 °C; (e) DMAP/TFAA/DCM; (f) Et_2O, 20% aq HCl; (g) subs-aniline, $NaNO_2$, HCl, AcOH; (h) $SnCl_2$, H_2O, HCl, ethylacetate; (i) MeOH reflux; (j) TFA/DCM; (k) $(Ph_3P)_4Pd$, K_3PO_4, dioxane; (l) amine (2 equiv), $NaCNBH_3$; (m) H_2O_2, NaOH (10%); (n) MCPBA/DCM; (o) [H]Pd/C 10%, MeOH; (p) Ac_2O, TEA, DCM; (q) NaOCN, AcOH heat; (r) MsCl, pyridine, DCM.

if they provided superior profiles previously observed with BMS-740808 and DPC423. Comparable fXa binding affinities were observed for the *o*-methylsulfonyl compound **8a** (fXa K_i = 0.74 nM) and the dimethylaminomethyl biaryl compound **6a** (fXa K_i = 0.82 nM). However, unlike compound **9** (fXa K_i = 0.04 nM),[8] the 3-(*R*)-hydroxy-pyrrolidinomethyl biaryl P4 compounds **7a** (fXa K_i = 1.2 nM) and **8a** (fXa K_i = 0.74 nM) were less potent. Similarly, the compound bearing the 3-(*R*)-hydroxypyrrolidinomethyl biaryl P4 moiety **7c** (fXa K_i = 0.76 nM) was less potent than the compound bearing the dimethylaminomethyl biaryl P4 moiety **8c** (fXa K_i = 0.18 nM), and the corresponding dimethylaminomethyl biaryl P4 compound **6k** (fXa K_i = 0.34 nM). The 3-amidophenyl P1 compound **7b** (fXa K_i = 0.72 nM) was also less potent when compared to the corresponding 3-amidophenyl compound **6d** (fXa K_i = 0.18 nM) (Table 1). Di-substituted phenyl P1 compounds (**8d**–**f**) did not

Table 1. In vitro activity for various bicyclic P1 moieties

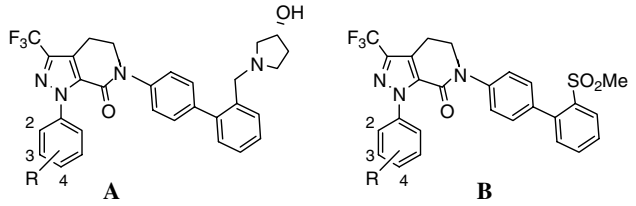


9

Compound	R	fXa K_i (nM)	PT EC_{2X} (μM)
9	—	0.04	2.70
6a	2-SO_2NH_2	0.82	2.50
6b	2-$CONH_2$	2.70	—
6c	3-CN	12.0	—
6d	3-$CONH_2$	0.18	2.63
6e	3-NO_2	20.0	—
6f	3-NH_2	2.00	15
6g	3-NHCOMe	88.0	—
6h	3-$NHCONH_2$	54.0	—
6i	3-$NHSO_2Me$	47.0	—
6j	4-Et	2.60	228.3
6k	4-OMe	0.35	6.40

K_is obtained from purified human enzymes and are averaged from multiple determinations ($n = 2$). PT values are measured according to Ref. 6.

Table 2. Comparative in vitro fXa binding affinity of pyrazolopyridinone compounds bearing novel P1 moieties



A **B**

Compound	Type	R	fXa K_i (nM)	PT EC_{2X} (μM)
7a	A	2-SO_2NH_2	1.20	4.30
7b	A	3-$CONH_2$	0.72	3.50
7c	A	4-OMe	0.76	8.20
8a	B	2-SO_2NH_2	0.74	6.20
8b	B	2-$CONH_2$	2.00	9.90
8c	B	4-OMe	0.18	31.9
8d	B	2-$CONH_2$, 4-OMe	0.18	31.9
8e	B	2-SO_2NH_2, 4-OMe	0.12	—
8f	B	2-NH_2, 4-OMe	0.20	13.2
BMS-740808			0.03	3.60

K_is obtained from purified human enzymes and are averaged from multiple determinations ($n = 2$). PT values are measured according to Ref. 6.

show any enhancements in binding affinities when compared to the mono-substituted 4-methoxyphenyl P1 compound **8c**. The 3-amidophenyl P1 compounds **6d** and **7b**, and the 2-aminosulfonylphenyl P1 compounds **6a** and **7a** provided the best combination of in vitro potency and clotting activity.

