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1-(2-Naphthyl)-1*H*-pyrazole-5-carboxylamides as potent factor Xa inhibitors. Part 3: Design, synthesis and SAR of orally bioavailable benzamidine-P4 inhibitors

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Abstract—Using *N*,*N*-dialkylated benzamidines as the novel P4 motifs, we have designed and synthesized a class of 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides as highly potent and selective fXa inhibitors with significantly improved hydrophilicity and in vitro anticoagulant activity. These benzamidine-P4 fXa inhibitors have displayed excellent oral bioavailability and long half-life.

1. Introduction

The design and discovery of orally active small molecule competitive human factor Xa (fXa) inhibitors as novel therapies for thromboembolic disorders have been a major focus in the pharmaceutical industry.[1] We have recently reported a series of 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides as highly potent and selective fXa inhibitors with respectable oral bioavailability and half-life.[2,3] However, compared to our benzamidine-P1 fXa inhibitors with similar binding affinity, many of the 2-naphthyl-P1 fXa inhibitors are much weaker in vitro anticoagulants judged by the thrombin generation (TG) assay in human plasma.[2b,4,5] The poor in vitro anticoagulant activity has been believed due to their low hydrophilicity which could lead to extensive protein binding in plasma. We have explored a variety of P4 strategies to increase hydrophilicity and in vitro anticoagulant activity.[2b] In this communication, we describe our discovery and SAR study of a class of highly potent 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide fXa inhibitors with *N*,*N*-dialkylated benzamidines as the P4 motifs.

2. Results and discussion

Unsubstituted benzamidines have long been employed in fXa inhibitors as binding ligands in both the S1 and S4 pockets.[1] However, most of these benzamidine compounds suffer poor oral bioavailability and short half-life, and are not good development candidates for oral fXa inhibitors. The *N*,*N*-dialkylated benzamidine moieties have been known to improve oral absorptions from the unsubstituted benzamidine in the platelet glycoprotein IIb-IIIa antagonist literature.[6,7] Moreover, Berlex compound ZK-807834[8] has demonstrated *N*-methylimidazoline, a special form of *N*,*N*-dialkylamidine, to be a highly potent fXa P4 ligand. Thus, we hypothesized that the *N*,*N*-dialkylated benzamidine-P4 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides (**1**, **2** and **3**) could be highly potent fXa inhibitors with desired hydrophilicity and good oral PK properties. Our com-

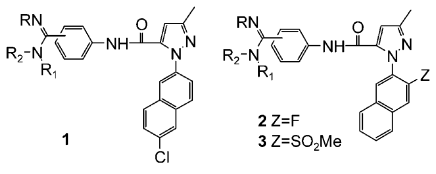

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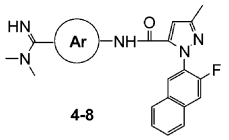
Table 1. Effects of the aromatic moiety on fXa potency



4-8

Compd	Ar	fXa IC_{50} (nM)
4		511
5		377
6		479
7		18
8		22

puter-based modeling suggested that the fXa S4 pocket could accommodate a variety of substituted amidines. At physiological pH, the *N*,*N*-dialkylated amidine would be positively charged. This charged P4 ligand not only would increase the inhibitors hydrophilicity, but also would increase its binding affinity through π-cation interactions in fXa S4 pocket.

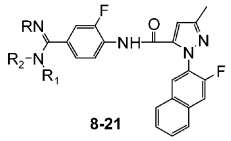
To examine our hypothesis, we prepared the 3-fluoro-2-naphthyl analogues **4–8** using the simplest *N*,*N*-dimethylamidine as the P4 element. As shown in Table 1, the low nanomolar fXa inhibitory activity of compounds **7** (18 nM) and **8** (22 nM) has proved our hypothesis. It has also been clear that the 1,4-phenyl linkage is optimal for fXa binding affinity.

To explore the effects of P4 amidine substitution on fXa activity, we then synthesized compounds **9–21**. As listed in Table 2, unsubstituted amidine **9** (777 nM) and *N*-monosubstituted amidine **10** (114 nM) are not very active. The *N*-ethyl-*N*-methyl substituted analogue **11** (22 nM), pyrrolidine containing analogue **17** (6 nM), piperidine containing analogue **18** (8 nM) and *N*-methylimidazoline analogue **21** (18 nM) display equal or slightly better fXa activity than lead **8** (22 nM). All other amidine substitutions have resulted in a loss in fXa binding potency.

