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Highly efficacious factor Xa inhibitors containing α-substituted phenylcycloalkyl P4 moieties

Jennifer X. Qiao *, Sarah R. King, Kan He, Pancras C. Wong, Alan R. Rendina, Joseph M. Luettgen, Baomin Xin, Robert M. Knabb, Ruth R. Wexler, Patrick Y. S. Lam

Research and Discovery, Bristol-Myers Squibb Company, P.O. Box 5400, Princeton, NJ 08543-5400, USA

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ABSTRACT

We previously disclosed a series of highly potent FXa inhibitors bearing α-substituted ($CH_2NR^1R^2$) phenylcyclopropyl P4 moieties in the pyrazolodihydropyridone core system. Herein, we describe our continuous SAR efforts in this series. Effects of the C-3 substitution of the pyrazolodihydropyridone core and the α-substitution (R group) of the cyclopropyl ring on FXa binding affinity (FXa K_i), human plasma anticoagulant activity (PT $EC_{2\times}$) and permeability are discussed. A set of compounds obtained from optimization of the R group and the C-3 substituent were orally bioavailable in dogs. Furthermore, representative compounds were highly efficacious in the rabbit arterio-venous shunt thrombosis model (EC_{50}s = 29–81 nM).

Anticoagulants are key agents for the prophylaxis and treatment of thromboembolic disorders. Limitations of the existing anticoagulants warfarin and heparins establish a need for newer therapies. The past decade saw the development of a class of novel anticoagulants designed to inhibit thrombin generation by targeting the direct inhibition of coagulation factor Xa (FXa), a serine protease at the conjunction of the intrinsic and the extrinsic pathways in the coagulation cascade. Both preclinical and clinical data have shown that inhibition of FXa is an effective approach in the treatment of venous and arterial thrombosis.[1,2] Several selective and orally active small-molecule FXa inhibitors, such as razaxaban,[3] apixaban,[4] LY517717,[2g] YM150,[2g] DU-176b,[2g] and rivaroxaban,[2g] have entered clinical development, some of which are in the late-stage clinical trials for the prevention and treatment of thromboembolic diseases.

We previously discussed[5] the discovery of a series of highly potent and selective pyrazole bicyclic-based FXa inhibitors bearing α-substituted ($CH_2NR^1R^2$) phenylcyclopropyl P4 moieties. These have the general structure **A**[3] shown in Figure 1, where the perpendicular conformation of the phenylcyclopropyl groups in **A** was used to mimic the bioactive conformation of the *ortho*-substituted biphenyl moieties in **B** (Fig. 1).[5] We herein describe our continuous SAR efforts on this series with a general structure **C** (Fig. 1) by varying both the C-3 substituent of the pyrazolodihydropyridone core and the α-substituent (R group) on the phenylcyclopropyl group to improve anticoagulant activity, and to modulate physicochemical properties such as permeability. A set of compounds in this series underwent PK studies and four compounds were tested in the rabbit arterio-venous shunt model for antithrombotic effects.

We began to investigate the effects of polar C-3 substituents of the pyrazolodihydropyridone core on FXa potency and anticoagulant activity in the early analogs[5] (R = $CH_2NR^1R^2$). Table 1 shows a comparison of α-$CH_2NR^1R^2$-substituted phenylcyclopropyl P4 analogs **1–6** bearing various C-3 groups. Replacing CF_3 in **1a–5a** with a SO_2Me, $CONH_2$, or CN group resulted in compounds with increased polarity, indicated by the increased polar surface area (PSA) and lowered overall lipophilicity (clog*P*). Compounds **1b–5b**, **1c–4c**, and **1d–4d** bearing a SO_2Me, $CONH_2$, or CN group, respectively, had similarly high FXa affinity as the corresponding CF_3 analogs **1a–5a** (FXa K_i in the pM range). Furthermore, compounds **1b–5b**, **1c–4c**, and **1d–4d** generally had higher anticoagulant activity (PT $EC_{2\times}$) compared with the corresponding CF_3 analogs **1a–5a**. This is particularly true for the less basic compounds, such as the morpholinyl analogs **4a–4d** (PT $EC_{2\times}$ of CF_3 analog **4a** was 14 μM, while PT $EC_{2\times}$ values of **4b** (SO_2Me), **4c** ($CONH_2$) and **4d** (CN) were 1.7, 1.5, and 4.1 μM, respectively). The improved in vitro clotting activity can be attributable to lower protein binding, that is, the increased free fraction in human plasma caused by the more polar C-3 groups. On the other hand, both the basic pyrrolidines **3b** (SO_2Me C-3) and **3c** ($CONH_2$ C-3) and the neutral pyrrolidones **6b** and **6c** showed good FXa binding activity and good PT anticoagulant activity.

Table 1 indicates that the Caco-2 apparent permeability values (P_{app}, apical to basolateral) followed a general trend: compounds

* Corresponding author. Tel.: +1 609 818 5298; fax: +1 609 818 6810.
E-mail address: jennifer.qiao@bms.com (J.X. Qiao).