The Caco-2 permeability (P_{app}), dog pharmacokinetics (PK), and efficacy in the rabbit arteriovenous shunt (AV Shunt) thrombosis models for compounds **6a**, **6d** and **7a**–**b** are shown in Table 3. In general, the compounds showed good Caco-2 permeability (P_{app}) values, and correlated well with the high oral bioavailability (F%) seen in dogs. The pharmacokinetic profile (dogs) for these compounds shows a moderate clearance profile, moderate to high volume of distribution (V_{dss}) and long terminal half-lives ($t_{1/2}$). In the rabbit AV Shunt thrombosis model, compounds **6d**, **7a**, and **7b** inhibited thrombus formation in a dose-dependent manner, but at significantly higher IC_{50} values when compared to razaxaban and or BMS-740808.[6–8] Compounds **6d** and **7a** compared favorably to razaxaban and BMS-740808. However, the analogs were less potent in the rabbit arteriovenous shunt (AV Shunt) thrombosis model.

The X-ray structure of the 3-carboxamido-phenyl compound **6d**[18] bound to factor Xa (2.1 Å resolution) is shown in Figure 2. Overall the compound binds to fXa in a similar manner to BMS-740808.[8] A strong interaction between the P1 amidophenyl NH proton with Asp 189 (2.92Å) of Xa is prominent in the S1 region of the enzyme. However, the X-ray structure does not show any specific S1 interaction with the P1 amidophenyl carbonyl moiety. The pyrazole N-2 nitrogen interacts with Gln192 backbone. The pyrazolopyridinone carbonyl forms a strong interaction with Gly216 and the dimethylaminomethyl biaryl P4 is neatly stacked between the S4 enzyme residues Tyr99, Phe174, and Trp215 thus making for a tight enzyme–inhibitor complex.

Figure 3 shows an overlap model of the 4-methoxyphenyl P1 compound **6k** and the 2-aminosulfonylphenyl compound **8a**. The oxygen atom of the 4-methoxy P1 moiety appears to form a lipophilic-π interaction with the S1 Tyr228 residue at the bottom of the S1 pocket of fXa. The loss of the fXa binding affinity seen with the 4-ethyl compound **6j** highlights the importance of the oxygen atom in compound **6k**. In the fXa model, the 2-aminosulfonyl functionality (compound **6a**) appears to orient toward the catalytic triad, and interacts with Ser195 and the carbonyl oxygen atom of the inhibitor itself. Interestingly, this binding mode differs from the binding mode previously seen with the *ortho*-benzylamine P1 compound DPC602,[9] wherein the amino moiety of the P1 benzylamine interacts with Asp 189. The rest of the P4–S4 interactions are identical. Based on the overlap model of **6a** and **6k**, it was clear that combining the *ortho* and *para* phenyl P1 substituents on one molecule should be beneficial in terms of potency. This was confirmed by the high fXa potencies seen with compounds **8d**–**f**. Unfortunately, these analogs were poor in the clotting assay, presumably due to an increase in protein binding.

Key kinetic parameters for compound **6d** from detailed mechanism studies are summarized in Table 4. As expected for an active site inhibitor, **6d** is competitive toward a tripeptide chromogenic substrate, but is a mixed-type inhibitor (with ca. 3-fold lower affinity for the ES complex) versus prothrombin, the physiological substrate, for which the binding interactions are

Table 3. Permeability, pharmacokinetic, and in vivo anti-thrombotic profiles

Compound	Caco-2[a] $P_{app} \times 10^{-6}$ cm	Cl[b] (L/kg/h)	V_{dss}[b] (L/kg)	$t_{1/2}$[b] (po) (h)	$F\%$[b] (po)	Rabbit[c] AV Shunt IC_{50} (nM)
6a	5.8	0.50	8.1	11.6	52	—
6d	5.5	0.43	4.0	13	93	500
7a	1.1	0.29	3.5	9.4	93	645
7b	2.9	0.43	2.6	7.2	72	>780
Razaxaban[6a]	5.56	1.1	3.4	5.3	84	340
BMS-740808	1.7	0.35	1.6	5.1	82	135

[a,b,c]Caco-2, dog PK, and rabbit AV Shunt were measured according to Ref. 6.

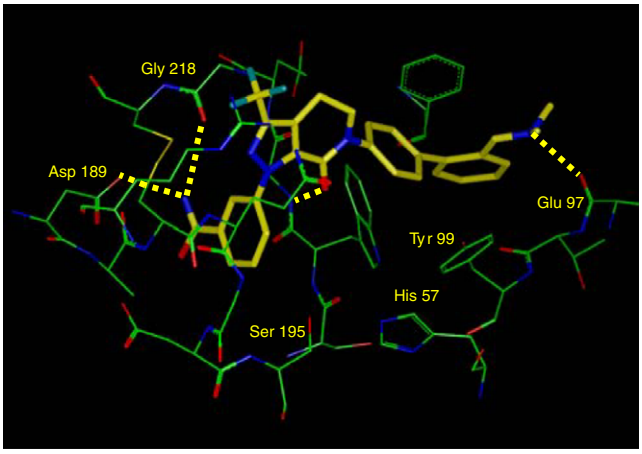


Figure 2. Factor Xa-bound X-ray structure of carboxamide **6d**.

