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Orally active factor Xa inhibitors: Investigation of a novel series of 3-amidinophenylsulfonamide derivatives using an amidoxime prodrug strategy

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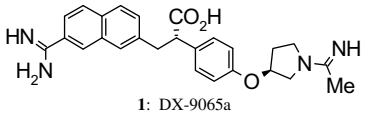
ABSTRACT

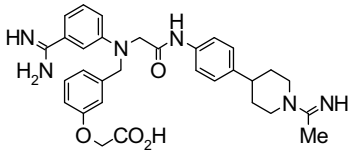
A series of novel and potent 3-amidinophenylsulfonamide derivatives of factor Xa inhibitors were designed and synthesized using an amidoxime prodrug strategy. We focused on systemic clearance of parent compounds in rats, and performed in vivo pharmacokinetic screening. Incorporation of a carboxymethoxy group markedly improved systemic clearance (compound **43**), and the related amidoxime **44** showed sufficient prodrug conversion. Compound **45**, the double prodrug of **43,** exhibited practicable bioavailability after oral administration in rats. Among the various compounds under investigation, KFA-1982 was selected for clinical development.

Thromboembolic diseases such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and thromboembolic stroke are major causes of morbidity and mortality in developed countries.[1] Currently available anticoagulants such as warfarin, heparin, and low-molecular-weight heparins are widely used for the treatment and prevention of thromboembolic diseases; however, these anticoagulants have many therapeutic limitations. Therefore, orally active anticoagulant drugs are attractive therapeutic targets.[2]

Activated blood coagulation factor X (fXa) is a trypsin-like serine protease. It resides at the juncture of the intrinsic and extrinsic pathways in the blood coagulation cascade, and plays a critical role in thrombus formation.[3] Since the 1990s, a number of small-molecule fXa inhibitors, including DX-9065a (Fig. 1, compound **1**), have been reported as promising anticoagulant drugs.[2,4] More recently, several orally active small-molecule fXa inhibitors such as rivaroxaban and apixaban are in late-stage clinical trials.[5,6] These reports have prompted us to disclose our efforts for the discovery of novel fXa inhibitors. In this paper, we describe the discovery and optimization of novel sulfonamide derivatives as orally active fXa inhibitors.



1: DX-9065a



2: KFA-1411

Figure 1. Structures of bisamidine fXa inhibitors.

Initial research in our laboratory focused on bis-amidine compounds. We have already reported a potent and selective fXa inhibitor, KFA-1411 (Fig. 1, compound **2**), that exhibits effective anticoagulant activity in an animal hemodialysis model.[7] Unfortunately, however, **2** showed marginal oral anticoagulant activity, probably because of its high polarity due to the presence of two amidino groups and one carboxyl group.

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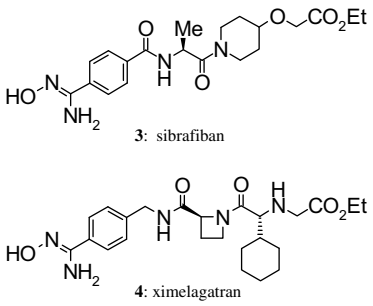


Figure 2. Structures of amidoxime prodrugs.

Amidoximes have been well known as prodrugs of amidine-containing drugs,[8] including sibrafiban and ximelagatran (Fig. 2).[9–12] These efforts convinced us that the amidoxime prodrug strategy, at least for mono-amidine derivatives, could be one of the most promising approaches for the development of orally active fXa inhibitors.

Results based on docking studies of our compounds with fXa suggested that the interaction of the 3-amidinophenyl moiety (A) with Asp189 in the S1 pocket, and the rigid phenylene moiety (B) toward the hydrophobic S4 pocket, may play critical roles in inhibitor-protein binding (Fig. 3). We initially sought to replace the acetimidoyl moiety at the P4 position in the S4 pocket by non-polar substituents and explored various linkers; these efforts led to the discovery of compounds of a novel 3-amidinophenylsulfonamide series.

