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Preparation of 1-(4-methoxyphenyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones as potent, selective and bioavailable inhibitors of coagulation factor Xa

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Abstract—Previously, potent factor Xa inhibitors were described based on a pyrazole core. Modifications of the pyrazole core have provided additional novel, highly potent factor Xa inhibitors. This manuscript will describe the synthesis and biological activity of factor Xa inhibitors containing the 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one and related bicyclic cores. Many of these compounds are potent, selective, and orally bioavailable inhibitors of coagulation factor Xa.

Thromboembolic diseases remain the leading cause of death and disability in developed countries. This reality, combined with the limitations of current therapies, has led to extensive efforts to develop novel antithrombotic agents.[1] Factor Xa has become a major focus of pharmaceutical intervention in the past decade because of its central role in the blood coagulation cascade.[2] Extensive preclinical and clinical evidence has demonstrated that inhibition of factor Xa is efficacious in both venous and arterial thrombosis.[3,4]

Previously, it was demonstrated that a series of *N*-arylpyrazole carboxamides, represented by the P1 benzylamine analog DPC423 (**1**),[5] were highly potent, selective, and orally bioavailable small molecule inhibitors of factor Xa (Fig. 1). Subsequently, razaxaban (**2**),[6a] with an aminobenzisoxazole P1, was discovered and has been shown to be efficacious in phase II deep vein thrombosis (DVT) clinical trials.[6b] Furthermore, it was demonstrated that the 4-methoxyphenyl residue could be an effective P1 group when combined with an optimized pyrazole-P4 subunit, as in compound **3**.[7] Thus, the *N*-arylpyrazole carboxamides have been shown to be a versatile and highly efficacious class of fXa inhibitors.

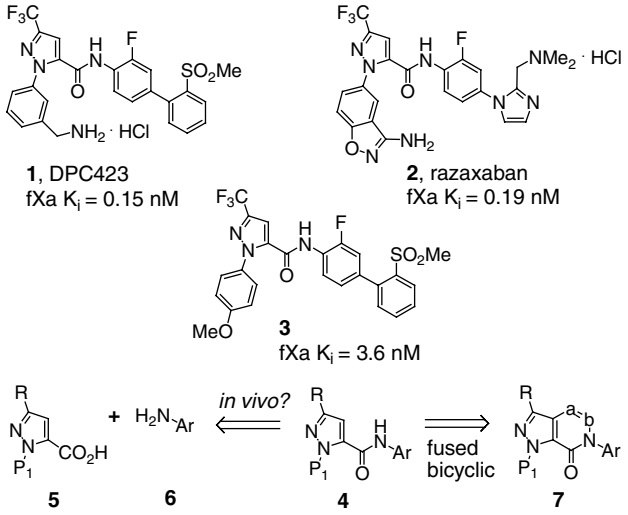

Figure 1.

However, it was recognized that the common pyrazole carboxamide **4,** present in all of the compounds **1**–**3,**

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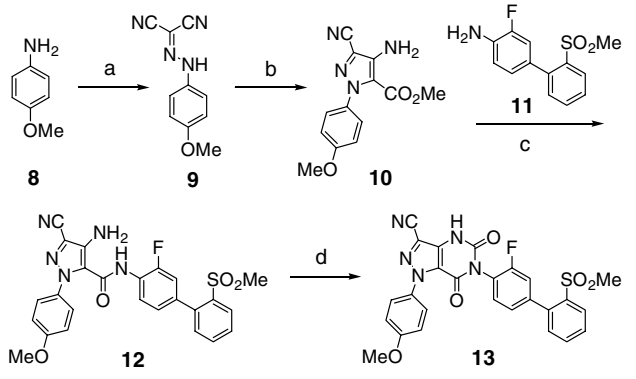
can potentially be hydrolyzed in vivo to liberate a pyrazole carboxylic acid **5** and a biarylaniline **6** (Fig. 1). This was of concern due to the known mutagenicity of many anilines/biarylanilines.[8] Furthermore, it was discovered that there was no clear SAR in terms of mutagenicity within this biarylaniline P4 series, necessitating that any aniline of interest would require rigorous purification and mutagenicity testing. Thus, in efforts to discover back-up compounds to razaxaban, several strategies were pursued that were designed to avoid the potential formation of an aniline fragment. One such strategy involved incorporating the amide within a bicyclic core structure **7**. This was expected to provide protection from in vivo aniline formation by rendering the amide less likely to be hydrolyzed and also by requiring an additional step (cleavage of the N–b bond) to liberate the free aniline. This manuscript describes the initial success in realizing this strategy,[9] where it was discovered that several bicyclic cores maintained fXa potency and served as effective mimics of the pyrazole carboxamide moiety when 4-methoxyphenyl was utilized as the P1 recognition group.[7,10]

