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Achieving structural diversity using the perpendicular conformation of *alpha*-substituted phenylcyclopropanes to mimic the bioactive conformation of *ortho*-substituted biphenyl P4 moieties: Discovery of novel, highly potent inhibitors of Factor Xa

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ABSTRACT

Ortho-substituted biphenyl moieties are widely used in drug design. We herein report a successful use of the perpendicular conformation of the *alpha*-substituted phenylcyclopropyl groups to mimic the aplanar, biologically active conformation of the *ortho*-substituted biphenyl moieties to achieve structural diversity. This is exemplified by the design and synthesis of a series of highly potent pyrazole bicyclic-based Factor Xa (FXa) inhibitors bearing *alpha*-substituted phenylcyclopropyl P4 moieties. The designed perpendicular conformation was confirmed by the X-ray structure of FXa-bound compound **2r**. The potential structural basis for the high FXa potency in the phenylcyclopropyl P4 analogs and their improved FXa inhibitory activities compared with the biphenyl P4 counterparts are discussed.

Thrombotic diseases, such as myocardial infarction, stroke, unstable angina, deep vein thrombosis, and pulmonary embolism, remain the major causes of deaths and disabilities in developed countries. Existing antithrombotic therapies using either parenteral anticoagulants, such as heparins, or the oral anticoagulants, such as warfarin (coumadin®), have multiple limitations and complications. There still exists a large unmet need for safer and more efficacious oral anticoagulants. One approach to producing such anticoagulants is to inhibit thrombin generation by targeting the inhibition of coagulation Factor Xa (FXa). FXa is a key enzyme in the coagulation cascade, located at the convergence of the extrinsic and the intrinsic activation pathways. It is believed that inhibition of FXa prevents thrombus formation without compromising normal hemostasis and platelet activation because the basal thrombin level is maintained. Selective and orally active FXa inhibitors are believed to have higher efficacy, fewer bleeding risks, and a more favorable safety/efficacy ratio, compared with current treatments.[1,2] In the recent past, both preclinical and clinical data showed the inhibition of FXa to be an effective approach for the treatment of arterial and venous thrombosis.[1,2]

We have previously reported on a series of 7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine (fused-pyrazole bicyclics) FXa inhibitors containing *ortho*-substituted biphenyl P4 moieties, wherein the potent substituent at the *ortho* position was a basic group ($R'=CH_2NR^1R^2$) with a general structure **1** (Fig. 1).[3] The driving force behind the present work was to further explore the structural diversity of the P4 region[4] of the fused-pyrazole bicyclic series **1** to identify compounds with superior potency, and in vitro and in vivo profile to razaxaban.[5a] In this paper, we first describe our use of the perpendicular conformation of *alpha*-substituted phenyl-cyclopropanes (Fig. 2 shows the structure of alpha-methyl substituted phenylcyclopropane) to mimic the biological conformation of *ortho*-substituted biphenyl P4 groups. We then present the initial P4 SAR of a series of highly potent and selective fused-pyrazole bicyclic FXa inhibitors containing such *alpha*-substituted phenylcyclopropyl P4 moieties with general structure **2** (Fig. 1). We next describe the X-ray structure of a representative analog, and discuss the potential structural basis for the improved FXa inhibitory activity of this series of compounds compared with the corresponding *ortho*-substituted biphenyl P4 counterparts.

X-ray crystallographic analysis and modeling studies of **1a** bearing an *ortho*-*N*,*N*-dimethylaminomethyl biphenyl P4 group and its related analogs revealed that the biphenyl group extends into the S4 pocket formed by the side-chains of Y99, F174, and W215 of FXa. The two phenyls are twisted, adopting a near orthogonal conformation, which according to quantum mechanical calculations[6a–c] contains modest strain. The *ortho* substituent ($R'=CH_2NR^1R^2$) on