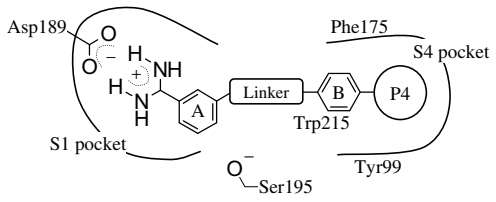
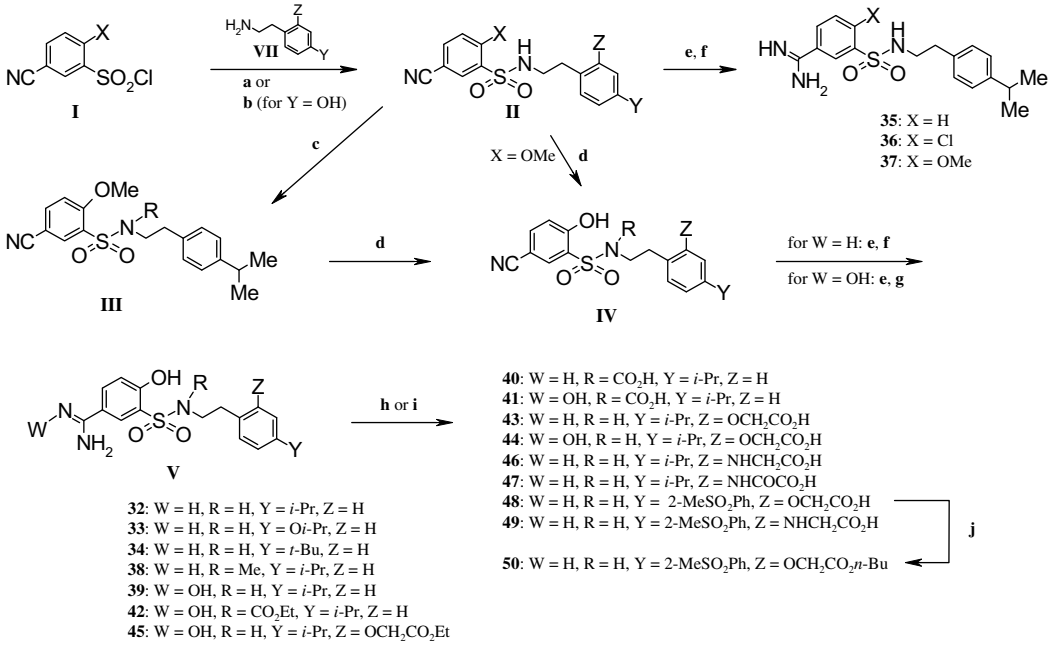


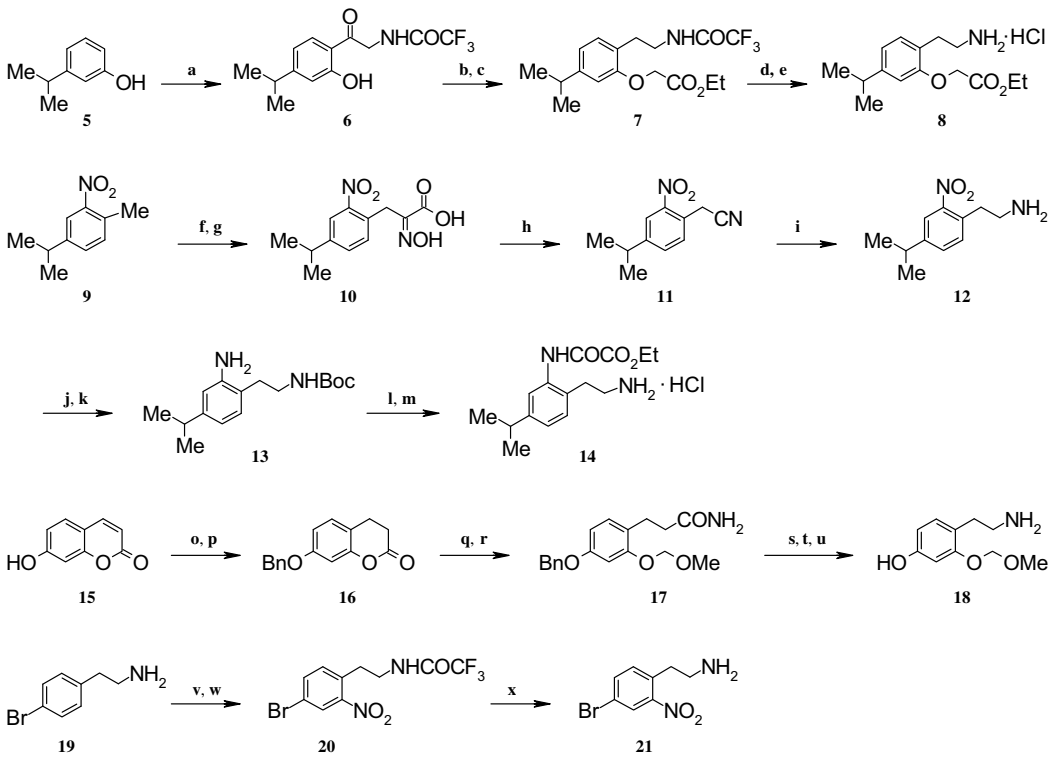
Figure 3. Schematic of essential interactions between inhibitor and fXa.