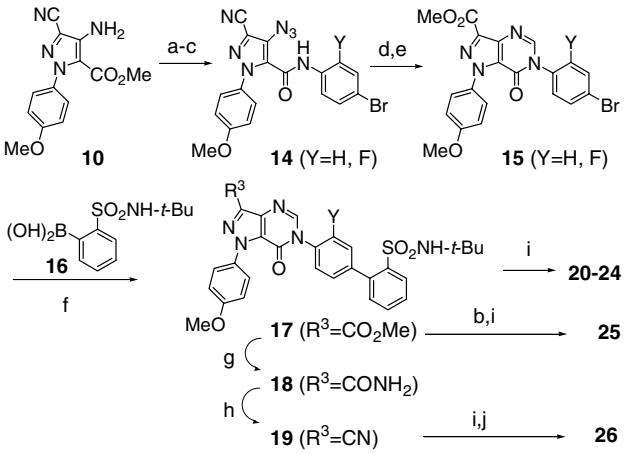
The initial bicyclic core example, the 1*H*-pyrazolo-[4,3-*d*]pyrimidin-5,7(4*H*,6*H*)-dione **13**, was prepared as described in Scheme 1. Diazotization of *p*-anisidine **8** was followed by treatment with malonitrile to afford the dicyanohydrazone **9**. Treatment of this hydrazone with methyl bromoacetate and K_2CO_3 at 90 °C gave the 4-aminopyrazole **10** by N-alkylation and in situ ring closure. Weinreb coupling with the highly optimized biphenylaniline **11**[7] afforded the amide **12** in a low an irreproducible yield, which was subsequently cyclized to compound **13**, also in low yield, by treatment with carbonyl diimidazole.

The initial 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one examples **20**–**26**, with a biphenylsulfonamide P4 group, were prepared as shown in Scheme 2. A more stepwise approach was taken to avoid the low-yielding Weinreb amide coupling. Aminopyrazole **10** was diazotized and treated with sodium azide to form a 4-azidopyrazole, where the azide functionality essentially served as an amine protecting group. Ester hydrolysis and amide coupling via the acid chloride afforded amides **14**. Reduction of the azide was accomplished with tin(II) chloride hydrate in refluxing methanol, conditions that also effected the conversion of the nitrile to a methyl ester. The resulting 4-aminopyrazole-5-carboxamide was cleanly cyclized to the 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one bicyclic core **15** by refluxing in formic acid. Suzuki coupling with boronic acid **16**[6a] smoothly furnished the protected biphenylsulfonamide **17**. The pyrazole ester **17** was converted to the primary amide **18** by treatment with ammonium hydroxide in dioxane, and the amide was subsequently dehydrated with $POCl_3$ in refluxing benzene to afford the nitrile **19**. Compounds **17**–**19** were deprotected with TFA to give compounds **20**–**24**. The ester **17** was converted to the carboxylic acid **25** by hydrolysis and subsequent TFA deprotection. TFA-catalyzed deprotection of **19** followed by nitrile reduction furnished the primary amine **26**.