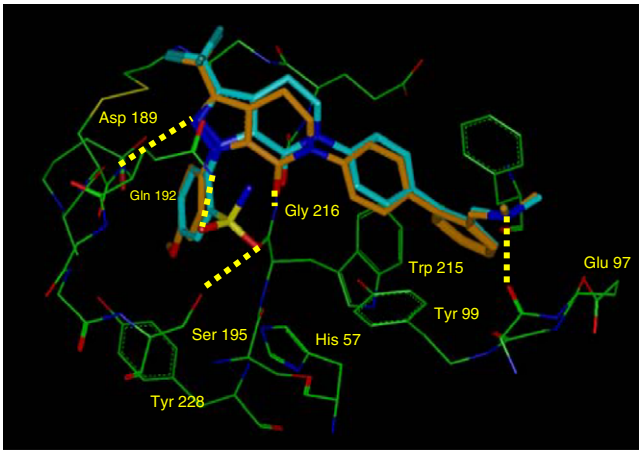


Figure 3. Overlap fXa model of the 4-methoxyphenyl P1 compound **6k** and 2-aminosulfonyl P1 compound **8a**.

predominantly at exosites.[13] Similar substrate-dependent inhibition mechanisms were also observed with the Daiichi fXa inhibitor, DX-9065a.[14] As a result of this inhibition mechanism, **6d** is a potent, low nanomolar inhibitor in the presence or absence of saturating levels of the physiological substrate. The second-order rate constant for association determined by stopped-flow spectrofluorimetry is rapid and near the diffusion controlled limit at both 25 °C and 37 °C. Similar rapid onset of inhibition has been reported for the Pfizer Xa inhibitor PD0313052,[15] and optimized thrombin inhibitors.[16] Plots of the observed rate constants versus inhibitor

Table 4. Detailed factor Xa kinetic parameters for **6d**

Human factor Xa parameter	**6d** Parameter value
25 °C K_i (tripeptide substrate)	0.14 nM
37 °C K_i (tripeptide substrate)	0.41 nM
37 °C K_i (prothrombin)	1.3 nM
37 °C K_i (saturating prothrombin)	3.7 nM
25 °C association rate constant	2.9×10^7 M^{-1} s^{-1}
25 °C dissociation rate constant	4.1×10^{-3} s^{-1}
37 °C association rate constant	2.1×10^7 M^{-1} s^{-1}
37 °C dissociation rate constant	8.4×10^{-3} s^{-1}

K_is obtained from purified human enzymes and are averaged from multiple determinations ($n = 2$). Prothrombinase inhibition, association, and dissociation rate constants were measured according to Ref. 12.

were linear up to 5 μM **6d**, suggesting that binding occurs either by a simple one step mechanism or by a two-step mechanism with very weak initial complex formation (initial $K_i \gg 5$ μM). Differences in the dissociation rate constants calculated from the relationship, $K_i = k_{dissoc}/k_{assoc}$, account for the higher K_is at 37 °C. Similar results were obtained with razaxaban and will be reported elsewhere.[12]

Table 5 shows the enzyme selectivity profile of **6d** compared to razaxaban. The compound is highly selective over a range of enzymes evaluated.

In summary, we have further demonstrated the effectiveness of the pyrazolopiperidinone scaffold to accommodate numerous neutral P1 moieties which bind to factor Xa in a highly optimized manner. The 3-[6-(2′-dimethylaminomethyl-biphenyl-4-yl)-7-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-pyrazolo [3,4-*c*]pyridine-l-yl]-benzamide **6d** provides the best balance of fXa potency, enzyme selectivity, oral bioavailability, and the potency in the AV Shunt antithrombotic model. Compound **6d** was selected for further pre-clinical evaluations. Various

Table 5. Enzyme selectivity profile of **6d**

Human enzyme	K_i (μM)	
	6d	Razaxaban[6a]
Factor Xa	0.00018	0.00019
Thrombin	0.78	0.540
Chymotrypsin, trypsin, APC, factor IXa, factor VIIa, plasmin, urokinase, tPA	>1.8	>2.3

K_is obtained from purified human enzymes and are averaged from multiple determinations.[17]

other optimization strategies using this pyrazole scaffold will be reported in due course.

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