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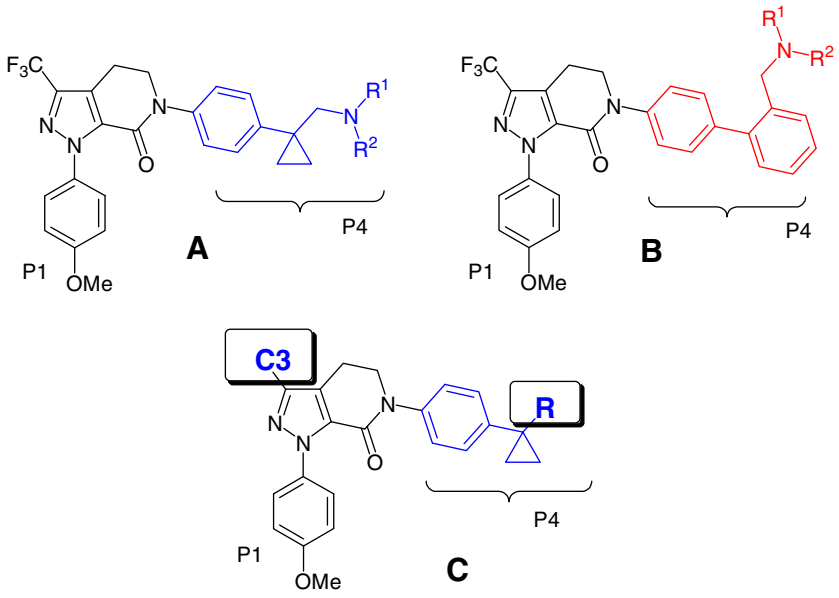
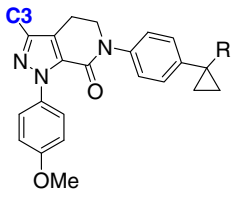


Figure 1. General structures.

Table 1
Effect of C-3 substitution in phenylcyclopropylmethylamine derivatives (R = $CH_2NR^1R^2$)[a,b]



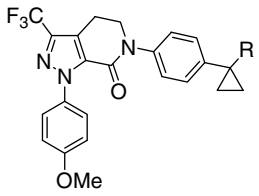
Compound	C3	R	FXa K_i (nM)	PT $EC_{2\times}$ (μM)	Caco-2 P_{app} (nm/s)[c]	HPLC Log*P*	PSA (Sq. Ang.) (PreCalc)[e]	*c*log*P* (PreCalc)[e]
1a	CF_3	CH_2NHMe	0.18	2.9	26	3.2	58	3.54
1b	SO_2Me	CH_2NHMe	0.24	1.2	1	—	95	1.31
1c	$CONH_2$	CH_2NHMe	0.055	0.86	1	—	99	1.24
1d	CN	CH_2NHMe	0.15	1.5	6	2.1	75	2.14
2a	CF_3	CH_2NMe_2	0.035	1.3	85	3.4	47	4.08
2b	SO_2Me	CH_2NMe_2	0.051	0.83	8	—	80	1.85
2c	$CONH_2$	CH_2NMe_2	0.041	1.2	5	1.6	89	1.78
2d	CN	CH_2NMe_2	0.048	0.79	46	2.5	67	2.68
3a	CF_3	CH_2-*N*-pyrrolidinyl	0.021	1.4	70	3.4	46	4.88
3b	SO_2Me	CH_2-*N*-pyrrolidinyl	0.054	0.73	10	—	82	2.65
3c	$CONH_2$	CH_2-*N*-pyrrolidinyl	0.074	0.70	10	—	89	2.58
3d	CN	CH_2-*N*-pyrrolidinyl	0.027	1.1	72	—	65	3.48
4a	CF_3	CH_2-*N*-morpholinyl	0.064	14	ndsd[d]	—	56	4.23
4b	SO_2Me	CH_2-*N*-morpholinyl	0.079	1.7	143	—	94	2.00
4c	$CONH_2$	CH_2-*N*-morpholinyl	0.042	1.5	90	3.3	99	1.93
4d	CN	CH_2-*N*-morpholinyl	0.093	4.1	137	4.0	76	2.83
5a	CF_3	CH_2-2-Me-imidazol-1-yl	0.025	2.7	70	—	56	4.32
5b	SO_2Me	CH_2-2-Me-imidazol-1-yl	0.073	0.79	11	—	91	2.09
6b	SO_2Me	CH_2-2-pyrrolidone-1-yl	0.24	1.6	20	—	96	1.43
6c	$CONH_2$	CH_2-2-pyrrolidone-1-yl	0.11	2.8	8	—	103	1.37

[a] All compounds were purified by either reverse-phase HPLC or preparative LC/MS (water/acetonitrile or water/methanol 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 are averages from multiple determinations ($n \geqslant 2$). K_i values and PT $EC_{2\times}$ (the concentration of the inhibitor that doubles the clotting time compared to the control in the prothrombin time assay) values were measured as described in Refs. 3 and 6. Same for all the tables in this publication.
[c] Caco-2 P_{app} values were measured according to Ref. 7.
[d] Not detected in sample or donor.
[e] Polar surface area (PSA) and *c*log*P* (pH 7.4) values were calculated using the ADME profiler in SMART prototype.

bearing a $CONH_2$ or SO_2Me group had lower Caco-2 permeability than those bearing a CN group, which in turn had lower Caco-2 permeability than those bearing a CF_3 group.