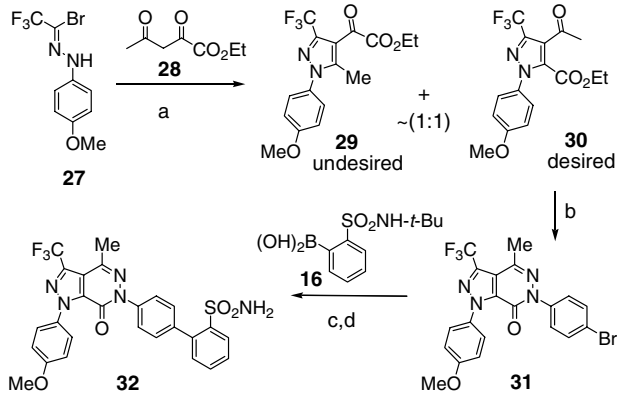
The 1*H*-pyrazolo-[3,4-*d*]-pyridazin-7(6*H*)-one core analog **32** was prepared as described in Scheme 3.



Scheme 1. Reagents and conditions: (a) $NaNO_2$, HCl/H_2O, 0 °C; then malonitrile, NaOAc, $MeOH/H_2O$, 0 °C (70–80%); (b) $BrCH_2CO_2Me$, K_2CO_3, DMF, 90 °C (35%); (c) **11**, $AlMe_3$, CH_2Cl_2, 40 °C (10–20%); (d) CDI, THF (20%).



Scheme 2. Reagents and conditions: (a) $NaNO_2$, TFA, 0 °C; then NaN_3 (75%); (b) LiOH, THF/H_2O (90–95%); (c) $(COCl)_2$, CH_2Cl_2; then 4-bromoaniline or 4-bromo-2-fluoroaniline (70–80%); (d) $SnCl_2 \cdot H_2O$, MeOH, 65 °C (55–65%); (e) 95% HCO_2H, reflux (80–85%); (f) **16**, $Pd(PPh_3)_4$, Na_2CO_3, benzene, H_2O, 80 °C (75–80%); (g) NH_4OH, dioxane, 80 °C (50–60%); (h) $POCl_3$, benzene, reflux (50%); (i) TFA, CH_2Cl_2, 25 °C (40–60%); (j) H_2 (1 atm), 10% Pd/C, EtOH, TFA (50%).



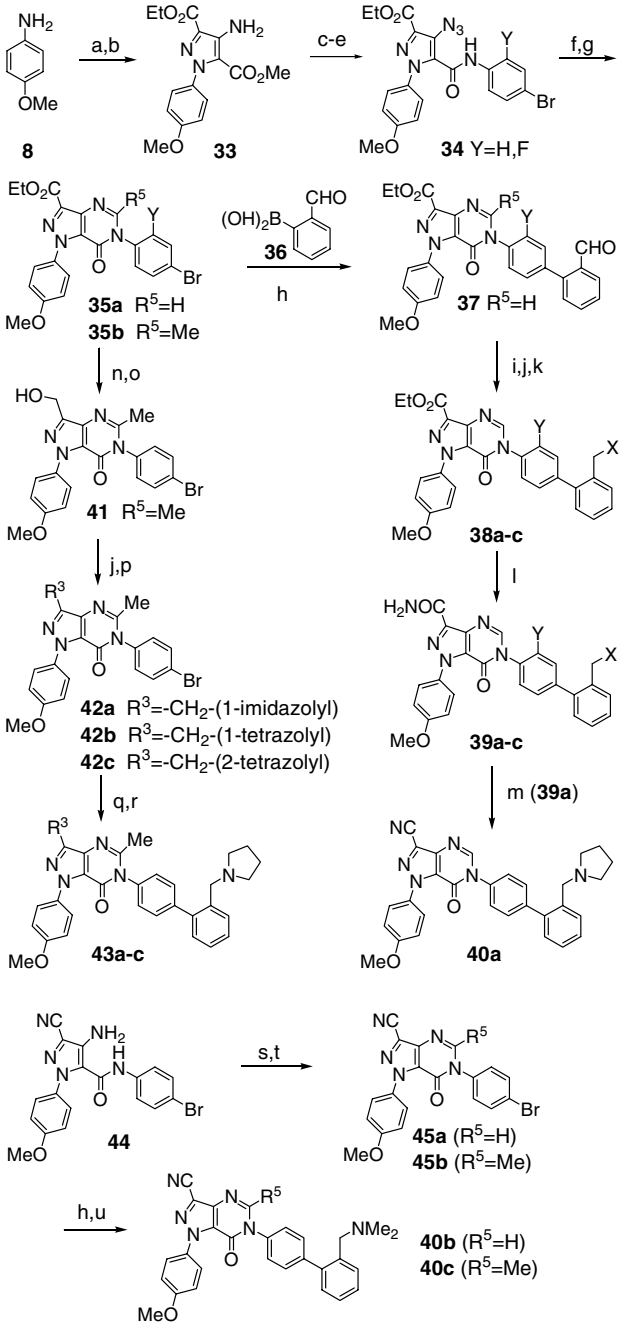
Scheme 3. Reagents and conditions: (a) **28**, NaOEt, EtOH (75%); (b) 4-bromophenylhydrazine, EtOH, reflux (80%); (c) **16**, $Pd(PPh_3)_4$, Na_2CO_3, benzene, H_2O, 80 °C (80%); (d) TFA, CH_2Cl_2, 25 °C (60%).