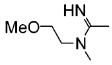
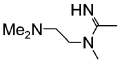
To improve fXa activity, we prepared compounds **22–25** to incorporate a trifluoromethyl group into the pyrazole.[9] We also synthesized the corresponding tetrazole analogues **26–29** to probe the modification of the central nucleus.[10] As summarized in Table 3, the trifluoromethyl group improves fXa potency only for *N*,*N*-dimethylamidine analogue **22** (4 nM). For the other analogues (**23–25**), there is no gain by the trifluoromethyl substituent. The tetrazole analogues (**26–29**) are not as potent as the corresponding 3-methylpyrazole fXa inhibitors (**8**, **17**, **18** and **21**).

To survey the effects of the 2-naphthyl substitution along with nucleus modification on fXa potency, we prepared compounds **30–45**. As shown in Table 4, in terms of fXa inhibitory activity, the 6-chloro-2-naphthyl

Table 2. Effects of amidine substitution on fXa potency



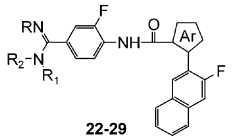
8-21

Compd		fXa IC_{50} (nM)
8		22
9		777
10		114
11		22
12		34
13		110
14		48
15		80
16		50
17		6
18		8
19		134
20		50
21		18

analogues (**30–41**) are more potent than the 3-fluoro-2-naphthyl (**8–29**) and the 3-methylsulfonyl-2-naphthyl (**42–45**) analogues. This trend matches what we observed before in the 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide-based fXa inhibitors with a variety of other P4 motifs.[2b] For the 6-chloro-2-naphthyl analogues with *N*,*N*-dialkylated amidines in P4 (**34–37**), the trifluoromethyl substituent in the pyrazole scaffold has enhanced the fXa inhibitory activity.[9] Meanwhile, the displacement of the 3-methylpyrazole nucleus by tetrazole has little effect on fXa activity for the 6-chloro-2-naphthyl analogues (**38–41**).

The K_i value and in vitro anticoagulant activity of the leading fXa inhibitors disclosed above are summarized in Table 5. Interestingly, by fXa inhibitory activity, tri-

Table 3. Effects of central nucleus modification on fXa potency



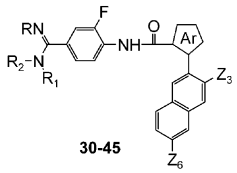
22-29

Compd	Ar	RN / R2-N / R1	fXa IC_{50} (nM)
22			3
23			10
24			11
25			31
26			16
27			24
28			76
29			110

fluoromethyl substituted compounds **34** (IC_{50} 1 nM; K_i 0.9 nM) and **37** (IC_{50} 2 nM; K_i 1.2 nM) are more potent than analogues **30** (IC_{50} 5 nM; K_i 0.7 nM) and **33** (IC_{50} 8 nM; K_i 1.0 nM). However, in terms of fXa K_i, there is no difference at all in regard to their potency. Overall, this class of fXa inhibitors has displayed good to excellent in vitro anticoagulant activity in our human plasma TG assays. As expected, the 6-chloro-2-naphthyl analogues are the most active, judged by both fXa IC_{50} and K_i values. But, due to relatively lower hydrophilicity, their strong fXa potency has not been translated into the desired in vitro anticoagulant activity. Despite of relatively weaker activity (fXa IC_{50} and K_i), the more hydrophilic 3-methylsulfonyl-2-naphthyl analogues **42** (2×TG 0.53 μM) and **45** (2×TG 0.78 μM) are however the most potent in vitro anticoagulants. Moreover, it seems that the trifluoromethyl substituent on the pyrazole plays a detrimental effect on the in vitro anticoagulant activity. For example, judged by the TG assay outcome, inhibitors **34** (2×TG 1.8 μM) and **37** (2×TG 4.5 μM) are less active in vitro anticoagulants than **30** (2×TG 0.83 μM) and **33** (2×TG 0.91 μM), even though their K_i values are about equal. Furthermore, the tetrazole nucleus is also disadvantageous to in vitro anticoagulant activity, as demonstrated by inhibitor **38** (K_i 0.7 nM; 2×TG 2.5 μM).