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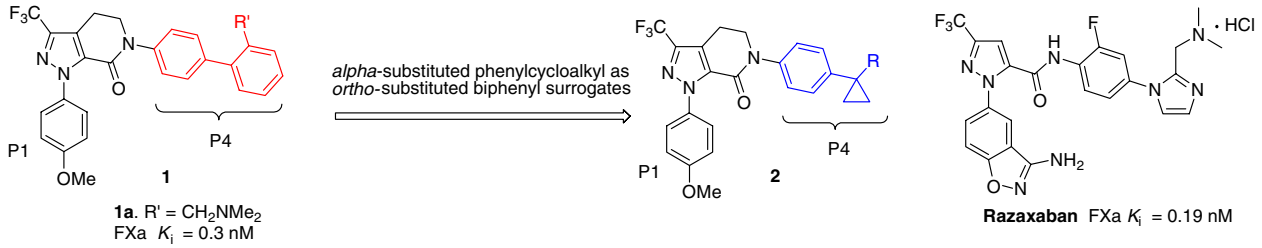


Figure 1. Overall strategy.

the biphenyl moiety is partially positioned outside of the S4 pocket in solvent. We speculate that the nitrogen atom in R′ may engage in polar interactions, possibly water-mediated, with one or more of the backbone carbonyl or side-chain of E97, or the backbone carbonyl of K96. Based on the aplanar and hydrophobic feature of the biphenyl group in **1**, we hypothesized that *alpha*-substituted phenylcycloalkyls might serve as rigid frameworks to direct the substituent on the quaternary carbon to the same space occupied by the *ortho* substituent of the biphenyls (such as $CH_2NR^1R^2$ in the P4 moiety of **1**).

Phenylcyclopropanes exist in two limiting conformations (Fig. 2):[7] (1) the *perpendicular conformation* **P**, in which the normal vector to the phenyl ring (the vector that is perpendicular to the plane in which the phenyl ring lies) is perpendicular to the C(2)–C(3) bond of the cyclopropane ring and (2) the *bisected conformation* **B**, in which the phenyl plane bisects the three-membered ring. As shown in Figure 3, we envisioned that we could achieve structural diversity using the perpendicular conformation of *alpha*-substituted phenylcyclopropyl to mimic the biologically active conformation of the *ortho*-substituted biphenyl moiety.

Phenylcyclopropanes without *alpha*-substitution adopt a bisected conformation in the solid state.[8] Quantum calculations

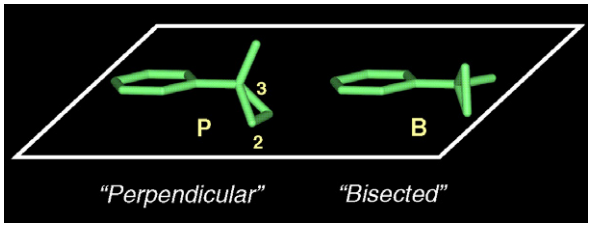


Figure 2. The perpendicular conformation (P) and the bisected conformation (B) of *alpha*-methyl phenylcyclopropane.

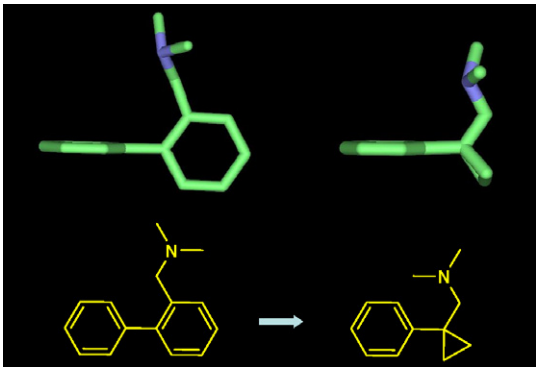


Figure 3. The bioactive conformation of 2′-CH_2NMe_2-1,1′-biphenyl group in **1a** vs the proposed perpendicular conformation of α-CH_2NMe_2phenylcyclopropyl group in **2**.

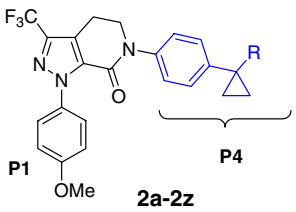
and other structural analysis methods[9] also suggested the bisected conformation to be preferable over the perpendicular conformation. *Alpha*-substitution on phenylcyclopropanes is expected to both sterically and electronically affect the relative conformation between the cyclopropyl and the phenyl ring.[9–11] A simple *alpha*-methyl substitution resulted in the preference of the perpendicular form as indicated by both photoelectron spectra (PES)[10a] and NMR studies.[10b] In-house quantum mechanical calculations supported this observation, showing that methyl substitution at the *alpha* position induces distinct preferences for both the perpendicular conformation and the bisected conformation (two minima) with the perpendicular conformation marginally more favorable (0.7 kcal).[12] Surprisingly, little investigation, either experimental or theoretical, has been reported regarding the conformational preference of the *alpha*-substituted phenylcyclopropanes other than with simple alkyl groups.