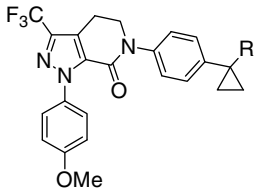
Continuing the search for diverse P4 groups,[8] we screened a variety of α-substituents (R groups) beyond the initial leads (R = $CH_2NR^1R^2$)[5] using CF_3 as the C-3 substituent (see Tables 2–4).

Table 2
SAR of phenylcyclopropylamines with CF_3 as the C-3 substituent



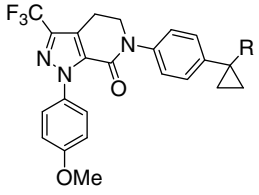
Compound	R	FXa K_i (nM)	PT EC_{2x} (μM)	Caco-2 P_{app} (nm/s)
7a	NH_2	0.78	6.4	nd
8a	NHMe	0.16	4.4	49
9a	NMe_2	0.085	9.2	92
10a	$N(Me)CH_2CH_2OH$	0.12	15	113
11a	$N(Me)CH_2CONH_2$	0.14	7.1	180
12a	NHCOMe	5.1	—	—
13a	$NHSO_2Me$	3.0	—	—
14a	NHCOOMe	11	—	—
15a	N(Me)COMe	1.5	11	
16a	$N(Me)SO_2Me$	2.9	—	—
17a	*N*-Pyrrolidine-2-one	7.6	—	—
18a	*N*-Piperidine-2-one	20	—	—

Table 3
SAR of homologous R groups with CF_3 as the C-3 substituent



Compound	R	FXa K_i (nM)	PT $EC_{2\times}$ (μM)
8a	NHMe	0.16	4.4
1a	CH_2NHMe	0.18	2.9
19a	CH_2CH_2NHMe	0.55	12
9a	NMe_2	0.085	9.2
2a	CH_2NMe_2	0.035	1.3
20a	$CH_2CH_2NMe_2$	0.020	2.7
3a	CH_2N-pyrrolidinyl	0.024	1.4
21a	CH_2CH_2N-pyrrolidinyl	0.020	2.3
4a	CH_2N-morpholinyl	0.064	14
22a	CH_2CH_2N-morpholinyl	0.21	15

Table 4
SAR of heterocyclic R groups in the phenylcyclopropyl analogs with CF_3 as the C-3 substituent



Compound	R	FXa K_i (nM)	PT EC_{2x} (μM)	Caco-2 P_{app} (nm/s)
23a	COOMe	1.5	>20	ndsd
24a	4,5-Dihydro-1*H*-imidazol-2-yl	0.021	0.69	1
25a	4,5-Dihydro-1*H*-imidazol-1-methyl-2-yl	0.16	1.8	7
26a	4,5-Dihydro-1*H*-imidazol-1-methanesulfonyl-2-yl	4.9	—	—
27a	4,5-Dihydro-oxazol-2-yl	2.5	>20	145
28a	4,5-Dihydro-4,4-diMe-oxazol-2-yl	1.1	38	44
29a	1*H*-Imidazol-2-yl	1.1	25	57
30a	1*H*-Imidazol-1-methyl-2-yl	6.4	—	—

Phenylcyclopropylamines: The less basic phenylcyclopropyl amine analogs **8a** and **9a** (Table 2) maintained potency (FXa K_i) and slightly increased Caco-2 values, but showed decreased anticoagulant activity (PT $EC_{2\times}$) compared with the phenylcyclopropyl methylamine analogs **1a** and **2a**. The dimethylamine **9a** was slightly more potent than the methylamine **8a**, which was slightly more potent than the primary amine **7a**. Compared with the parent methylamine **8a**, the less basic compounds **10a** and **11a** showed similar binding affinity, slightly decreased anticoagulant activity, yet improved cell permeability. On the other hand, the neutral amide **15a** and sulfonamide **16a** as well as the lactams **17a** and **18a**, were significantly less active than **8a**, presumably due to the steric conflict between the CO or SO_2 group and the backbone of E97 in the S4 pocket of FXa.

Homologous R groups: Table 3 shows that the methylene spacer has little effect on the binding activity (FXa K_i) within a series of homologues, for example, **9a** versus **2a** versus **20a**. In general, compounds with a trisubstituted amine ($R = (CH_2)_{1-2}NR^1R^1$) had better anticoagulant activity (PT $EC_{2\times}$) compared with the corresponding compounds with a di-substituted amine ($R = (CH_2)_{1-2}NHR^1$) with the exception of the phenylcyclopropyl amine analogs **8a** and **9a**.

