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Pyrazole-based factor Xa inhibitors containing *N*-arylpiperidinyl P4 residues

Jennifer X. Qiao,* Xuhong Cheng, Joanne M. Smallheer, Robert A. Galemmo, Spencer Drummond, Donald J. P. Pinto, Daniel L. Cheney, Kan He, Pancras C. Wong, Joseph M. Luettgen, Robert M. Knabb, Ruth R. Wexler and Patrick Y. S. Lam

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5400, Princeton, NJ 08543-5400, USA

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Abstract—The synthesis, SAR, pharmacokinetic profile, and modeling studies of both monocyclic and fused pyrazoles containing substituted *N*-arylpiperidinyl P4 moieties that are potent and selective factor Xa inhibitors will be discussed. Fused pyrazole analog **16a**, with a 2′-methylsulfonylphenyl piperidine P4 group, was shown to be the best compound in this series (FXa K_i = 0.35 nM) based on potency, selectivity, and pharmacokinetic profile.

Thromboembolic diseases remain the leading cause of death and disability in developed countries. Conventional antithrombotic therapies using either heparin or warfarin have some limitations. In the past decade, several approaches have been pursued to discover safer and more efficacious oral anticoagulants. One promising strategy is to inhibit thrombin generation by targeting the inhibition of coagulation factor Xa (FXa). In the coagulation cascade, FXa serves as the convergent point of the intrinsic and extrinsic pathways. FXa binds phospholipid, factor Va, and calcium ions to form the prothrombinase complex. This complex converts prothrombin to thrombin. Thrombin catalyzes the conversion of fibrinogen to fibrin to form a clot. Studies in animal models of thrombosis suggest that specific FXa inhibitors might be more efficient, and have fewer bleeding risks with a more favorable safety/efficacy ratio compared to direct thrombin inhibitors.[1,2]

Previously, **DPC423** (**1**) was reported as a highly potent and orally bioavailable inhibitor of FXa from our laboratories.[3,4] Subsequently, **Razaxaban** (**2**), another pyrazole-based FXa inhibitor, with good potency, selectivity, and efficacy in humans was disclosed.[5,6] Recently, using structure-based approaches, the monocyclic pyrazole SAR was extended to include potent fused pyrazole FXa inhibitors such as **3**.[7]

Both **1** and **2** contain an amide bond which could undergo in vivo hydrolysis to release a biarylaniline fragment which has the potential to be mutagenic.[7] A non-aromatic ring, such as 4-aminopiperidine, can be used in place of the aniline moiety to remove this potential liability (see Fig. 1, step one). Tying back the amide bonds in the resulting monocyclic pyrazoles led to a series of 7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine bicyclics (fused pyrazoles, Fig. 1, step two). In this paper, we present the SAR and syntheses of both monocyclic and fused pyrazoles bearing substituted *N*-arylpiperidinyl moieties that occupy the S4 binding pocket of FXa.

Monocyclic pyrazoles bearing N-arylpiperidinyl P4 moieties. Structural modifications of **1** (**DPC423**), in which the inner 2-fluorophenyl ring in **1** was replaced by an aliphatic ring, are shown in Table 1. Compounds **4**–**7** had decreased FXa activity compared with **1**, presumably due to the changes in relative spatial orientation between the two substituents at the 1 and 4 positions of the aliphatic rings. Cyclohexenyl, *trans*-cyclohexyl, and piperidinyl analogs **4**, **5**, and **7** were all about 10 times less potent against FXa than **1**. In contrast, the *cis*-cyclohexyl isomer **6** was 300-fold less potent. The similar FXa activity observed in the *trans*-cyclohexyl isomer **5** and piperidine **7** is most likely due to the resemblance

Keywords: Factor Xa inhibitors; Pyrazole-based; SAR; *N*-Arylpiperidine.
* Corresponding author. Tel.: +1 609 818 5298; fax: +1 609 818 6810; e-mail: jennifer.qiao@bms.com