The readily available 1-ethylidene-2-phenylhydrazine **27**[11] was treated with ethyl 2,4-dioxovalerate **28** in the presence of ethanolic sodium ethoxide to afford a good yield of a separable 1:1 mixture of pyrazole regioisomers **29** and **30**. The desired **30** was smoothly condensed with 4-bromophenylhydrazine in refluxing ethanol to give the 1*H*-pyrazolo-[3,4-*d*]-pyridazin-7(6*H*)-one core **31**, which crystallized out of solution upon cooling. Suzuki coupling with the boronic acid **16** and TFA deprotection afforded **32**.

Compounds with a basic *N*,*N*-dialkylaminomethyl residue appended onto the terminal aryl ring of the P4 were prepared as described in Scheme 4. The pyrazole diester **33** was prepared analogously to compound **10**, except that ethyl cyanoacetate was used instead of malonitrile. The azidoamide **34** was also prepared as described previously, with the key step being the selective hydrolysis of the methyl ester with lithium hydroxide. Tin(II) chloride reduction of **34** proceeded cleanly to afford the 4-aminopyrazole, which was cyclized as before with formic acid to give **35a** (R^5 = H). Alternatively, cyclization of the 4-aminopyrazole in refluxing glacial acetic acid produced **35b** (R^5 = Me). Suzuki coupling of **35a** with 2-formylphenylboronic acid **36** afforded the biphenyl aldehyde **37**. Reductive amination to introduce the *N*,*N*-dialkylaminomethyl group was generally unsatisfactory. A three-step protocol was more efficient, involving sodium borohydride reduction of the aldehyde, phosphorus tribromide-mediated bromination of the alcohol, and displacement of the bromide with an appropriate cyclic or acyclic secondary amine, to afford compounds **38**. As previously, the pyrazole ester was readily converted to the primary amides **39** with ammonium hydroxide and then subsequently dehydrated in one case (**39a**) to form the nitrile **40a**.

Also in Scheme 4, conversion of **35b** to the alcohol **41** was accomplished by hydrolysis and subsequent reduction of the acid via sodium borohydride reduction of an acid-derived mixed anhydride. Treatment of **41** with phosphorus tribromide afforded the bromide, which was displaced by imidazole to give **42a**, and by tetrazole to give an inseparable mixture of the two tetrazole regioisomers **42b** and **42c**. Suzuki coupling of **42** with boronic acid **36** was followed by reductive amination with pyrrolidine and sodium triacetoxyborohydride, which in this case gave serviceable yields of compounds **43**. The isomers **43b** and **43c** were separable by HPLC. Compound **46** was prepared from **31** by procedures described above.