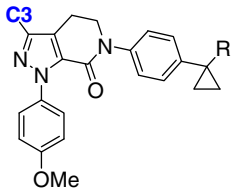
Heterocyclic R groups: Table 4 shows FXa K_i, PT $EC_{2\times}$, and Caco-2 values for several compounds bearing five-membered heterocyclic R groups as potential COOMe or COOH isosteres. Compared with the methyl ester **23a**, the basic cyclic amidine derivatives **24a** and **25a** were highly potent (FXa $K_i = 21$ and 155 pM, and PT $EC_{2\times} = 0.69$ and 1.76 μM, respectively), but neither had good permeability. The cyclic amidinyl sulfonamide **26a** showed a 200-fold drop in FXa potency compared with the unsubstituted **24a**. The neutral oxazoline derivative **27a** was much less potent than **24a**, but had greater Caco-2 permeability. Dimethyl substitution on the oxazoline ring as shown in **28a** did not significantly improve FXa potency. Aromatization of cyclic amidines **24a** and **25a** resulted in much decreased FXa potency as shown in the imidazole derivatives **29a** and **30a**.

Using a strategy similar to that demonstrated in Table 1, we replaced the CF_3 group in analogs having FXa K_i less than 1 nM with a more polar C-3 substitution, such as $CONH_2$ or CN. As exemplified in Table 5, the resulting compounds showed similarly high FXa inhibitory activity and improved anticoagulant activity in human plasma for $CONH_2$ and CN analogs compared with the corresponding CF_3 analogs (e.g., **8b** and **8c** vs **8a**, **9b** and **9c** vs **9a**, **22b** and **22c** vs **22a**), suggesting lower protein binding for $CONH_2$ and CN analogs as previously observed in other series.[4] In particular, replacing the CF_3 group in **31a** and **33a** with a $CONH_2$ group in **31b** and **33b** led to >fivefold improvement of anticoagulant activity.

By choosing the proper combination of R groups and C-3 groups, we identified multiple compounds which maintained high FXa binding affinity (FXa $K_i < 1$ nM) and improved anticoagulant activity (PT $EC_{2\times} < 5$ μM), while keeping Caco-2 permeability in a reasonable range. Selection of compounds for dog PK studies was based on the aforementioned activity and liability profile. Table 6 illustrates the pharmacokinetic profile of some representative compounds.

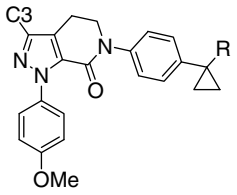
The basic analogs with $R = CH_2NR^1R^2$ such as CH_2NMe_2 and CH_2-*N*-pyrrolidine had large V_{dss} and moderate systematic CL in dogs as shown in compounds **2d**, **3b**, **3c**, and **3d**. Compounds **2d**, **3b**, and **3d** showed good bioavailability ($F = 40$–100%). Compound **3d** with a CN C-3 group and a CH_2-*N*-pyrrolidinyl phenylcyclopropyl P4 group showed a PK profile similar to that of raxazaban. Reducing the basicity of **3b** by changing the pyrrolidine into a morpholine led to reduced V_{dss} (7.7 in **3b** vs 1.9 L/kg in **4b**) and decreased CL (3.3 in **3b** vs 0.8 L/h/kg in **4b**). On the other hand, compound **5b** containing a 2-methylimidazole R group, had negligible oral bioavailability and high clearance in both dogs and short half-lives in liver microsomal incubation presumably caused by

Table 5
SAR of example compounds with different C-3 substitution



Compound	R	C3	FXa K_i (nM)	PT $EC_{2\times}$ (μM)	Caco-2 P_{app} (nm/s)
8a	NHMe	CF_3	0.16	4.4	49
8b	NHMe	$CONH_2$	0.065	0.60	39
8c	NHMe	CN	0.31	2.0	110
9a	NMe_2	CF_3	0.085	9.2	92
9b	NMe_2	$CONH_2$	0.043	1.1	125
9c	NMe_2	CN	0.084	1.9	170
22a	CH_2CH_2N-morpholinyl	CF_3	0.21	15	—
22b	CH_2CH_2N-morpholinyl	$CONH_2$	0.14	2.8	45
22c	CH_2CH_2N-morpholinyl	CN	0.74	4.0	—
27a	4.5-Dihydro-oxazol-2-yl	CF_3	2.5	>20	145
27b	4.5-Dihydro-oxazol-2-yl	$CONH_2$	0.56	13	62
31a	COMe	CF_3	1.0	36	ndsd
31b	COMe	$CONH_2$	0.18	3.2	227
32a	CH_2SO_2Me	CF_3	0.32	11	—
32b	CH_2SO_2Me	$CONH_2$	0.071	2.5	145
32c	CH_2SO_2Me	CN	0.29	5.5	152
33a	CH_2CONH_2	CF_3	0.59	15	—
33b	CH_2CONH_2	$CONH_2$	0.36	1.9	28