General synthetic routes of the 3-amidinophenylsulfonamide series are outlined in Scheme 1. The phenylsulfonylchlorides **I** were coupled with appropriate phenethylamines **VII** to give the sulfonamides **II**. The N-substituted sulfonamides **III** were prepared by alkylation of the sulfonamides **II** in the presence of K_2CO_3. Conversion of the 2-methoxyphenylsulfonamides **II** and **III** to the corresponding 2-hydroxy derivatives **IV** was accomplished by heating with LiCl in DMF. Treatment of the benzonitriles **II** and **IV** with ethanolic HCl followed by ammonium acetate or hydroxylammonium acetate gave the corresponding amidines or amidoximes (**35**–**37** and **V**). The carboxylic acids **40**, **41**, **43**, **44**, and **46**–**49** were prepared from the corresponding esters of **V** by hydrolysis under acidic or basic conditions. The carboxylic acid **48** was heated with *n*-butanolic HCl to give the *n*-butyl ester **50**.

The phenethylamines **8**, **12**, **14**, **18**, and **21** were prepared as shown in Scheme 2. The phenol **5** was acylated by Friedel–Crafts-type reaction with *N*-cyanomethyl-2,2,2-trifluoroacetamide to give the aminoacetophenone derivative **6**. Reduction of the ketone with triethylsilane in TFA followed by alkylation of the phenolic hydroxy group with ethyl bromoacetate gave compound **7**. Hydrolysis of the protecting group of **7** followed by treatment with ethanolic HCl gave the phenethylamine **8**. The 2-nitrotoluene **9** was successively treated with $(CO_2Et)_2$/NaOEt, aqueous NaOH, and hydroxylamine to give oxime **10**. The oxime **10** was converted to the nitrile **11** in the presence of acetic anhydride, and then hydrogenated with BH_3 to give the 2-nitrophenethylamine **12**. The anilide **14** was prepared from **12** via conventional synthesis. Boc protection of the amino group of **12** followed by reduction of the nitro group to give **13**, which was acylated with ethyl oxalyl chloride and then treated with ethanolic HCl to give **14**. Catalytic hydrogenation of 7-hydroxychromen-2-one (**15**) followed by masking of phenol as a benzyl ether gave the chroman-2-one **16**, which was treated with ammonia followed by alkylation of phenolic hydroxy group with chloromethyl methyl ether to give the phe-