We selected the *alpha*-substituted phenylcyclopropyl moiety as a potential P4 surrogate based on the potential conformational predisposition of the *alpha*-substituted phenylcyclopropyl ligand toward the perpendicular conformation, which mimics the biologically active conformation of *ortho*-biphenyl P4 groups, as well as based on the small size and metabolic stability of the cyclopropyl group compared with other cycloalkyls.

Table 1 depicts the initial SAR of the *alpha*-substituent (R group) of the phenylcyclopropyl P4 analogs. Compounds with small, neutral, and polar R groups containing one or more hydrogen bond donors or acceptors, such as COOMe (**2a**), CN (**2b**), CH_2OH (**2c**), CH_2OMe (**2d**), or $CONH_2$ (**2e**), showed low nM in vitro FXa binding affinity. Though they were ten times less potent than **1a** (FXa K_i = 0.3 nM), they were generally more potent than the corresponding biphenyl compounds with these same substituents.[3] The data suggest that the cyclopropyl group, though 'wider' than the distal phenyl group, was easily accommodated by the S4 pocket of FXa. Compounds **2f–2k** exemplified the variety of amide substituents we studied. Smaller alkyl amides, such as $CONMe_2$ in **2f**, as well as the heteroaryl amides, such as thiadiazole **2j** and tetrazole **2k**, gave subnanomolar FXa inhibition similar to that observed with the small neutral R groups in compounds **2a–2e**. In contrast, compounds containing larger di-substituted amides, such as **2h** and **2i**, were much less active.

Replacement of the amide carbonyl in compounds **2e–2k** with a methylene group resulted in significantly more potent FXa inhibitors. For instance, **2h** containing a pyrrolidine amide had a FXa K_i = 179 nM. The corresponding *des*-carbonyl analog **2r** had a FXa K_i = 21 pM, an 8000-fold increase in binding affinity. Several of the basic *N*-alkylaminomethyl or *N*,*N*-dialkylaminomethyl analogs achieved FXa binding affinity in the pM range. Among these, compounds **2n**, **2q**, **2r**, **2t**, and **2s**, with cyclic or acyclic tertiary amines, were slightly more active than compounds with secondary amines (such as **2m** and **2p**), and the primary amine analog **2l**. Compound **2v**, bearing a less basic *N*-thiazolyl aminomethyl group,[13a] had a FXa K_i of 50 pM, and was equipotent to the more basic secondary alkyl amines such as **2o** (FXa K_i = 42 pM). The basic

Table 1 [a,b]



2a-2z

Compound	R	FXa[b] K_i (nM)	PT[b] EC_{2x} (μM)
2a	–COOMe	1.9	83
2b	–CN	1.8	36
2c	$-CH_2OH$	2.4	nd
2d	$-CH_2OMe$	1.6	nd
2e	$-CONH_2$	3.3	nd
2f	$-CONMe_2$	5.8	nd
2g	–CONH-cyclopentyl	30	nd
2h	–CO-*N*-pyrrolidine	169	nd
2i	–CO-4-OH-piperidin-1-yl	54	nd
2j	–CONH-1,3,4-thiadiazol-2-yl	1.8	31
2k	–CONH-1*H*-tetrazol-5-yl	3.0	nd
2l	$-CH_2NH_2$	0.57	4.4
2m	$-CH_2NHMe$	0.18	2.9
2n	$-CH_2NMe_2$	0.035	1.3
2o	$-CH_2NH$-isopropyl	0.042	2.4
2p	$-CH_2NH$-cyclopentyl	0.12	3.2
2q	$-CH_2NEt_2$	<0.02	1.9
2r	$-CH_2$-*N*-pyrrolidine	0.021	1.4
2s	$-CH_2$-*N*-pyrrolidine-2-(*R*)-OH	0.038	2.4
2t	$-CH_2$-*N*-morpholine	0.064	14
2u	$-CH_2$-*N*-piperidine-4-OH	0.14	9.0
2v	$-CH_2NH$-thiazole-2-yl	0.054	3.4
2w	$-CH_2$-2-Me-1*H*-imidazol-1-yl	0.025	2.7
2x	$-CH_2$-N(Me)COMe	0.055	5.6
2y	$-CH_2$-N(Me)SO_2Me	0.074	24
2z	$-CH_2$-N(Me)CONHEt	0.14	12