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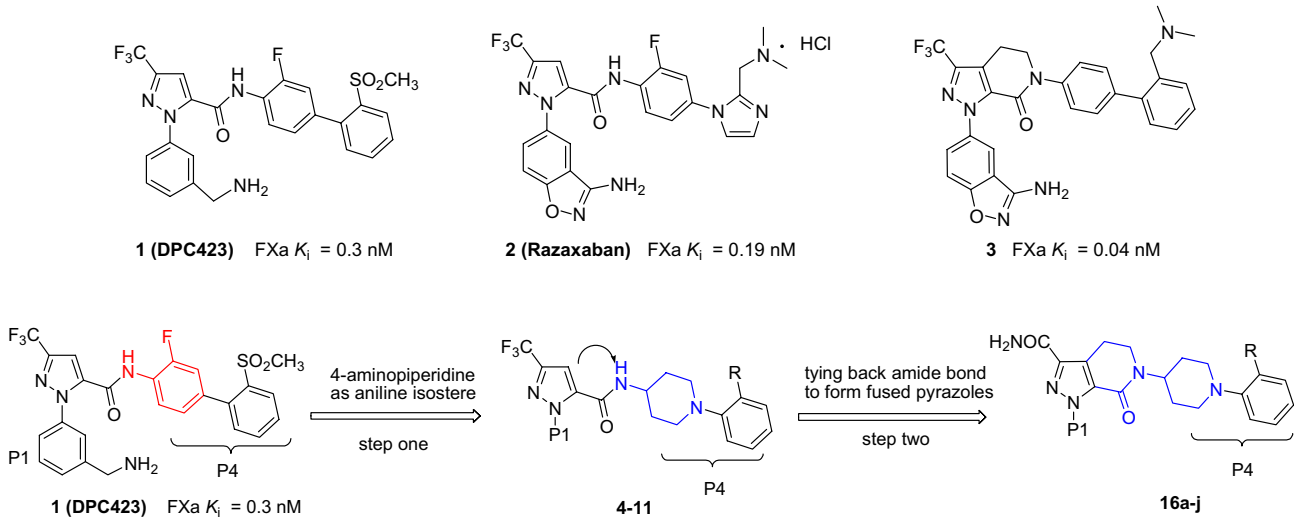


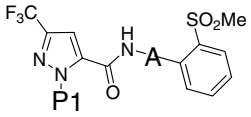
Figure 1. Overall strategy.

of the preferred bioactive conformations in these two molecules: 1,4 di-equatorial substitution.

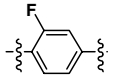
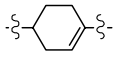
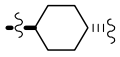
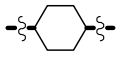
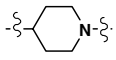
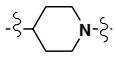
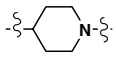
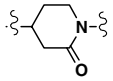
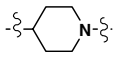
Among analogs bearing different P1 groups (compounds **7**, **8**, **9a**, and **11a** in Table 1), the 3-aminobenzisoxazole analog **9a** (FXa $K_i = 1.7$ nM) was the most potent. Introduction of a piperidinone ring in **10** in place of the piperidine ring resulted in a 50-fold decrease of FXa activity. Replacement of the 3-aminobenzisoxazole P1 group with the neutral *p*-methoxyphenyl P1 group in **11a** led to a 10-fold drop in FXa activity.