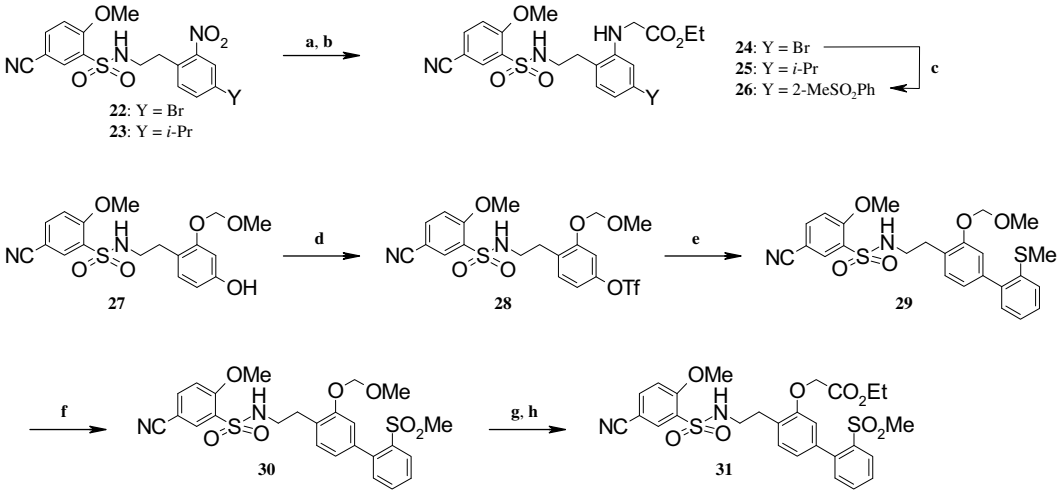
Scheme 1. General synthetic routes of 3-amidinophenylsulfonamide derivatives. Reagents and conditions: (a) Et_3N or K_2CO_3, THF, H_2O, rt; (b) $NaHCO_3$, THF, H_2O, rt; (c) $BrCH_2CO_2Et$ or MeI, K_2CO_3, DMF, rt; (d) LiCl, DMF, 140 °C; (e) HCl (gas), EtOH, rt; (f) NH_4OAc, EtOH, rt; (g) $NH_2OH{\cdot}HOAc$, EtOH, rt; (h) 1 N HCl, CH_3CN, 60 °C; (i) 2 N NaOH, EtOH or CH_3CN, 0 °C to rt; (j) HCl (gas), *n*-BuOH, 100 °C.



Scheme 2. Preparation of phenethylamines. Reagents and conditions: (a) $CF_3CONHCH_2CN$, BCl_3, $AlCl_3$, CH_2Cl_2, rt; (b) Et_3SiH, TFA, rt; (c) $BrCH_2CO_2Et$, K_2CO_3, DMF, rt; (d) K_2CO_3, H_2O, MeOH, rt; (e) HCl, EtOH, rt; (f) $(CO_2Et)_2$, NaOEt, THF, reflux, then NaOH aq. 60 °C; (g) NH_2OH·HCl, pyridine, EtOH, 70 °C; (h) Ac_2O, AcOH, 50 °C; (i) BH_3-THF, THF, rt; (j) Boc_2O, THF, rt; (k) H_2, Pd-C (10%), EtOH, rt; (l) $ClCOCO_2Et$, pyridine, CH_2Cl_2, rt; (m) HCl (gas), EtOH, rt; (o) H_2, Pd-C (10%), THF, EtOH, 65 °C; (p) BnCl, K_2CO_3, DMF, rt; (q) NH_3 aq, THF, rt; (r) NaH, DMF, 50 °C, then CH_3OCH_2Cl, rt; (s) NBS, DBU, MeOH, 65 °C, (t) KOH aq., EtOH, reflux; (u) H_2, Pd-C (10%), EtOH, rt; (v) TFAA, Et_3N, CH_2Cl_2, rt; (w) NO_2BF_4, CH_3CN, rt; (x) NaOH aq., MeOH, 50 °C.

nylpropionamide **17**. Conversion of the amide **17** into the amine **18** was performed by the Hoffmann rearrangement followed by treatment with KOH and deprotection of the benzyl group. Protection of amino group of 4-bromophenetylamine **19** by trifluoroacetylation followed by treatment with nitronium tetrafluoroborate gave *o*-nitrophenethylamine **20**, and then the trifluoroacetyl group was removed by hydrolysis to give 4-bromo-2-nitrophenetylamine **21**.

The synthetic route of compounds **24** and **25**, which have an ethoxycarbonylmethylamino group, and compounds **26** and **31**, which have a biphenyl moiety, are shown in Scheme 3. Compounds **24** and **25** were prepared from the corresponding nitro derivatives **22** and **23** by reduction followed by alkylation with ethyl bromoacetate, respectively. The phenol **27** was treated with trifluoromethanesulfonic anhydride in the presence of 4-dimethylaminopyridine to give the triflate **28**. The biphenyl compounds **26** and **29** were synthesized from **24** and **28**, respectively, using the Suzuki coupling reaction. Oxidation of the methylthio group of compound **29** resulted in the methanesulfonyl derivative **30**.