[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] K_i values were obtained from purified human enzymes and were averaged from multiple determinations ($n \geqslant 2$). K_i and PT values were measured as described in Ref. 5a.

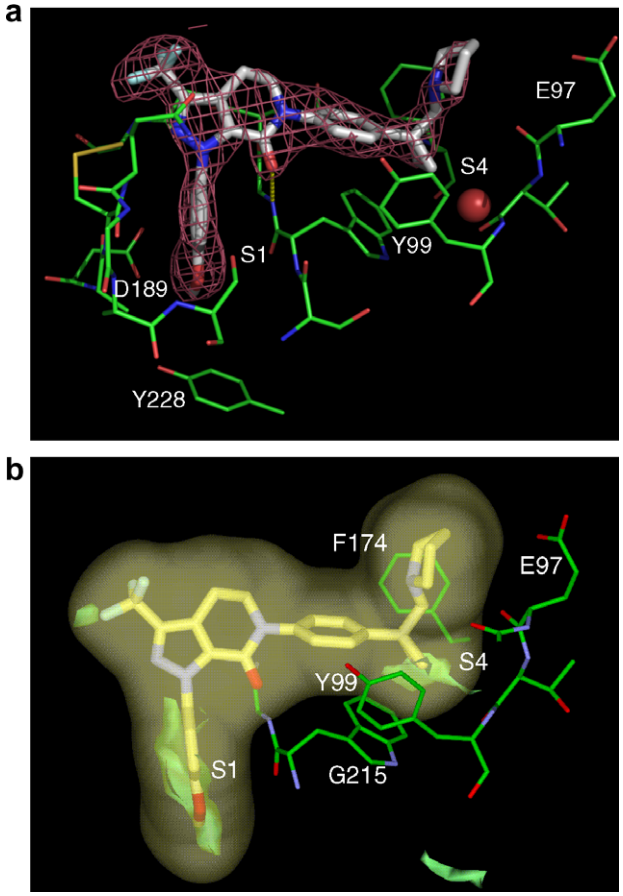


Figure 4. (a) Electron density around **2r** (FXa K_i = 21 pM) shown with the initial 2Fo-Fc electron density map contoured at 0.7σ in magenta mesh in the active site of human Factor Xa. Graphic was created using PyMol.[15] (b) Transparent connelly surface of compound **2r** is shown in light yellow. Using the GRID program, the interaction of a hypothetical aromatic CH probe is contoured in light green at −3.5 kcal, a level that generally coincides with strong hydrophobic interactions. For simplicity, only key residues in the S4 pocket are shown.

N-(1-methyl-imidazole-2-yl)aminomethyl analog **2w**[13b] was also highly active with a FXa K_i of 25 pM. Unlike the *ortho*-*N*-methylaminomethyl biphenyl analogs previously studied,[6] neutralization of *N*-methylaminomethyl moiety in **2m** to form amide **2x**, sulfonamide **2y**, and urea **2z** did not decrease FXa binding affinity. Because we were interested in compounds with relatively good aqueous solubility and low log*P*, compounds with all-carbon side-chains were not studied.

The basic analogs **2l**–**2w**, except for the morpholinyl analog **2t** and the piperidinyl analog **2u**, showed good anticoagulant activity with PT EC_{2x} less than 5 μM in human plasma. Despite having pM binding activity, sulfonamide **2y** and urea **2z** had significantly weaker anticoagulant activity compared with the parent methylamine analog **2m**, presumably resulting from the increased lipophilicity. Thus, compounds **2y** and **2z** were projected to have higher protein binding. Compounds in Table 1 were generally selective against other related human serine proteases (inactive against trypsin, FIXa, FVIIa, plasmin, chymotrypsin, tPA, plasma kallikrein, and APC, and were more than 5000-fold selective against thrombin).