Table 6
Dog pharmacokinetic profiles of example α-substituted phenylcycloalkyl analogs[a]



Compound	R	C3	FXa K_i (nM)	PT $EC_{2\times}$ μM)	HLM/DLM $t_{½}$ (min)	Caco-2 P_{app} (nm/s)	CL (L/h/kg)	V_{dss} (L/kg)	$t_{½}$ (po) (h)	F (%)
2d	CH_2NMe_2	CN	0.048	0.79	178/73	46	1.37	11.7	6.4	41
3b	CH_2-*N*-pyrrolidinyl	SO_2Me	0.054	0.73	37/—	10	3.3	7.7	2.3	100
3c	CH_2-*N*-pyrrolidinyl	$CONH_2$	0.074	0.70	>200/60	6	1.7	7.1	4	6
3d	CH_2-*N*-pyrrolidinyl	CN	0.027	1.1	>200/—	72	1.1	6.6	5.0	48
4b	CH_2-*N*-morpholinyl	SO_2CH_3	0.079	1.7	25/—	143	0.8	1.9	4.0	61
5b	CH_2-2-Me-imidazol-1-yl	SO_2CH_3	0.073	0.79	5/—	11	4.2	4.0	na	0.2
6c	CH_2-2-pyrrolidone-1-yl	$CONH_2$	0.11	2.8	10/11	8	0.25	0.20	0.99	3.1
8a	NHMe	CF_3	0.16	4.4	123/83	49	0.46	13.9	24	100
8b	NHMe	$CONH_2$	0.065	0.60	146/36	39	1.8	4.4	1.6	15
10b	$N(Me)CH_2CH_2OH$	$CONH_2$	0.068	1.4	47/180	24	1.2	4.1	4.3	67
33b	CH_2CONH_2	$CONH_2$	0.36	1.9	97/99	28	0.49	0.65	1.9	27
Raxazaban[3]	—	—	0.19	1.9	—	56	1.1	5.3	3.4	84
Apixaban[4]	—	—	0.08	3.8		9	0.02	0.2	5.8	58

[a] Compounds were dosed as the TFA salts in an N-in-1 format at 0.5 mg/kg iv and 0.2 mg/kg po ($n = 2$).

extensive first pass metabolism. The metabolism for the phenylcyclopropyl methylamine derivatives (R = $CH_2NR^1R^2$) mainly consists of α-carbon oxidation of the cyclopropyl methylamines to form the corresponding aldehydes/carboxylic acids. In addition, demethylation products were also formed when either R^1 or R^2 was a methyl group.

The neutral pyrrolidinone **6c** had very low V_{dss} (0.20 L/kg and low *CL* (0.25 L/h/kg) compared with the corresponding basic pyrrolidinyl analog **3c**. However, **6c** was unstable in liver microsomal incubations (HLM $t_{1/2}$ = 10 min). The difference between the in vitro intrinsic clearance and the whole body systemic clearance may be due to protein binding or unknown in vitro clearance mechanisms. The low oral bioavailability of **6c** is presumably because of its relatively poor absorption and low Caco-2 value.

The cyclopropylamine analog **8a** showed moderate CL (0.46 L/kg/h) and high V_{dss} (13.9 L/kg) in dogs. The compound was 100% bioavailable and showed a longer $t_{1/2}$ (24 h) than the rest of the compounds because of the combined effects of slightly reduced

Table 7
Anticoagulant activity in rabbits

Compound	PT $EC_{2\times}$ (rabbit) (μM)	Rabbit A-V shunt EC_{50} (nM)	Rabbit A-V shunt ID_{50} (μmol/kg/h)
2d	<2.5	47	0.27
3b	0.32	29	0.08
3d	<2.5	68	0.19
5b	0.75	81	0.16
Raxazaban[3]	1.9	340	1.6
Apixaban[2e,4]	2.3	325	0.57