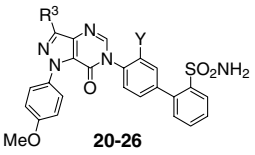
Finally in Scheme 4, attempted ring closure of the cyanopyridine **44**[12] under the standard conditions (formic acid 85 °C) or other conditions (*N*,*N*-DMF dimethyl acetal or $HC(OEt)_3$, 100 °C) did not afford the desired bicyclic core **45a**. In all cases the expected intermediate was formed (*N*-formyl or *N*′,*N*′-dimethyl-*N*-formamidine) but ring closure of the amide nitrogen onto this intermediate did not take place. It was presumed that the nitrile was having a negative effect on either the amide reactivity or the basicity of the intermediates, or both. This problem was circumvented by



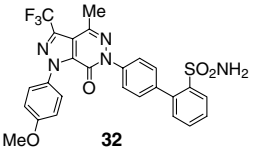
Scheme 4. Reagents and conditions: (a) $NaNO_2$, HCl/H_2O, 0 °C; then ethyl cyanoacetate, NaOAc, $MeOH/H_2O$, 0 °C (85%); (b) $BrCH_2CO_2Me$, K_2CO_3, DMF, 90 °C (25%); (c) $NaNO_2$, TFA, 0 °C; then NaN_3 (90%); (d) LiOH, THF/H_2O (75%); (e) $(COCl)_2$, CH_2Cl_2; then 4-bromoaniline or 4-bromo-2-fluoroaniline (80–90%); (f) $SnCl_2$–H_2O, MeOH, 65 °C (50–60%); (g) 95% HCO_2H, reflux (R^5 = H, 80–85%), or HOAc, reflux (R^5 = Me, 80–85%); (h) **36**, $Pd(PPh_3)_4$, Na_2CO_3, benzene, H_2O, 80 °C (75–85%); (i) $NaBH_4$, MeOH (60–70%); (j) PBr_3, CH_2Cl_2 (80–90%); (k) HNRR′, CH_3CN, (60–70%); (l) NH_4OH, dioxane, 80 °C (50–60%); (m) $POCl_3$, benzene, reflux (50%); (n) KOH, $MeOH/THF/H_2O$, (85%); (o) IBCF, NMM, THF, 0 °C; then $NaBH_4$, MeOH, (75%); (p) imidazole, DMF or tetrazole, K_2CO_3, DMF (80–90%); (q) **36**, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 80 °C, (55–75%); (r) pyrrolidine, $NaBH(OAc)_3$, HOAc, THF (30–50%); (s) *N*,*N*-DMF dimethyl acetal, 100 °C (R^5 = H), or *N*,*N*-dimethylacetamide dimethyl acetal, 100 °C (R^5 = Me); (t) 95% HCO_2H, reflux (R^5 = H, 80% two steps), or HOAc, reflux (R^5 = Me, 75% two steps); (u) $HNMe_2$, $NaBH(OAc)_3$, HOAc, THF (40–50%).

employing an efficient two-step cyclization procedure. Thus, treatment of **44** with *N*,*N*-DMF dimethyl acetal at 100 °C afforded the expected *N*′,*N*′-dimethyl-*N*-formamidine intermediate, which does not close to the desired bicyclic under the conditions in which it is formed. However, when this intermediate is isolated and subjected to refluxing formic acid, smooth ring closure to **45a** occurs. Therefore, the *N*′,*N*′-dimethyl-*N*-formamidine intermediate is more reactive to ring closure relative to the *N*-formyl intermediate, but requires acidic conditions for ring closure to occur. Likewise, compound **44** was treated sequentially with *N*,*N*-dimethylacetamide dimethyl acetal at 100 °C and then with refluxing glacial acetic acid to prepare **45b**. Compounds **45a**,**b** were treated as previously disclosed to afford compounds **40b**,**c**, respectively.