The crystal structure of **2r** (FXa K_i = 21 pM) complexed to human FXa was solved at 2.0 Å resolution with a crystallographic ***R*** factor of 0.22.[14] Figure 4 a depicts the electron density of **2r** in the active site of FXa. The overall L-shaped configuration is similar to that observed for other pyrazole analogs.[3,4] The molecule adopts an extended binding mode with the *para*-methoxyphenyl group located in the S1 pocket and the α-CH_2-*N*-pyrrolidinyl phenylcyclopropyl group occupying the S4 pocket. It is noteworthy that the phenylcyclopropyl ring adopts the perpendicular conformation, which was a central feature of our inhibitor design.

Numerous in-house modeling studies and crystal structures indicated that **2r** interacts with the enzyme in essentially the same way as other pyrazole bicyclic analogs do, other than the interactions in the S4 pocket. As shown in Figure 4b, the cyclopropane ring sits above the indole ring of W215 and is sandwiched between the aromatic residues of Y99 and F174, suggesting the presence of extensive hydrophobic interactions in the S4 pocket of the **2r**-FXa complex. Indeed, the cyclopropane carbons coincide closely with a high-affinity hydrophobic region predicted by the GRID program (Fig. 4b).[16]

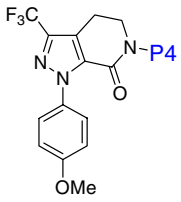
In addition, part of the side-chain CH_2-*N*-pyrrolidinyl group is close to the backbone of E97 and T98. Although the precise origin is unclear, the increase in potency from this pendant cyclopropyl methylene substituents is likely due to a combination of (1) the favorable hydrophobic interactions between the methyl pyrrolidinyl group with the edges of F174 and Y99, and the backbone atoms of E97 and T98, and (2) the conformational bias toward the perpendicular conformation of the phenyl cyclopropane placing the bulky methylene side-chain orthogonal to the plane of the phenyl ring. Little in the X-ray models suggests that H-bonding or Coulombic interactions with the 90's loop contribute to potency. Neither can

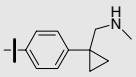
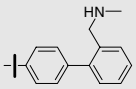
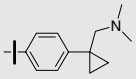
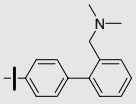
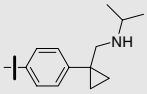
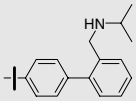
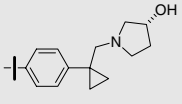
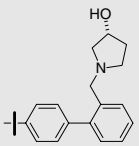
a strong case be made for the interactions of the cationic groups with the aryl rings of Y99 or F174 in a π-cation sense, given the concentration of the charge at the periphery of the S4 pocket.[17]

In Table 2, the in vitro FXa activity of compounds bearing *alpha*-substituted phenylcyclopropyl P4 groups is compared with corresponding compounds containing the biphenyl P4 moieties. In general, the phenylcyclopropyl analogs were more potent than the corresponding *ortho*-substituted biphenyl P4 analogs, for example, **2n**, **2o**, and **2s** showed 20- to 30-fold improvement of FXa binding affinity compared with **1a**, **1c**, and **1d**, respectively. In addition, compounds with phenylcyclopropyl P4 moieties were threefold to fivefold more potent in anticoagulant activity as measured by the EC_{2x} in the prothrombin assay.

Comparison of the crystal structures of the two series may offer some insight into the basis for the higher affinity of the phenylcyclopropane series relative to the biphenyl analogs. Among the

Table 2 [a]



Compound	P4	FXa[a] K_i (nM)	PT[a] EC_{2x} (μM)
2m		0.18	1.8
1b		0.28	8
2n		0.035	1.3
1a		0.41	6.4
2o		0.042	2.3
1c		1.4	nd
2s		0.038	2.3
1d		0.76	8.2

[a] K_i's obtained from purified human enzymes and were averaged from multiple determinations ($n \geqslant 2$). K_i and PT values are measured according to Ref. 5a.