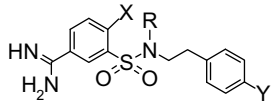
Scheme 3. Reagents and conditions: (a) Zn, HCl (conc.), AcOH, THF, rt; (b) $BrCH_2CO_2Et$, *i*-Pr_2NEt, DMF, 55 °C; (c) (i) bis(pinacolato)diboron, Pd(dppf)Cl_2, dppf, KOAc, dioxane, 80 °C; (ii) 2-$BrPhSO_2Me$, Pd(dppf)Cl_2, K_3PO_4, dioxane, 80 °C; (d) $(CF_3SO_2)_2O$, DMAP, CH_2Cl_2, 0 °C; (e) 2-MeSPhB$(OH)_2$, Pd$(PPh_3)_4$, (*n*-Bu)$_4$NBr, Na_2CO_3, H_2O, toluene, 85 °C; (f) Oxone®, $NaHCO_3$, acetone, H_2O, water cooling; (g) HCl (conc.), *i*-PrOH, THF, 50 °C; (h) $BrCH_2CO_2Et$, *i*-Pr_2NEt, DMF, 50 °C.

Deprotection of the methoxymethyl ether group of compound **30** followed by alkylation with ethyl bromoacetate gave compound **31**.

Table 1 shows the anti-fXa, anti-thrombin, and anti-trypsin activities of compounds **1**, **2**, and **32**–**38**. The 3-amidinophenylsulfonamide with an isopropyl group substituted at the P4 position (**32**) showed potent anti-fXa activity and good selectivity against thrombin and trypsin. Replacement of the isopropyl group with an isopropoxy group reduced the activities of both anti-fXa and anti-trypsin (**33** vs **32**). Upon replacement with a more bulky substituent, a *tert*-butyl group, the anti-fXa activity was retained (**34** vs **32**). Incorporation of a methyl group at the sulfonamide nitrogen was tolerable (**38**). Elimination or replacement of the hydroxy group resulted in a significant decrease in the anti-fXa activity and loss of selectivity over trypsin (**35**–**37**). We considered that this fXa-specific effect of the hydroxy group is probably due to the interaction with the characteristic residue in fXa (e.g., Tyr99).

A rat pharmacokinetic study for the mono-amidine compound **32** showed low bioavailability (Table 2). The related prodrug of amidoxime **39** showed good oral absorption (F = 29%), but the prodrug conversion to parent **32** was negligible. These results suggested that low bioavailability of the parent **32** after oral administration of the prodrug **39** may be due to relatively high systemic clearance of **32** and **39** compared with the prodrug conversion rate of **39** to **32**. Previous literature suggested that the nature of the parent depends significantly on the substituent incorporated.[11,12] Successful approaches using amidoxime prodrugs such as sibrafiban (**3**) and ximelagatran (**4**) have been reported;[9,10,12] these prodrugs have a carboxyl moiety in their parent compounds. We therefore explored the incorporation of a carboxyl group at the position that allows

Table 1
Inhibitory activity of compounds **1**, **2**, and **32**–**38** against human fXa, thrombin, and trypsin



Entry	X	R	Y	K_i[a] (nM)		
				fXa	Thrombin	Trypsin
1		(DX-9065a)		41[b]	> 2,000,000[b]	620[b]
2		(KFA-1411)		1.73	26,000	6170
32	OH	H	*i*-Pr	29	> 10^{-5} M	800
33	OH	H	Oi-Pr	100	> 10^{-5} M	(1700)
34	OH	H	*t-Bu*	27	NT	NT
35	H	H	*i*-Pr	2100[c]	> 10^{-5} M	(9700)
36	Cl	H	*i*-Pr	3000	NT	4000
37	OMe	H	*i*-Pr	14,000	NT	NT
38	OH	Me	*i*-Pr	59	NT	770

[a] K_i values were measured as described in reference 7a ($n \geqslant 2$). Data in parentheses represent IC_{50} values.
[b] Ref. 4a.
[c] K_i value calculated according to the Cheng–Prusoff equation: $K_i = IC_{50}/(1 + [S]/K_m)$.[15]