The enzyme selectivity and rat PK profiles[11] of four representative fXa inhibitors (**8**, **21**, **22** and **30**) are

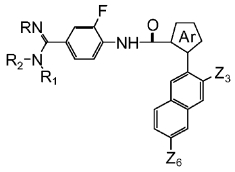
Table 4. Effects of 2-naphthyl substitution and nucleus modification on fXa potency



30-45

Compd	Z_3	Z_6	Ar	RN / R2-N / R1	fXa IC_{50} (nM)
30	H	Cl			5
31	H	Cl			7
32	H	Cl			7
33	H	Cl			8
34	H	Cl			1
35	H	Cl			2
36	H	Cl			4
37	H	Cl			2
38	H	Cl			2
39	H	Cl			7
40	H	Cl			8
41	H	Cl			15
42	SO_2Me	H			12
43	SO_2Me	H			15
44	SO_2Me	H			28
45	SO_2Me	H			14

Table 5. The in vitro anticoagulant activity results of the leading *N*,*N*-dialkylated benzamidine-P4 fXa inhibitors

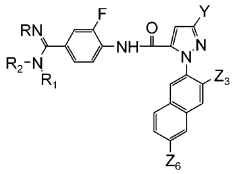


Compd	Z_3	Z_6	Ar	RN, R_2-N, R_1	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)
8	F	H			22	3.9	1.0
17	F	H			6	4.1	1.4
18	F	H			8	5.2	1.5
21	F	H			18	8.0	1.7
22	F	H			3	0.7	1.4
30	H	Cl			5	0.7	0.83
33	H	Cl			8	1.0	0.91
34	H	Cl			1	0.9	1.8
37	H	Cl			2	1.2	4.5
38	H	Cl			2	0.7	2.5
42	SO_2Me	H			12	2.8	0.53
45	SO_2Me	H			14	3.9	0.78

displayed in Table 6. Like our other 2-naphthyl-P1 fXa inhibitors,[2] the above *N*,*N*-dialkylated benzamidine 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides have excellent fXa selectivity (>1000-fold by IC_{50}) against thrombin, trypsin, *t*-PA, aPC, plasmin and kallikrein. All of these four compounds have excellent oral bioavailability and long half-life. In regard to the P4 modification, the *N*-methylimidazoline group (**8**) gives higher bioavailability and lower volume distribution than the *N*,*N*-dimethylamidine group (**21**). In regard to the pyrazole nucleus modification, the trifluoromethyl substituent (**22**) provides considerable improvement for all PK parameters as we expected. As for the 6-chloro-2-naphthyl-P1 analogue (**30**), it displays a very long half-life, a relatively large volume distribution and fairly good bioavailability.

To evaluate our fXa inhibitors in vivo, we examined compounds **22** (2×TG 1.4 μM) and **30** (2×TG 0.83 μM)

Table 6. The selectivity and PK profiles of four fXa inhibitors



Compd	**8**	**21**	**22**	**30**
Z_3	F	F	F	H
Z_6	H	H	H	Cl
Y	CH_3	CH_3	CF_3	CH_3
RN, R_2-N, R_1				
fXa IC_{50} (nM)	22	18	3	5
Thrombin IC_{50} (μM)	>10	>10	>10	>10
Trypsin IC_{50} (μM)	>10	>10	>10	>10
t-PA IC_{50} (μM)	>10	>10	>10	>10
aPC IC_{50} (μM)	>10	>10	>10	>10
Plasmin IC_{50} (μM)	>10	>10	>10	>10
Kallikrein IC_{50} (μM)	>10	>10	>10	>10
F(%)	24.3	43.9	46.9	13.8
$T_{1/2}$ (IV) (h)	3.1	1.8	8.8	18.0
Vd (L/kg)	49.4	7.6	11.0	82.5
CL (mL/min/kg)	54.3	49.3	14.7	55.9

in the rabbit deep vein thrombosis (DVT) model.[12] Infusion of fXa inhibitor **22** produced a 51% inhibition of thrombus accretion at a plasma level of 4.6 μM and an ex vivo prothrombin time (PT) change of 1.53-fold. At a plasma concentration of 3.9 μM, 20% inhibition and 1.43-fold ex vivo PT change were found. Infusion of fXa inhibitor **30** generated a 56% inhibition of thrombus accretion at a plasma level of 4.5 μM and an ex vivo PT change of 1.66-fold. At a plasma concentration of 3.7 μM, 20% inhibition and 1.56-fold ex vivo PT change were produced.