Table 1. Bicyclic cores with biphenylsulfonamide P4



20-26



32

Compound[a]	R^3	Y	fXa K_i[b] (nM)	aPTT IC2×[c] (μM)	PT IC2×[c] (μM)
2	—	—	0.19	6.1	2.1
3	—	—	3.5	104	
12	—	—	8.4		
13	—	—	3.0	197	
20	CO_2Me	H	2.8	7.1	
21	CO_2Me	F	1.8		
22	$CONH_2$	H	1.7	8.7	
23	$CONH_2$	F	1.2	9.8	
24	CN	H	1.9	5.8	
25	CO_2H	H	38		
26	CH_2NH_2	H	22		
32	—	—	2.8		

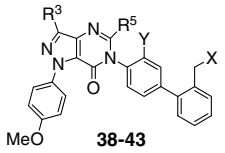
[a] All final compounds were purified by prep HPLC and gave satisfactory spectral data.

[b] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 6a.

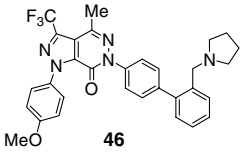
[c] The aPTT (activated partial thromboplastin time) and PT (prothrombin time) in vitro clotting assays were performed in human plasma as described in Ref. 6a.

The SAR for the initial set of compounds, where the P4 was a biphenylsulfonamide residue, is shown in Table 1. The initial bicyclic example, **13**, illustrated the feasibility of this strategy. This compound was equipotent with **3**, a highly optimized analog in the 4-methoxyphenyl P1 series,[7] and more potent than the uncyclized **12**, thereby suggesting that the bicyclic core effectively orients the biphenyl residue for binding in the P4 pocket. However, the poor potency of **13** in the in vitro aPTT clotting assay indicated that the 1*H*-pyrazolo[4,3-*d*]pyrimidin-5,7(4*H*,6*H*)-dione core might suffer from very high protein binding. The 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one, the major focus of this manuscript, appears to be a more promising bicyclic core. Compounds **20**–**24** all have equal or more potent binding than **13**, and also appear to have significantly lower protein binding as indicated by their more potent activities in the aPTT assay, which are comparable to that of razaxaban and more favorable than those of **3** and **13**. The data show that ester, primary amide, and nitrile are well tolerated as 3-substituents and appear to be suitable replacements for the CF_3 group. Further SAR around the 3-substituent demonstrated that the carboxylic acid **25** and the

Table 2. Incorporation of a basic P4 group



38-43



46

Compound[a]	R^3	R^5	Y	X	fXa K_i[b] (nM)	aPTT IC2×[c] (μM)	PT IC2×[c] (μM)
2	—	—	—	—	0.19	6.1	2.1
38a	CO_2Et	H	H	*N*-Pyrrolidine	3.8	1.8	
38b	CO_2Et	H	F	*N*-Pyrrolidine	3.6		
38c	CO_2Et	H	H	OH	45		
39a	$CONH_2$	H	H	*N*-Pyrrolidine	1.1	4.0	2.2
39b	$CONH_2$	H	F	*N*-Pyrrolidine	0.74	3.9	3.4
39c	$CONH_2$	H	H	3-(*R*)-OH-*N*-pyrrolidine	1.5	5.0	3.6
40a	CN	H	H	*N*-Pyrrolidine	1.7		
40b	CN	H	H	NMe_2	2.1		
40c	CN	Me	H	NMe_2	1.8		
43a	$–CH_2$-(1-imidazolyl)	Me	H	*N*-Pyrrolidine	2.1		
43b	$–CH_2$-(1-tetrazolyl)	Me	H	*N*-Pyrrolidine	1.4		
43c	$–CH_2$-(2-tetrazolyl)	Me	H	*N*-Pyrrolidine	1.9	20.1	6.5
46	—	—	—	—	2.8	53	62

[a] All final compounds were purified by prep HPLC and gave satisfactory spectral data.