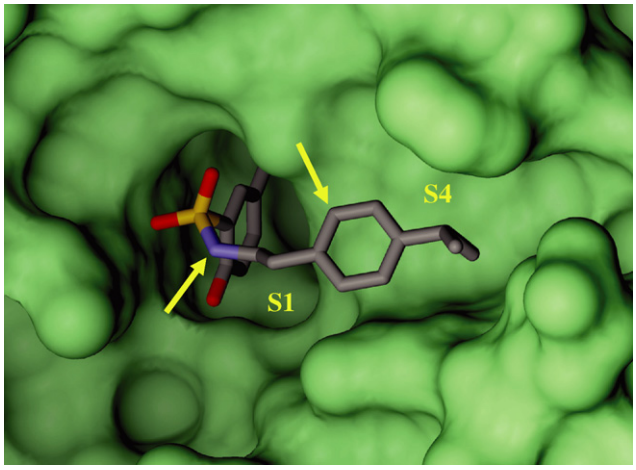
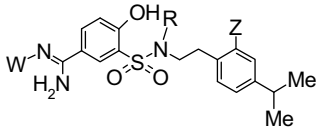


Figure 4. Binding model of compound **32** bound to fXa. The protein surface is colored light green; tolerable substitution points are indicated by yellow arrows. Water molecules in the crystal structure have been removed for clarity. Coordinates of fXa can be obtained from the Protein Data Bank (PDB entry: 1FJS).

Table 2
Factor Xa inhibitory activities, anticoagulant activities, and PK parameters for compounds **2**, **32,** and **39**–**45**



Entry	W	R	Z	fXa K_i[a] (nM)	PT2[c] (μM)	Cl_{tot}[d] (mL/min)	Prodrug conversion[e] (%)	F[f] (%)
2		(KFA-1411)		1.7	0.84	23	—	0.9
32	H	H	H	29	2.6	27	—	3.7
39	OH	H	H	7300[b]	NT	27	1	6.6 (29[g])
40	H	CH_2CO_2H	H	14	1.4	8.1	—	NT
41	OH	CH_2CO_2H	H	7000[b]	NT	13	16	NT
42	OH	CH_2CO_2Et	H	3700[b]	NT	NT	NT	< 1 (7.0[h])
43	H	H	OCH_2CO_2H	51	7.2	1.7	—	NT
44	OH	H	OCH_2CO_2H	> 10^{-5} M	NT	7.5	57	9.2 (2.5[i])
45	OH	H	OCH_2CO_2Et	3500[b]	NT	NT	NT	13 (4.0[i])

[a] Against human fXa: K_i values were measured as described in Ref. 7a ($n \geqslant 2$).
[b] K_i value calculated according to the Cheng–Prusoff equation: $K_i = IC_{50}/(1 + [S]/K_m)$.[15]
[c] Human prothrombin time: plasma concentration required to double clotting time.
[d] Total body clearance after iv administration in rats ($n \geqslant 2$).
[e] Prodrug conversion was calculated by the dose-normalized AUC of the parent after intravenous administration of prodrug by the AUC of the parent after intravenous administration of parent in rats.
[f] Bioavailability (F%) was calculated by the dose-normalized AUC of the parent after oral administration of prodrug or parent by the AUC of the parent after intravenous administration of parent in rats.
[g] Bioavailability of the unchanged prodrug **39**.
[h] Bioavailability of compound **41**, the unchanged amidoxime.
[i] Bioavailability of compound **44**, the unchanged amidoxime.

extension without enzyme interaction. The binding model of compound **32** bound to fXa is shown in Figure 4. Incorporation of the substituent at the sulfonamide nitrogen (demonstrated above **38**) and the proximal position of the phenylene ring (indicated by arrows) were considered tolerable.

We focused on the systemic clearance of parent compounds; therefore, in vivo pharmacokinetic screening in the rat was carried out. Incorporation of a carboxymethyl group at the sulfonamide nitrogen (**40**) resulted in a twofold improvement in anti-fXa activity compared with **32**. Systemic clearance was also improved (reduced from 27 to 8.1 mL/min), but the prodrug conversion of the related amidoxime **41** was not sufficient. In contrast, introduction of a carboxymethoxy group at the proximal position of the phenylene ring (**43**) greatly improved systemic clearance, although anti-fXa activity was inconsiderably diminished compared with **32** (less than twofold). The related amidoxime **44** showed sufficient prodrug conversion. Compound **45**, a double prodrug of **43,** exhibited practicable bioavailability after oral administration in rats.