Computer-based docking studies using GOLD[13] as well as both published and in-house fXa crystal data suggested a reasonable binding mode hypothesis for this class of *N*,*N*-dialkylated benzamidine-P4 fXa inhibitors. As shown in Figure 1 for compound **30** (fXa K_i 0.7 nM), the 6-chloro-2-naphthyl P1 moiety fits in the fXa S1 pocket and points into the aromatic ring of Tyr228 at the bottom of the pocket. The *N*,*N*-dimethylamidine is positively charged at physiological pH. This positive charge facilitates the π-cation stacking interaction of the benzamidine with the aromatic functionalities in the S4 pocket.

In conclusion, by using *N*,*N*-dialkylated benzamidines as the P4 motifs, we have discovered a class of 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides as highly potent and selective fXa inhibitors with excellent oral bioavailablity, long half-life, and excellent in vitro anticoagulant potency. Our further optimization on the 2-naphthyl P1 moiety using two substitution groups will be reported in due course.

3. Chemistry

The preparation of the *N*,*N*-dialkylated benzamidine-P4 fXa inhibitors is illustrated by the synthesis of

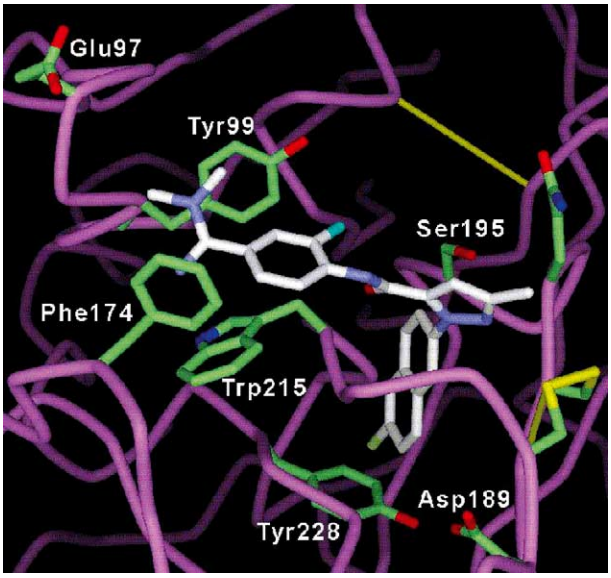
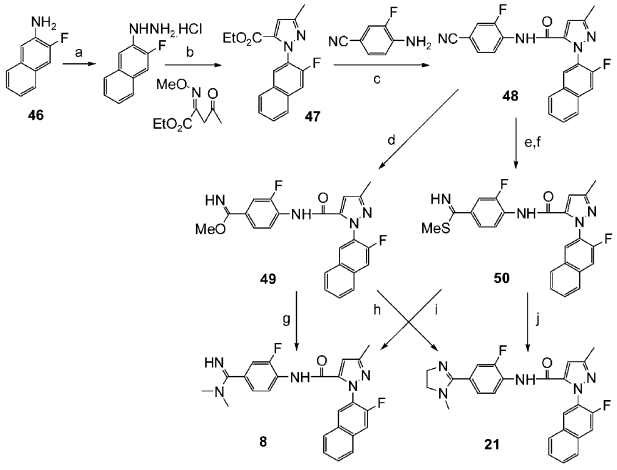


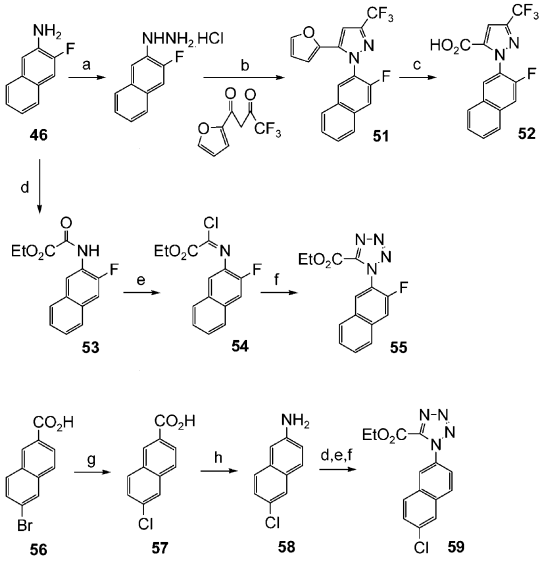
Figure 1. Computer modeling of compound **30** docked in fXa active enzyme pocket.

compounds **8** and **21**. Ethyl 1-(3-fluoro-2-naphthyl)-3-methyl-1*H*-pyrazole-5-carboxylate (**47**) was prepared from 3-fluoro-2-naphthylamine (**46**) as described in our previous communication.[2a] Compound **48**, assembled via a Weinreb reaction, was employed to produce **8** and **21** in two routes through methyl imidate **49** and methyl thioimidate **50**.