[b] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 6a.

[c] The aPTT (activated partial thromboplastin time) and PT (prothrombin time) in vitro clotting assays were performed in human plasma as described in Ref. 6a.

primary amine **26** were 10- to 15-fold less potent than **20**–**24**. The 1*H*-pyrazolo-[3,4-*d*]-pyridazin-7(6*H*)-one core analog **32** was also found to have comparable potency to compounds **20**–**24**.

Recently, inspired by the basic *N*,*N*-dimethylaminomethyl moiety present in razaxaban **2**, it was demonstrated that the sulfonamide group on the terminal aryl ring of the P4 biphenylsulfonamides could be effectively replaced by a variety of cyclic and acyclic *N*,*N*-dialkylaminomethyl, *N*-alkylaminomethyl, and related residues.[13] This strategy was also employed in this series, with the expectation that the resulting compounds might have greater potency, both in fXa binding and in the in vitro clotting assays.

The SAR for these compounds are shown in Table 2. In general, there was little difference in fXa potency upon replacing the terminal ring sulfonamide with *N*,*N*-dialkylaminomethyl residues. Compounds **38a**,**b**, **39a**–**c**, and **40a**,**b** were all potent fXa inhibitors, comparable to the corresponding analogs from Table 1. The alcohol **38c**, an intermediate from Scheme 4 with a non-basic sulfonamide replacement, was an order of magnitude less potent than the corresponding *N*-pyrrolidine **38a**. Compound **40c** demonstrates that 5-methyl substitution is tolerated on the bicyclic core. Despite no improvement in potency, compounds **38a** and **39a**–**c** show slightly enhanced activity in the aPTT assay relative to similar sulfonamide analogs from Table 1, suggesting that the basic P4 substitution may be having a favorable effect in lowering protein binding. The aPTT and PT profiles of the 3-amido analogs **39a**–**c** are comparable to that of razaxaban. Additional 3-substituents, represented by **43a**–**c**, were explored for the possibility of further improving fXa potency. However, these compounds offered no potency advantage relative to the nitrile **40c**. Furthermore, the 2-tetrazolylmethyl analog **43c** was less potent in the in vitro clotting assays relative to **39a**–**c**, suggesting an unfavorable effect on protein binding. Compound **46** was equipotent with the corresponding 1*H*-pyrazolo-[3,4-*d*]-pyridazin-7(6*H*)-one example **32**, but had poor activity in the aPTT and PT assays, again indicative of high protein binding, which is likely highly influenced by the 3-trifluoromethyl substituent.

Compounds with the 4-methoxyphenyl P1 residue have previously been reported to show high selectivity for fXa versus thrombin and trypsin.[7] Additional selectivity data are shown for selected compounds in Table 3. Compounds **39a**, **39b**, and **40a** all showed >1000-fold selectivity relative to trypsin, aPC, factor IXa, factor VIIa, plasmin, tPA, plasma kallikrein, and urokinase. They are less selective relative to thrombin and chymotrypsin, but still show >600-fold selectivity in all cases. The overall selectivity profile for these compounds in most cases is comparable to that of razaxaban.

The pharmacokinetic profiles of compounds **39a**, **b**, and **40a** were studied in dogs via a cassette dosing format, with dosing at 0.5 mg/kg intravenously and 0.2 mg/kg orally (Table 4). The amides **39a** and **b** compare very favorably with razaxaban, with each having lower clearance, longer half-life, higher bioavailability, and comparable volume of distribution.

Table 3. Human enzyme selectivity profile

Enzyme K_i (nM)	**39a**	**39b**	**40a**	Razaxaban
fXa	1.1	0.74	1.7	0.19
Thrombin	1600	1800	1100	540
Trypsin	>4200	>2500	>2500	>10,000
aPC	>76,000	>76,000	48,710	19,700
fIXa	>41,000	>15,000	>15,000	9000
fVIIa	>15,000	>15,000	>15,000	>15,000
Plasmin	>15,000	>15,000	>15,000	>15,000
tPA	>33,000	>33,000	>33,000	>33,000
Urokinase	>13,000	>13,000	>13,000	>13,000
Chymotrypsin	7930	530	2030	8500

All K_is were obtained from purified human enzymes and are averaged from multiple determinations ($n = 2$). See Ref. 6a for more details.