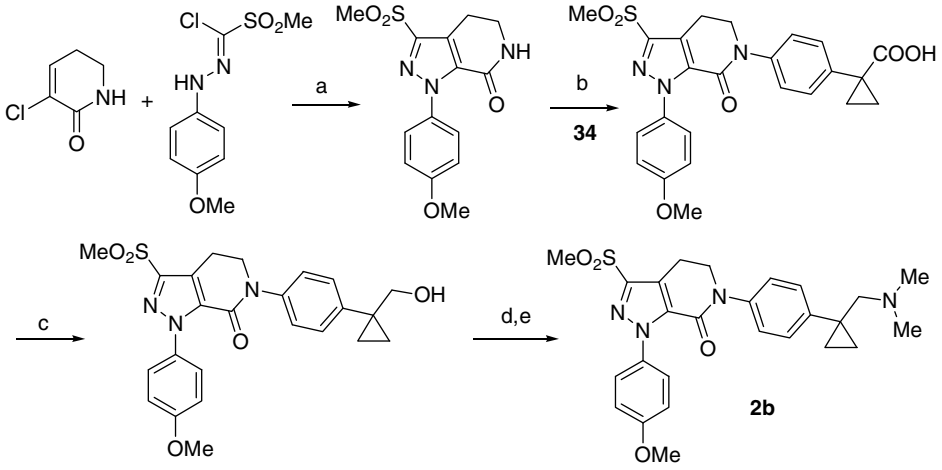
CL and increased V_{dss}. Changing the CF_3 in **8a** to a $CONH_2$ led to **8b** with reduced V_{dss} but shorter $t_{1/2}$ and lower oral bioavailability. The major metabolites for **8a** and **8b** were N-demethylated products. Being less basic, compound **10b** with a $N(Me)CH_2CH_2OH$ group showed increased oral bioavailability, slightly decreased V_{dss} and CL, and dramatically increased $t_{1/2}$ in DLM incubation compared with **8b**. The neutral analog **33b** with a primary acetamide had relatively low CL (0.49 L/h/kg) and low V_{dss} (0.65 L/kg) compared with other compounds bearing the same $CONH_2$ C-3 group in this series.

Some compounds were stable in human liver microsomal incubation (e.g., **2d**, **3c**, and **8b**), but had a short $t_{1/2}$ in dog liver microsomal incubation, suggesting species differences in metabolism (Table 6). Overall, compounds in this series generally had higher V_{dss} and CL than apixaban, other than the neutral compounds **6c** and **33b**, which were poorly bioavailable in dogs.

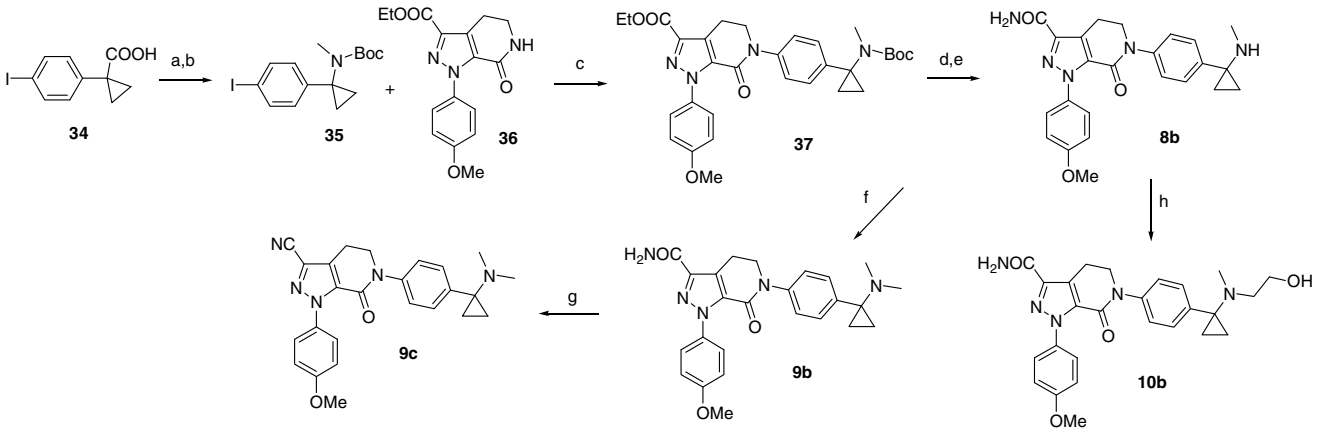
Representative compounds **2d**, **3b**, **3d**, and **5b**, when dosed intravenously in the rabbit arterio-venous (A-V) shunt thrombosis model,[9] demonstrated concentration-dependent antithrombotic effects. The ID_{50} values (doses that produce 50% inhibition of thrombus formation) for **2d**, **3b**, **3d**, and **5b** were 0.27, 0.08, 0.19, and 0.16 μmol/kg/h, respectively, and the IC_{50} values were 47, 29, 68, 81 nM, respectively. Consistent with the high in vitro potency (FXa K_i and PT EC_{2x}),[10] the four compounds provided strong antithrombotic effects, and in fact, they were more efficacious than razaxaban and apixaban in the A-V shunt model. The plasma protein binding for **3d** was 68% in human serum and 72% in rabbit serum, lower than that of raxazaban (93% in rabbit) and apixaban (87% in rabbit) (Table 7).