A variety of N-substitutions on the piperidinyl ring of analog **9a** were then investigated. Table 2 shows the in vitro data and pharmacokinetic profiles in dogs of some representative compounds. *N*-phenyl piperidines with an *ortho* substituent on the phenyl ring, such as SO_2Me or $CH_2NR^1R^2$, provided the most potent FXa inhibitors, following the same SAR trend previously observed with the biaryl P4 analogs.[9] Benzylamine analogs **9b**–**9e** had FXa K_i less than 1 nM. Compounds **9a**–**9e** showed >1000-fold selectivity against thrombin and were inactive against a panel of serine proteases (trypsin, TPA, urokinase, activated protein C, chymotrypsin, plasmin, and kallikrein). Good anticoagulant activity in the human prothrombin time (PT) assay[6] was observed. However, these monocyclic pyrazole analogs had undesirable pharmacokinetic profiles in dogs with high *Cl* and moderate oral bioavailability (see Table 2). The negligible *F*% in **9c** and **9d** is probably due to their low permeability and/or the high first pass effect. Poor permeability was consistent with the low P_{app} values observed in the Caco-2 assay. In addition, compounds in Table 2 showed poor metabolic stability when incubated with human liver microsomes (HLM). Despite its moderate PK profile, compound **9b** demonstrated a concentration-dependent antithrombolic effect with an EC_{50} value of 740 nM in the rabbit arterio-venous shunt thrombosis model.[10]

Table 1. Structural modifications of **1** (**DPC423**)[a,b]



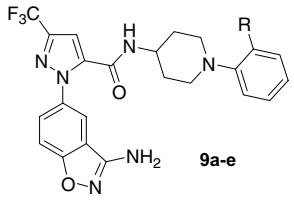
1, **4-11a**

Compound	P1	A	FXa K_i (nM)
1	3-NH_2CH_2-Phenyl		0.30
4	3-NH_2CH_2-Phenyl		3.0
5	3-NH_2CH_2-Phenyl		5.7
6	3-NH_2CH_2-Phenyl		2000
7	3-NH_2CH_2-Phenyl		4.9
8	2-NH_2CH_2-Phenyl		2.4
9a	3-Aminobenzisoxazole-5-yl		1.7
10	3-Aminobenzisoxazole-5-yl		92
11a	4-Methoxyphenyl		14

[a] All compounds were purified by either reverse phase HPLC or preparative LC/MS (water/acetonitrile gradient + 0.5% TFA). The basic compounds were isolated as TFA salts following lyophilization. All compounds gave satisfactory spectral and analytical data.

[b] Human purified enzymes were used. Values were averages from multiple determinations ($n > 2$) and the standard deviations were <30% of the mean. K_i values were measured as described in Ref. 8a.

Table 2. In vitro and dog PK profiles of monocyclic pyrazole analogs containing *N*-aryl piperidine P4 residues



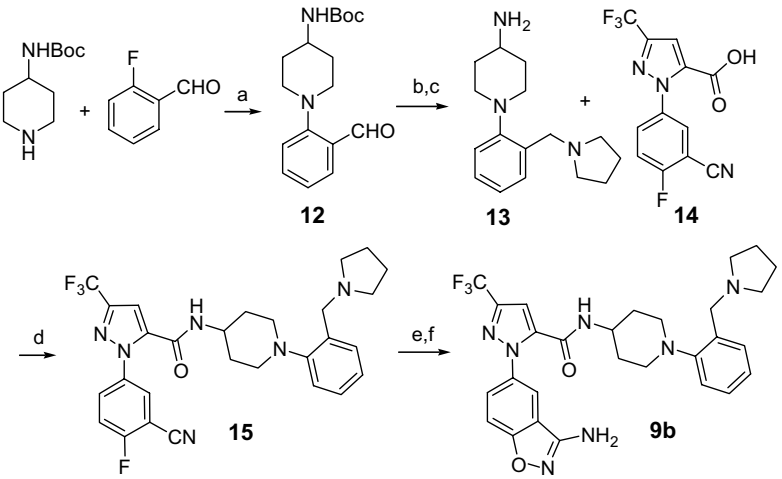
Compound	R	FXa K_i (nM)	PT IC_{2x} (μM)	Caco-2 $P_{app} \times 10^{-6}$ (cm/s)	HLM Cl_{int} (mL/min/mg)	Cl[a] (L/Kg/h)	V_{dss} (L/Kg)[a]	po $t_{1/2}$[b] (h)	F%[b]
9a	$-SO_2Me$	1.7	2.8	1.7	0.051	1.1	2.6	1.3	24
9b	$-CH_2$-*N*-Pyrrolidine	0.61	0.84	1.3	0.029	2.9	13	5.0	26
9c	$-CH_2$-*N*-Pyrrolidine-2-(*R*)-OH	0.73	0.83	0.2	0.040	2.2	5.4	[c]	[c]
9d	$-CH_2NHMe$	0.67	1.2	0.1	nd	6.4	21.5	0.3	1.7
9e	$-CH_2NMeEt$	0.70	1.1	2.7	0.029	4.3	12.8	2.5	23