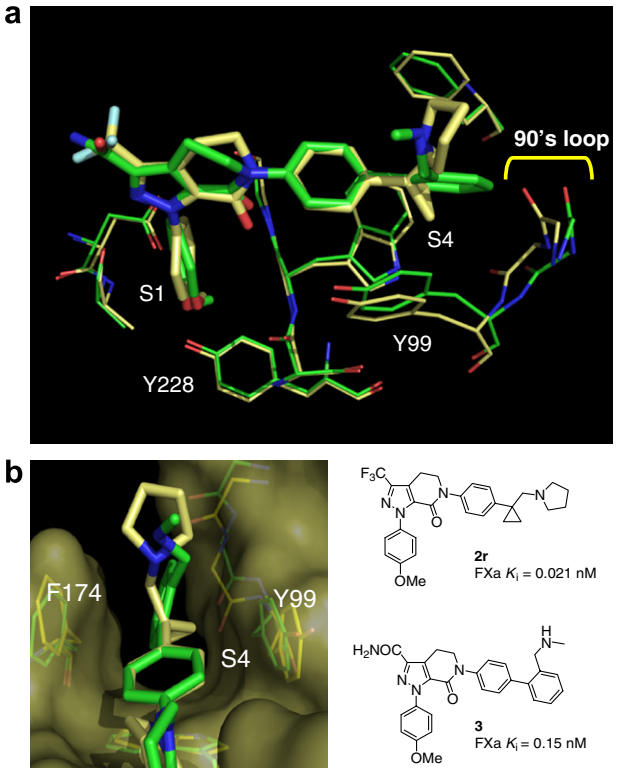
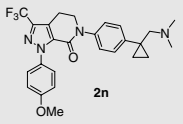


Figure 5. (a) Superposition of the X-ray structures of **3**-FXa (in green) bearing an *ortho*-substituted biphenyl P4 group and **2r**-FXa (in light yellow). Graphics were created using PyMol.[15] (b) View of the P4 region in the above overlay of the X-ray structures of **3**-FXa (in green) and **2r**-FXa (in light yellow). The transparent surface of S4 from **2r**-FXa is shown in light yellow. Graphics were created using PyMol.[15]

fused pyrazole analogs for which we have crystal structures, compound **3**[3a] was structurally similar to the phenylcyclopropyl analog **2r**, the principle difference being the presence of an amide group at the C3 position in compound **3**. Figure 5a shows the superposition of the crystal structures for the **2r**- and **3**-FXa complexes. In the **2r**-FXa complex, the side-chain of Y99 has moved 0.48–0.78 Å to accommodate the wider cyclopropane group. This is consistent with the literature observations[18] that the side-chains of Y99 and F174 can move to accommodate inhibitors of different sizes. Perhaps more striking is an observed shift (~1Å) between the 97–99 backbones in the two complexes, resulting from an expansion of the S4 pocket in the **3**-FXa complex to accommodate the biphenyl group. This shift has been consistently observed with other inhibitor-FXa complexes involving biphenyl P4 groups in the pyrazole bicyclic series.[3] The marked shift of the 97–99 backbone in the biphenyl analogs may involve some degree of strain and may reduce favorable interactions between the 97–99 backbone and N-alkyl side-chain as observed in the cyclopropane analog **2r**-FXa complex (Fig. 4), and consequently may contribute to the observed decrease in the binding affinity of the biphenyl analogs. While the electron density of these side-chains is generally not very well defined in the crystal structure, the closer proximity of the alkyl side-chain to the interior of the S4 pocket as suggested by Figure 5, may result in more favorable binding interactions in the phenylcyclopropane series.

Because of the low anticoagulant activity of the *ortho*-substituted biphenyl P4 analogs **1a–1d** with a CF_3 C3 group (Table 2, PT $EC_{2x} > 6$ μM), these compounds were not selected for dog PK studies. Table 3 compares the in vitro and pharmacokinetic profile of a representative phenylcyclopropyl analog **2n** with that of razaxaban.[5a] Compound **2n** was tenfold more potent in binding affinity (FXa K_i) than razaxaban, but only twofold more potent in

Table 3
Comparison of the in vitro and in vivo profile of a representative compound **2n**[a] with that of razaxaban