Scheme 1 illustrates the synthesis of compound **2b** bearing an α-CH_2NMe_2-substituted phenylcyclopropyl P4 group and a SO_2Me C-3 group by using procedures similar to those for the CF_3 analogs previously disclosed.[5]

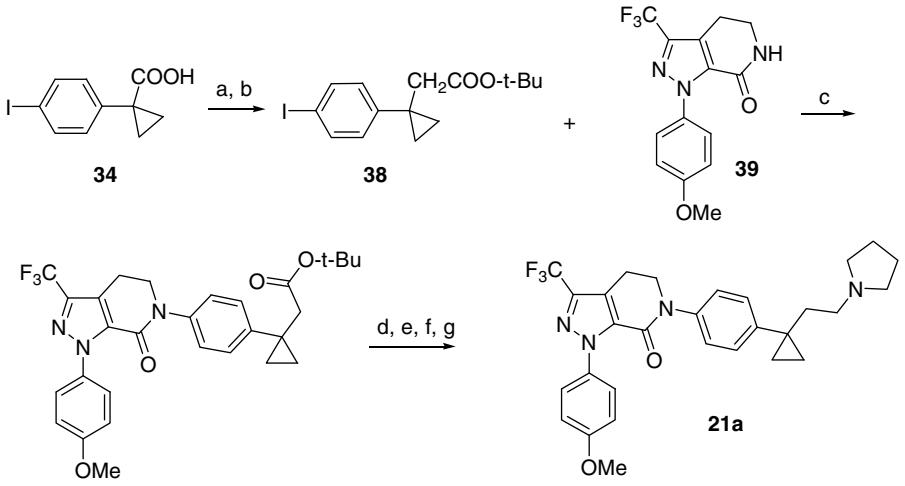
Scheme 2 depicts the preparation of phenylcyclopropyl amine derivatives using compounds **8b**, **9b**, **9c**, and **10b** as examples. Curtius rearrangement of the carboxylic acid **34** with DPPA followed by heating in *t*-BuOH and then methylation gave the Boc-protected



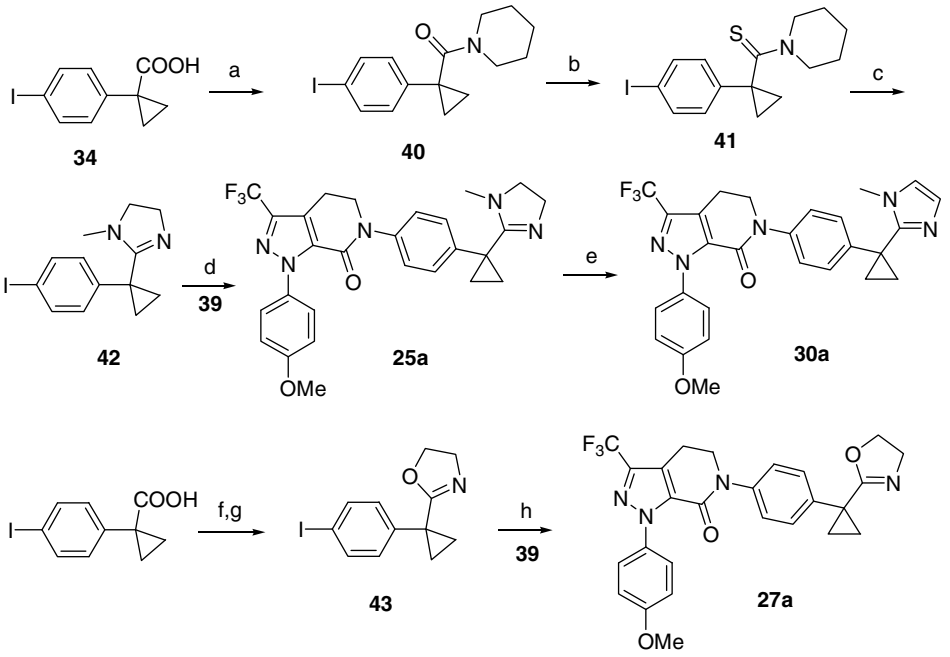
Scheme 1. Reagents and conditions: (a) Et_3N, toluene, 85 °C, 15 h, 31%; (b) 1-(4-Iodophenyl)cyclopropanecarboxylic acid (**34**), K_2CO_3, CuI, 1,10-phenanthroline, 120 °C, 1day, 90%; (c) ClCOOEt, Et_3N, THF, 0 °C, 20 min; then $NaBH_4$, THF/MeOH (5:1), 0 °C, 20 min, 85%; (d) PCC, NaOAc, 4 Å MS, CH_2Cl_2, rt, 2 h, 90%; (e) $NHMe_2$, $NaBH(OAc)_3$, cat. HOAc, $ClCH_2CH_2Cl$, rt, 2 h, 28% for two steps.



Scheme 2. Reagents and conditions: (a) DPPA, Et_3N, rt, overnight, then *t*-BuOH, reflux, 3 h, 65%; (b) MeI, NaH, THF, rt, overnight, 95%; (c) K_2CO_3, CuI, 1,10-phenanthroline, 120 °C, 2 h, 82%; (d) NH_3 in ethylene glycol, 80 °C, 3 h,%; (e) TFA, CH_2Cl_2, rt, 2 h, 98%; (f) Aqueous formaldehyde, $NaBH_3CN$, HOAc, CH_3CN, rt, 2 h, 92%; (g) $SOCl_2$, DMF, CH_2Cl_2, 90%; (h) $BrCH_2CH_2OH$, K_2CO_3, DMF, 70 °C, 2 h, 65%.