nd, not determined.
[a] iv dose: 0.5 mg/kg.
[b] po dose: 0.2 mg/kg.
[c] BQL.

Scheme 1 illustrates a representative synthetic route for the synthesis of the compounds in Table 2 using **9b** as an example. Arylation of 4-Boc-aminopiperidine with 2-fluorobenzaldehyde followed by reductive amination of **12** with pyrrolidine and $NaBH(OAc)_3$ afforded amino derivative **13**. Coupling of **13** with acid **14**[6] followed by aminobenzisoxazole ring formation generated the desired compound **9b**. Compounds **9c**–**9e** and **11a** were similarly prepared.

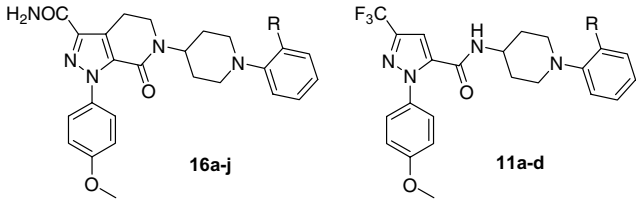
Fused pyrazoles bearing N-arylpiperidinyl P4 moieties. Work by others[11] in our laboratories with fused pyrazole analogs bearing biarylaniline P4 groups has demonstrated that the neutral *p*-methoxyphenyl P1 group might offer pharmacokinetic advantages. Further SAR studies around the neutral *p*-methoxyphenyl P1 analog **11a** with a variety of substituents on the piperidine ring provided compounds with moderate potency (e.g., see compounds **11b**–**d**, Table 3). To improve the potency of these neutral *p*-methoxyphenyl P1 analogs, the amide NH was tied back to the C-4 of the pyrazole ring to generate a series of fused pyrazoles **16a**–**16j** bearing substituted piperidine P4 moieties. In order to balance the polarity of these molecules, we selected a $CONH_2$ group[11] as the C-3 substituent on the pyrazole ring instead of the more lipophilic CF_3 group.

Table 3 shows the in vitro FXa activities of compounds **16a**–**j**. In general, these fused pyrazole analogs were more potent against FXa than their closely related monocyclic derivatives. For instance, compound **16a** with a 2′-methylsulfonylphenyl group (FXa $K_i = 0.35$ nM) was 40 times more potent than the corresponding monocyclic compound **11a** (FXa $K_i = 14$ nM). Similarly, **16b** bearing a *N*,*N*-dimethylmethylamine R group (FXa $K_i = 0.41$ nM) was 20-fold more active than its counterpart **11b** (FXa $K_i = 8.8$ nM). Among the wide variety of N-substituted piperidinyl derivatives prepared, the most potent compounds were those containing a substituted benzylamine or a 2′-methylsulfonylphenyl group. Other than some micromolar thrombin activity, the fused pyrazole analogs were selective over the other related serine proteases noted previously. These compounds



Scheme 1. Reagents and condition: (a) K_2CO_3, DMSO, 85 °C, 49%; (b) pyrrolidine, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (c) 4 N HCl/dioxane, then NaOH, 69% over 2 steps; (d) Castro's reagent, NMM, DMF; (e) $CH_3CONHOH$, K_2CO_3, DMF, H_2O; (f) HPLC, 52% over 3 steps.