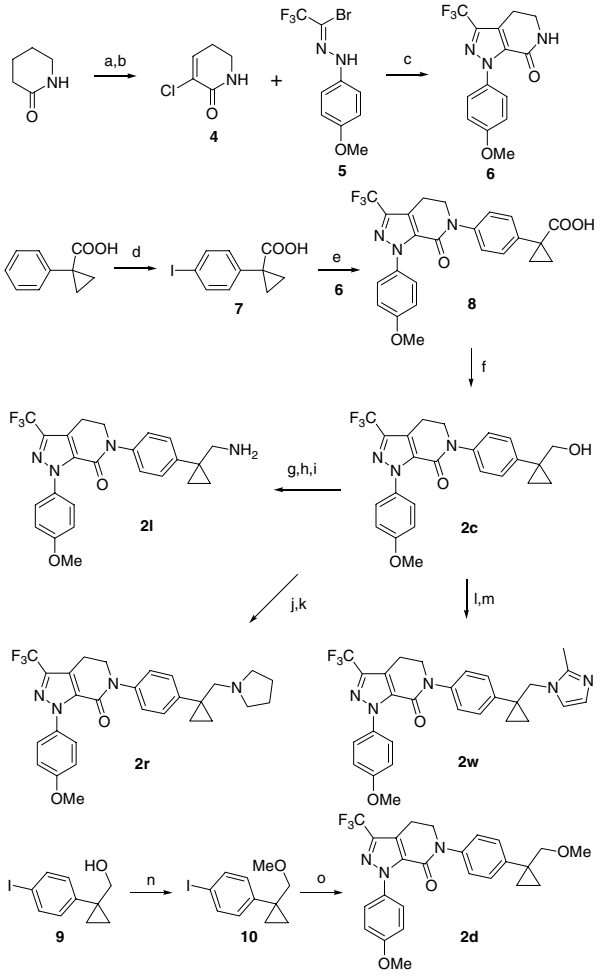
	 **2n**	Razaxaban
FXa K_i (nM)	0.035	0.19
PT EC_{2x} (μM)	1.3	3.0
Thrombin K_i (nM)	191	540
Trypsin K_i (nM)	>15,000	>10,000
Caco-2 $P_{app} \times 10^{-6}$ (cm/s)	8.5	5.6
HLM $t_{1/2}$ (min)	110	36
Cl (L/Kg/h)[b]	1.2	1.1
V_{dss} (L/Kg)	15	5.3
pot$_{1/2}$ (h)[c]	12	3.4
F%b	53	84

[a] Compound **2n** was dosed as TFA salt in an *N*-in-1 format.
[b] Iv dose: 0.5 mg/kg.
[c] Po dose: 0.2 mg/kg.

anticoagulant activity (PT EC_{2x}). Thus, it is likely that **2n** is highly protein bound. Both **2n** and razaxaban were selective against other related serine proteases (only trypsin and thrombin are illustrated). Both compounds show similarly moderate cell permeability. Compound **2n** has better human liver microsomal stability, moderate clearance, large V_{dss}, and good oral availability in dogs similar to razaxaban. Compound **2n** has a longer $t_{1/2}$ because of the larger V_{dss}.