As shown in Scheme 2, the synthesis of 1-(3-fluoro-2-naphthyl)-3-trifluoromethyl-1*H*-pyrazole-5-carboxylic acid (**52**) was accomplished through oxidative cleavage of the furyl group in compound **51**. To prepare ethyl 1-(3-fluoro-2-naphthyl)-1*H*-tetrazole-5-carboxylate (**55**), 3-fluoro-2-naphthylamine (**46**)[2a] was treated with ethyl



Scheme 1. (a) (1) $NaNO_2$ (1.1 equiv), concd HCl, 0 °C, 30 m; (2) $SnCl_2{\cdot}2H_2O$ (3 equiv), concd HCl, 0 °C, 1 h; filtration; (b) THF/HOAc (1:2), reflux, 2 h; (c) Me_3Al (2M in hexane, 5 equiv), DCM, overnight; (d) dry MeOH, saturated with HCl (g), 0 °C to rt, overnight; (e) Et_3N/dioxane (1:10), saturated with H_2S (g), rt, overnight; (f) MeI (10 equiv), acetone, reflux, 1–2 h; (g) Me_2NH (2M in MeOH, 5 equiv), dry MeOH, reflux, 1 h; (h) $MeNHCH_2CH_2NH_2$ (3 equiv), dry MeOH, reflux, 1 h; (i) Me_2NH (2M in MeOH, 3 equiv), HOAc (5 equiv), dry MeOH, reflux, 1 h; (j) $MeNHCH_2CH_2NH_2$ (3 equiv), HOAc (8 equiv), dry MeOH, reflux, 1 h.



Scheme 2. (a) (1) $NaNO_2$ (1.1 equiv), concd HCl, 0 °C, 30 m; (2) $SnCl_2{\cdot}2H_2O$ (3 equiv), concd HCl, 0 °C, 1 h; filtration; (b) THF/HOAc (1:2), reflux, 2 h; (c) $KMnO_4$ (5 equiv), acetone/water (2:1), 60 °C, 3 h; (d) EtO_2CCOCl (1.2 equiv), Et_3N (5 equiv), DCM, rt; (e) Ph_3P (2 equiv), CCl_4, reflux, overnight; (f) NaN_3 (1.2 equiv), MeCN, rt, overnight; (g) CuCl (10 equiv), CuI (1 equiv), DMF, reflux; (h) (1) DPPA (1.5 equiv), Et_3N (1.5 equiv), DMF, rt, 3 h; (2) water, rflx, 1 h.

oxalate to give **53**, which was converted to **54** by reacting with triphenylphosphine in carbon tetrachloride. Compound **54** then reacted with sodium azide to smoothly produce building block **55** in high yield. Ethyl 1-(6-chloro-2-naphthyl)-1*H*-tetrazole-5-carboxylate (**59**) was synthesized similarly from 6-chloro-2-naphthylamine (**58**), which had been prepared from commercial 6-bromo-2-naphthoic acid (**56**) in two steps. The synthesis of ethyl 1-(6-chloro-2-naphthyl)-3-methyl-1*H*-pyrazole-5-carboxylate and ethyl 1-(3-methylsulfonyl-2-naphthyl)-3-methyl-1*H*-pyrazole-5-carboxylate have been reported.[2] All the corresponding *N*,*N*-dialkylated benzamidine-P4 fXa inhibitors were made using the chemistry exemplified in Scheme 1.

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3. Part of the work described in this communication has been previously presented at the 226th ACS National Meeting in September 2003 in New York, New York (MEDI-32).
4. Thrombin generation in human plasma (TG) assay: Potential fXa inhibitors are dissolved in DMSO, and serial dilutions are made in wells of 96 well plates. Reptilase-treated human plasma is added to the inhibitors, followed by substrate (H-β-Ala-Gly-Arg-*p*-nitroanilide) and $CaCl_2$. The thrombin generation reaction is started by addition of 640 pmol/L of recombinant tissue factor. The absorbance is monitored at 405 nm at 37 °C for 22 min. The results are expressed as 2×TG, the concentration of an inhibitor required to double the time of maximum thrombin generation. A $\leq$ 1 μM 2×TG value is usually required for positively efficacious response in our rabbit DVT model.
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