Table 3. SAR of fused pyrazole analogs **16a**–**16j** bearing *N*-aryl piperidine P4 groups and comparison of factor Xa activities with the closely related monocyclic pyrazoles **11a**–**11d**[a,b]



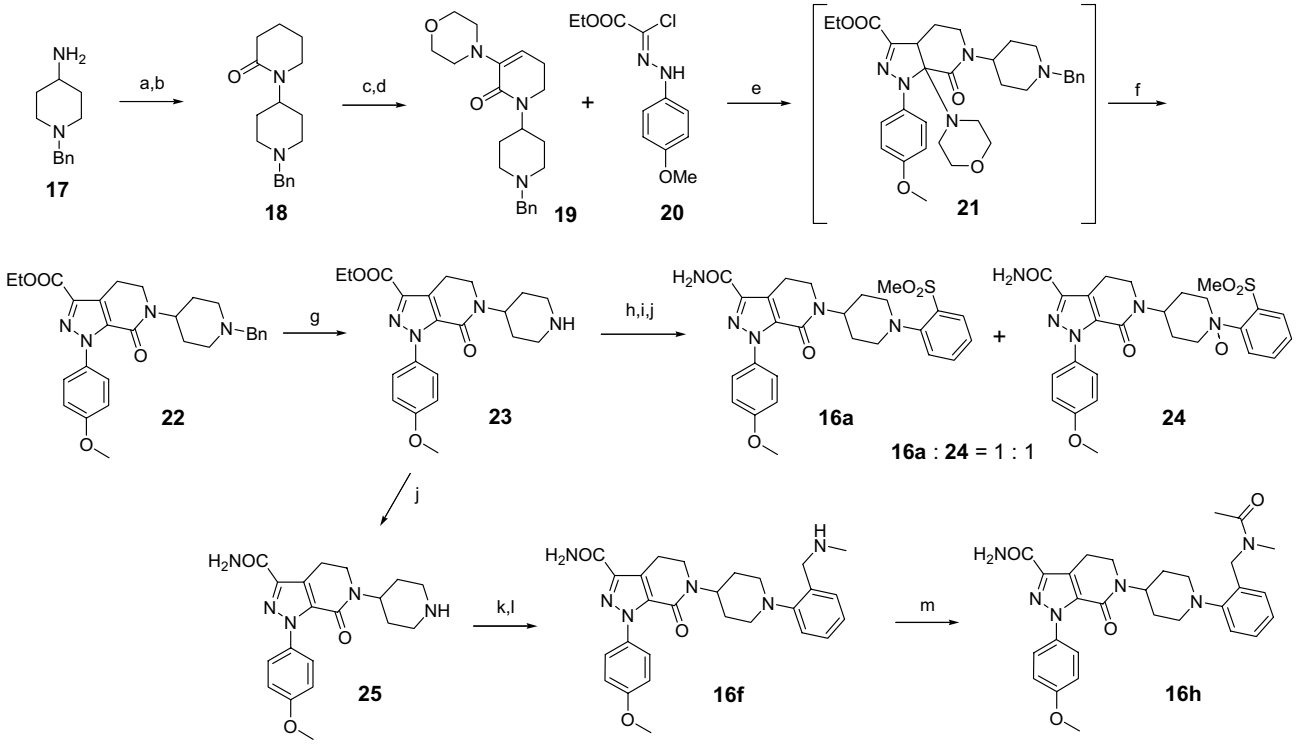
Compound **16a**–**j**	R	FXa K_i (nM)	PT IC_{2x} (μM)	Compound **11a**–**d**	FXa K_i (nM)
16a	SO_2Me	0.35	4.2	**11a**	14
16b	$CH_2N(Me)_2$	0.41	1.0	**11b**	8.8
16c	CH_2-*N*-Pyrrolidine	0.26	1.2	**11c**	29
16d	CH_2-*N*-Morpholine	0.57	3.5	**11d**	6.6
16e	CH_2-*N*-Pyrrolidine-2-(*S*)-OH	0.87	2.5		
16f	CH_2NHMe	1.0	1.8		
16g	CH_2NEt_2	0.26	1.5		
16h	$CH_2N(Me)COMe$	23	nd		
16i	$CH_2N(Me)SO_2Me$	81	nd		
16j	SO_2NH_2	3.9	nd		