The higher permeabilities for **39a**,**b** in the Caco-2 assay correlate with the observed higher bioavailabilities. These results demonstrate that the 3-amido group is a well-tolerated substituent on the 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one core. The fluoro substituent on the inner phenyl ring has little effect on the PK profile or Caco-2 permeability. The nitrile analog **40a** has an unfavorable PK profile, with very high clearance and volume of distribution.

Two of these compounds were also studied in the rabbit arterio-venous (A-V) shunt thrombosis model.[5b] Upon intravenous dosing, compound **39a** inhibited thrombus formation with an IC_{50} of 1200 nM and an ID_{50} of 5.5 μmol/kg/h (Table 5), which is about 3- to 4-fold less efficacious than razaxaban in this model. Compound **39b** is less potent, achieving only 33% inhibition of thrombus formation at 4.6 μmol/kg/h. The reduced activity of **39a** relative to **39b** may reflect the higher protein binding of **39b**, since the K_i and PT values are essentially equivalent. This level of activity for **39a** and **39b** is somewhat surprising, given the potent fXa inhibition, low clearance in the dog PK studies, and favorable protein binding in the rabbit, where these analogs are expected to have 2- to 3-fold higher free fraction relative to razaxaban. Apparently, their favorable PK and protein binding are not sufficient to overcome their diminished fXa potency compared to razaxaban. These results have led to the conclusion that the fXa binding potency

Table 4. Dog pharmacokinetic profiles

Compound	Cl (L/h/kg)	V_{dss} (L/kg)	$t_{1/2}$ (h)	F (%)	Caco-2 ($P_{app} \times 10^{-6}$ cm/s)
39a[a]	0.55	3.9	5.4	94	12
39b[a]	0.76	4.9	5.1	96	15
40a[a]	6.8	75	8.3	77	3.1
Razaxaban[b]	1.1	5.3	3.4	84	5.6

[a] Compounds were dosed as the TFA salts in an N-in-1 format at 0.5 mg/kg i.v. and 0.2 mg/kg p.o. ($n = 2$).
[b] Ref. 6a.

Table 5. Anticoagulant activity in rabbits

Compound	fXa K_i (rabbit) (nM)	PT IC2x (rabbit) (uM)	Rabbit A-V shunt[5b] IC_{50} (nM)	Rabbit A-V shunt[5b] ID_{50} (μmol/kg/h)	Protein binding[14] (rabbit) (% bound)
39a	1.0	1.8	1200	5.5	77
39b	1.2	1.6	>1000[b]	33% inh @ 4.6 μmol/kg/h	85
Razaxaban[a]	0.19	1.9	340	1.6	93

[a] Ref. 6a.
[b] Concentration at 4.6 μmol/kg/h.

of this series needs to be improved significantly in order to achieve potent activity in the rabbit A-V shunt thrombosis model.

In summary, the first examples of pyrazole-fused bicyclic core fXa inhibitors have been described. The 1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one core is especially promising as a means to maintain potent fXa inhibition, while also reducing the probability that in vivo amide hydrolysis will liberate an aniline fragment. Within this series, the 3-amido analogs **39a** and **39b** are not only potent fXa inhibitors, but they are also highly selective versus relevant serine protease inhibitors, have excellent pharmacokinetic profiles, and have relatively low protein binding. Unfortunately, these compounds were not highly efficacious in the rabbit A-V shunt thrombosis model, perhaps because they are not potent enough versus fXa, both compounds being about 5-fold less potent than razaxaban. Further efforts to increase the potency of this series will be described in due course.

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