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, DMF, rt, 2 h; (b) $TMSCHN_2$, CH_3CN/THF (1:1), 0 °C to rt, 4 h; then *t*-BuOH, AgOBz, Et_3N, reflux, 1 h, 35% for two steps; (c) K_2CO_3, CuI, 1,10-phenanthroline, 120 °C, 3 h, 67%; (d) TFA, CH_2Cl_2, rt, 2 h, 87%; (e) ClCOOEt, Et_3N, THF, 0 °C, 20 min; then $NaBH_4$, THF/MeOH (5:1), 0 °C, 20 min; (f) PCC, NaOAc, 4 Å MS, CH_2Cl_2, rt, 2 h; (g) Pyrrolidine, $NaBH(OAc)_3$, cat. HOAc, $ClCH_2CH_2Cl$, rt, 3 h, 35% for three steps.



Scheme 4. Reagents and conditions: (a) pentafluorophenol, DCC, CH_2Cl_2, rt, 2 h; then piperidine, overnight, 88%; (b) Lawesson's reagent, toluene, 110 °C, 1.5 h, 81%; (c) MeI, then $NHMeCH_2CH_2NH_2$, MeOH, 2 days, 65%; (d) **39**, K_2CO_3, CuI, 1,10-phenanthroline, 120 °C, overnight, 38%.**;** (e) $KMnO_4$, 1,4-dioxane, 80 °C, 12 h, 72%; (f) $(COCl)_2$, CH_2Cl_2, 0 °C, 1 h; then ethanolamine, rt, 1.5 h, 73%; (g) Burgess reagent, THF, 70 °C, 2 h, 74%; (h) **39**, K_2CO_3, CuI, 1,10-phenanthroline, 120 °C, overnight, 50%.

cyclopropylamine **35**, which was coupled with the lactam **36**[4] under Buchwald–Ullmann condition to afford intermediate **37**. Amination of the ethylester in **37** followed by removing Boc group afforded the methylamine **8b**. Starting from **8b**, compounds **9b**, **9c**, and **10b** were synthesized as illustrated in Scheme 2.

Scheme 3 illustrates the synthesis of cyclopropyl-ethylamine analogs using **21a** as an example. Homologation of acid **34** with $TMSCHN_2$ followed by heating in *t*-BuOH in the presence of silver benzoate and triethylamine afforded the Boc-protected homologous acid **38**. Ullmann coupling of **38** with lactam **39** followed by a similar sequence of transformations as described in Scheme 1 generated compound **21a**.

Scheme 4 illustrates the synthesis of phenylcyclopropyl analogs bearing heterocyclic R groups. N-acylation of the pentafluoroester, obtained from the acid via pentafluorophenol/DCC, with piperidine afforded the amide **40**. Formation of the thioamide **41** using Lawesson's reagent, then thioimidate via MeI, followed by cyclization of the thioimidate intermediate with ethylamine diamine in refluxing MeOH gave the methyl imidazoline intermediate **42**. Buchwald Ullmann coupling of **42** and lactam **39** yielded the imidazoline **25a**. Aromatization of **25a** with potassium permanganate in dioxane afforded the imidazole analog **30a**. On the other hand, cyclization of the β-hydroxyamide with Burgess reagent in THF at reflux afforded the oxazoline intermediate **43** in 74% yield. Utilizing Buchwald–Ullmann chemistry, **43** was coupled with the lactam **39** affording the desired product **27a.**

SAR studies of the C-3 substitution on the pyrazolodihydropyridone core and the R substitution on the phenylcyclopropyl group

of a series of pyrazole bicyclics bearing α-substituted phenylcycloalkyl groups resulted in a series of FXa inhibitors with high FXa binding affinity (FXa K_i of some in the picomolar range) and high anticoagulant activity (PT $EC_{2\times} < 3$ μM) in vitro. C-3 substitution of the pyrazole core with more polar groups such as SO_2Me, $CONH_2$, and CN, maintained FXa K_i potency and increased anticoagulant PT potency compared with the CF_3 C-3 analogs, suggestive of improved free fraction in protein binding. A set of compounds, obtained from optimization of the R group and the C-3 substituent, were orally bioavailable in dog PK studies. Representative compounds such as **3d** and **8a** showed moderate clearance, long $t_{1/2}$, and good bioavailability, but high V_{dss} in dogs. Compounds **2d**, **3b**, **3d**, and **5b** in this series were also highly efficacious in the rabbit A-V shunt thrombosis model ($EC_{50} < 85$ nM). Though highly efficacious, the pharmacokinetic properties of this series were less optimal compared with that of apixaban, which has a superior combination of exceptionally low CL and V_{dss} with a long half life and good oral bioavailability.

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