[a] All compounds were purified by either reverse phase HPLC or preparative LC/MS (water/acetonitrile gradient + 0.5% TFA). The basic compounds were isolated as TFA salts following lyophilization. All compounds gave satisfactory spectral and analytical data.

[b] Human purified enzymes were used. Values were averages from multiple determinations ($n > 2$) and the standard deviations were <30% of the mean. K_i values were measured as described in Ref. 8a. PT values are measured according to Ref. 6a.

also showed good anticoagulant activity in human plasma in the clotting time assay (PT $IC_{2x} < 5$ μM). Sulfonamide **16j** was 10-fold less potent than the corresponding methylsulfone **16a**. *N*-Acetyl analog **16h** and *N*-methylsulfonyl analog **16i** were 20- and 40-fold less potent, respectively, relative to the parent basic amine compound **16f**.

Scheme 2 exemplifies the synthesis of fused pyrazole analogs bearing substituted *N*-arylpiperidine P4 groups



Scheme 2. Reagents and conditions: (a) $Br(CH_2)_4COCl$, aq K_2CO_3 (20% w/w), EtOAc, rt, 1 h; (b) KO-*t*-Bu, THF, 0 °C, 0.5 h; 99% for 2 steps; (c) PCl_5, $CHCl_3$, reflux, 3 h, 85%; (d) morpholine, reflux, overnight, 86%; (e) Et_3N, toluene, 85 °C, overnight; (f) 4 N HCl, CH_2Cl_2, rt, 4 h, 41% for 2 steps; (g) H_2, Pd/C (10%), HOAc, MeOH, rt, 3 h, 94%; (h) *o*-SMe–$PhB(OH)_2$ (2 equiv), Et_3N (2 equiv), $Cu(OAc)_2$ (1.5 equiv), 4 Å freshly activated molecular sieves, rt, 72 h, 50%; (i) *m*-CPBA, CH_2Cl_2, rt; (j) NH_3 in ethylene glycol, 85 °C, 2 h, 53% for h–j; (k) *o*-F–Ph–CHO, K_2CO_3, DMSO, 85 °C, 16 h, 78%; (l) NH_2Me, $NaBH(OAc)_3$, MeOH/CH_2Cl_2 (3:1), HOAc, rt, 2 h, 86%; (m) $ClCOCH_3$, pyridine, CH_2Cl_2, rt, 2 h, 50%.