Scheme 1 illustrates the synthesis of fused pyrazole analogs bearing α-substituted phenylcyclopropyl P4 groups exemplified by the preparation of **2c**, **2d**, **2l**, **2r**, and **2w**. Treatment of δ-valerolactam with phosphorus pentachloride in hot chloroform yielded 3,3-dichloro-2-piperidinone. Using lithium carbonate as the base, a good yield of 3-chloro-5,6-dihydro-2(1*H*)-pyridinone **4** was obtained by heating the above dichloride in DMF. The pyridinone **4** was then coupled with the readily available 2,2,2-trifluoro-N′-(4-methoxyphenyl)acetohydrazonoyl bromide **5**[19] in the presence of triethylamine in EtOAc at reflux. After simple silica gel chromatography purification, the desired pyrazole bicyclic core **6** was obtained in a moderate 39% yield. On the other hand, electrophilic aromatic iodination of 1-phenylcyclopropyl carboxylic acid with sodium iodate and a catalytic amount of sulfuric acid in hot acetic acid afforded the 4-iodophenyl analog **7** regioselectively. The molecular skeleton **8** needed for P4 SAR studies was assembled from the pyridinone fragment **6** and the aryl iodide fragment **7** via amidation of the aryl iodide in the presence of Copper(I) iodide using 1,10-phenanthroline as the ligand and potassium carbonate as the base. The acid group in **8** was transformed to the alcohol in **2c** via reduction of the mixed anhydride with sodium borohydride. A variety of final compounds were then obtained through manipulation of **2c**. For example, mesylation of **2c**, azide displacement followed by reduction of the azide provided the methylamine analog **2l**. Treatment of **2c** with pyridinium chlorochromate and sodium acetate gave the aldehyde, which was subjected to reductive amination with pyrrolidine to afford the pyrrolidinylmethyl analog **2r**. Alcohol **2c** was transformed to the bromide with carbon tetrabromide and triphenylphosphine. The resulting bromide was then displaced with 2-methylimidazole to generate the imidazole analog **2w**. The methylether **2d** was prepared via methylation of the alcohol **9** with trimethyloxonium tetrafluoroborate, followed by amidation of the resulting iodide **10** with pyridinone **6**.

We identified *alpha*-substituted phenylcyclopropanes as viable conformational surrogates of *ortho*-substituted biphenyl groups,



Scheme 1. Reagents and conditions: (a) PCl_5 (3 equiv), $CHCl_3$, reflux, 85%; (b) Li_2CO_3 (3 equiv), DMF, 120 °C, 1 day, 87%; (c) Et_3N (5 equiv), toluene, 85 °C, 15 h, 30%; (d) I_2, $NaIO_3$, H_2SO_4, HOAc, 70 °C, 3 days, 81%; (e). K_2CO_3 (3 eq), CuI (0.2 equiv), 1,10-phenanthroline (0.2 eq), DMSO, 130 °C, 1 day, 94%; (f) ClCOOEt, Et_3N, THF, 0 °C, 20 min; then $NaBH_4$, THF/MeOH (5:1), 0 °C, 20 min, 95%; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaN_3, DMF, rt, overnight; (i) PPh_3, THF/H_2O, 50 °C, 2 h, 29% for 3 steps; (j) PCC, NaOAc, 4Å MS, CH_2Cl_2, rt, 2 h, 90%; (k) pyrrolidine, $NaBH(OAc)_3$, cat. HOAc, $ClCH_2CH_2Cl$, rt, 2 h, 86%; (l) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min, 99%; (m) 2-methylimidazole, K_2CO_3, DMF, 85 °C, 30 min, 27%; (n) $Me_3O^+BF_4^-$, 1,8-bis(dimethylamino)naphthalene, CH_2Cl_2, 47%; (o) CuI, K_2CO_3, 1,10-phenanthroline, DMSO, 120 °C, 38%.

generating a series of extremely potent pyrazole bicyclic-based FXa inhibitors bearing *alpha*-substituted phenylcyclopropyl P4 groups. These compounds exhibited FXa K_i's in the pM range, had highly potent anticoagulant activity in human plasma, and were generally more active than the corresponding *ortho*-substituted biphenyl counterparts. Structural modifications of the *alpha*-substituted phenylcyclopropane P4 analogs to modulate in vitro and in vivo properties shall be reported in future communications. X-ray structure analysis of **2r**-FXa revealed that the cyclopropyl ring adopted a perpendicular conformation, as designed. Comparison of the X-ray structures of the phenylcyclopropyl and the *ortho*-biaryl P4 analogs suggests that the increase in FXa affinity observed with the phenylcyclopropyl analogs may result from one or more of the following: (1) the extensive hydrophobic interactions in the S4 pocket of the phenylcyclopropyl analogs; (2) the slightly reduced strain energy involved in the phenylcyclopropyl analogs as a result of the conformational bias to adopt the preferred perpendicular conformation; (3) the potential strain generated by the 1 Å shift of the backbone of the 90's loop in the

biphenyl analogs. Because of the broad application of the *ortho*-substituted biphenyl moieties, use of the perpendicular conformation of the *alpha*-substituted arylcyclopropyls to mimic the bioactive conformation of *ortho*-substituted biaryl moieties can be generalized and applied to achieve structural diversification and novelty in future drug design.

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