using compounds **16a**, **16f**, and **16h** as examples. Starting from commercially available 4-amino-1-benzylpiperidine **17**, 1-(1-benzylpiperidin-4-yl)-piperidin-2-one **18** was formed in quantitative yield in two steps by condensation of **17** with 5-bromovaleryl chloride in the presence of aqueous potassium carbonate, followed by intramolecular displacement of the resulting bromide in the presence of potassium *tert*-butoxide. Treatment of **18** with three equivalents of phosphorus pentachloride followed by heating the resulting α,α-dichloropiperidinone intermediate in morpholine afforded the morpholino-enamine **19** in good yield at reflux. Condensation of **19** with the chlorohydrazone **20**[11] in the presence of two equivalents of triethylamine in hot toluene provided the morpholino intermediate **21**, which was then aromatized with 4 N HCl in methylene chloride to afford the desired bicyclic 7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine skeleton **22** in moderate yield. Removal of the benzyl group of **22** provided the key intermediate **23**. Intermediate **23** was treated with 2-(methylthio)phenylboronic acid, copper(II) acetate, and triethylamine in the presence of freshly activated molecular sieves under air, followed by oxidation with *meta*-chloroperbenzoic acid, and then C3 primary amide formation by heating in ethylene glycol saturated with ammonia to give a mixture of **16a** and its corresponding *N*-oxide **24**. Pure **16a** was obtained after reverse phase HPLC separation. Alternately, treatment of **23** with ammonia in ethylene glycol provided amide **25** which underwent S_NAr arylation with 2-fluorobenzaldehyde. Reductive amination with methylamine and sodium triacetoxyborohydride afforded amino derivative **16f**. Treatment of **16f** with acetyl chloride and pyridine provided the amide derivative **16h**.

The bioactive conformation of both fused pyrazole **16a** (Fig. 2) and monocyclic pyrazole **11a** (Fig. 3) was assigned on the basis of crystal structures of related FXa inhibitors bearing biaryl P4 moieties, for example, **1** (**DPC423**),[3] quantum mechanical calculations,[12] and small molecule crystallographic data.[13] Short MD simulations[14] suggested no significant differences in the overall binding motifs of **11a**-FXa and **16a**-FXa relative to **1**.

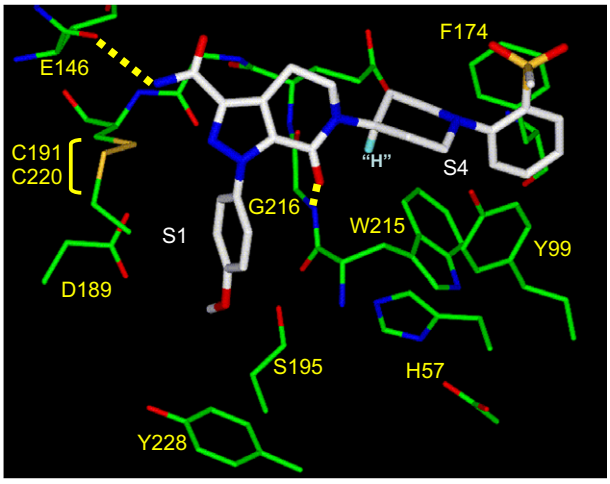


Figure 2. Proposed binding mode of **16a** in factor Xa.

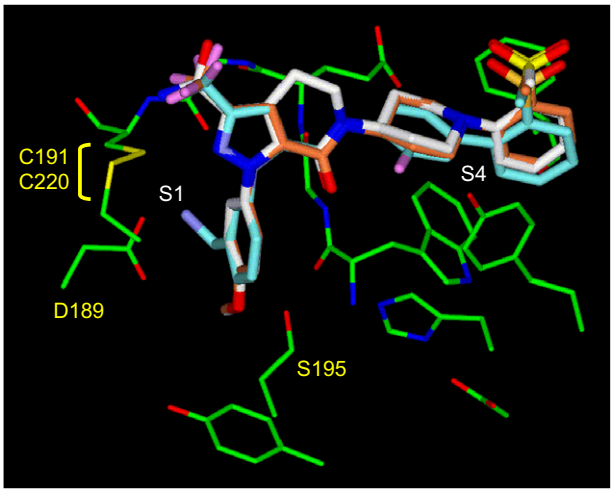


Figure 3. Overlay of proposed binding modes of **11a** and **16a** with crystal structure of **1** (**DPC423**) in factor Xa.

Quantum mechanical calculations and analysis of small molecule crystallographic data suggested that (1) the amide carbonyl, which forms a hydrogen bond with G216 NH, adopts a favored *syn* relationship with the adjacent piperidinyl tertiary CH (Fig. 2); and (2) the nitrogen atom of the *N*-arylpiperidine P4 group likely adopts a tetrahedral (sp^3) geometry, such that the piperidinyl C2 and C6 methylene groups are directed away from the bulky *ortho*-methylsulfonyl substituent of the phenyl ring.

Table 4 shows a comparison of the in vitro properties and PK profile of fused pyrazole analog **16a** and compound **1** (**DPC423**). Both had similar FXa inhibitory activity in the primary binding assay and similar potency in the functional clotting time assay. Compound **16a** had an improved selectivity profile compared with **1** with respect to trypsin and plasma kallikrein. Despite

Table 4. Comparison of in vitro and pharmacokinetic profiles (in dogs) of pyrazoles **1** (**DPC423**) and **16a**

In vitro and PK profiles	1 (DPC423)	**16a**
Factor Xa K_i (nM)	0.30	0.35
PT IC_{2x} (μM)	3.5	4.2
Thrombin K_i (nM)	6000	1200
Trypsin K_i (nM)	60	>20,000
Plasma kallikrein (μM)	61	>11,000
Activated protein C (μM)	1800	>37,600
Chymotrypsin (μM)	>17,000	4475
Urokinase (μM)	>19,000	>13,000
Plasmin (μM)	>35,000	>28,000
tPA (μM)	>45,000	>43,000
Caco-2 $P_{app} \times 10^{-6}$ (cm/s)	4.8	1.5
HLM $t_{1/2}$ (min)	124	117
Cl[a] (L/Kg/h)	0.24[c]	0.23[d]
V_{dss} (L/Kg)	0.99[c]	0.33[d]
po $t_{1/2}$[b] (h)	7.5[c]	0.8[d]
$F\%$[b]	57[c]	78[d]

[a] iv dose: 0.5 mg/kg.
[b] po dose: 0.2 mg/kg.
[c] From discrete dog PK study.
[d] From cassette dosing in dog PK studies.

a relatively low Caco-2 P_{app} value, **16a** showed good oral bioavailability in dogs with $F\% = 78\%$. In fact, **16a** showed low systematic clearance and good oral bioavailability in dogs similar to **1** (**DPC423**). However, **16a** had a shorter $t_{1/2}$ which may be due to its lower V_{dss}. Studies of possible metabolites of **16a**, and search for structural modifications to block or reduce the metabolic pathways may improve the pharmacokinetic profile of this series of compounds.

In summary, a series of pyrazole analogs bearing substituted piperidine P4 groups were synthesized and identified as potent and selective FXa inhibitors in both monocyclic pyrazole and bicyclic pyrazolopyridine series. The fused pyrazole analogs containing a neutral *p*-methoxyphenyl P1 group showed improved FXa inhibitory activity relative to their monocyclic counterparts. Compound **16a**, bearing a 2′-methylsulfonylphenyl piperidinyl P4 group, was one of the most potent and selective compounds prepared in this series, offering a PK profile with low *Cl* and good bioavailability similar to **1** (**DPC423**), but a shorter $t_{1/2}$.

References and notes

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12. (a) Conformational analysis was done using similar protocols for *N*-cyclohexylacetamide and *N*-(2-methylsulfonyl)phenyl piperidine as model systems. Conformational ensembles of each model system were manually generated in MacroModel (MMFFs force-field/GBSA solvent model), and passed onto Jaguar for estimates of relative conformational energies at LMP2/cc-pvtz(-f)++//B3LYP/6-31G*; (b) MacroModel 9.0, Jaguar 6.0 Schrodinger, Inc., NY.
13. Analysis of small molecular crystal data relating to the substructures of interest was done using Conquest 1.7, Cambridge Crystallographic Database, www.ccdc.cam.ac.uk.
14. MD simulations were conducted with Discover_3 using CFF98 force-field over 24 ps gas phase. www.accelrys.com.