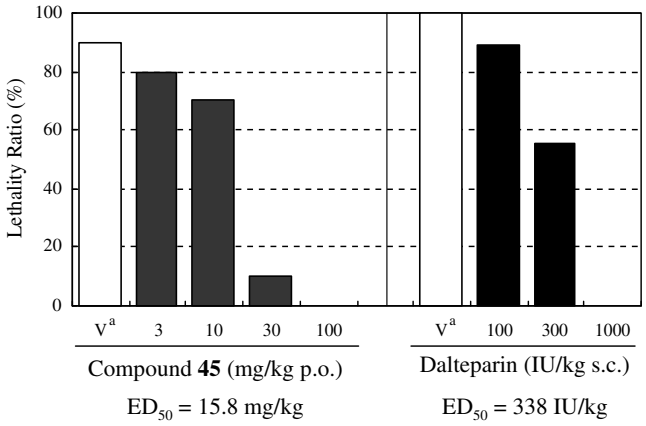
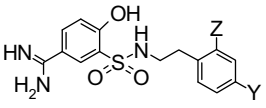
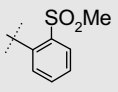
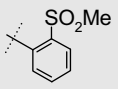


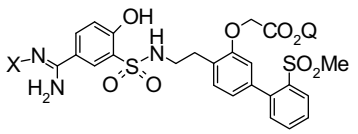
Figure 5. Preventive effects of compound **45** and dalteparin on thromboplastin-induced lethal thromboembolism in mice. Agents were administrated orally (compound **45**, suspended in 0.5% methyl cellulose) or subcutaneously (dalteparin sodium, diluted in 5 mL/kg saline) 30 min prior to thromboplastin injection (n = 9–10). Lethality (%) was calculated from the number of mice survived. [a]Vehicle.

Table 3
Factor Xa inhibitory activities and Cl_{tot} for compounds **43** and **46**–**49**



Entry	Z	Y	fXaK_i[a] (nM)	Cl_{tot}[c] (mL/min)
43	OCH_2CO_2H	*i*-Pr	51	1.7
46	$NHCH_2CO_2H$	*i*-Pr	62[b]	3.2
47	$NHCOCO_2H$	*i*-Pr	9.7[b]	20
48	OCH_2CO_2H		5.0	7.5
49	$NHCH_2CO_2H$		5.7[b]	25

[a] Against human fXa: K_i values were measured as described in Ref. 7a ($n \geqslant 2$).
[b] K_i value calculated according to the Cheng–Prusoff equation: $K_i = IC_{50}/(1 + [S]/K_m)$.[15]
[c] Total body clearance after iv administration in rats ($n \geqslant 2$).



X = H, Q = H
Free form **48**
HCl salt KFA-1829

X = OH, Q = *n*-Bu
Free form **50**
HCl salt KFA-1982

In vitro activities
Anti-fXa K_i = 5.00 nM
Anti-thrombin K_i = 57800 nM
Anti-trypsin K_i = 1170 nM
PT2 = 1.01 μM

Bioavailability
Mouse: 15%
Rabbit: 23%
Dog: 4.9%
Cynomolgus monkey: 11%

Figure 6. Structures and profiles of KFA-1982 and KFA-1829.

Figure 5 demonstrates evaluation of the preventive effects of the double prodrug **45** and low-molecular-weight heparin, dalteparin, on an in vivo thrombosis model in mice. Compound **45** exhibited encouraging oral antithrombotic activity in a dose-dependent manner, with an ED_{50} value of 15.8 mg/kg. Bioavailability of the parent **43** after oral administration of the double prodrug **45** (30 mg/kg) in mice was 38%.

We were concerned that compound **43**, the parent of compound **45**, would not have sufficient anti-fXa and anticoagulation activities for further development. Therefore, we carried out further optimization of the parent compounds (Table 3). Replacement of the carboxymethoxy group of **43** with the carboxymethylamino group (**46**) exhibited similar anti-fXa activity and increased systemic clearance by less than twofold. The oxalylamino analogue **47** showed a fivefold increase in anti-fXa activity, but unfortunately, the systemic clearance was also increased. Improvement in anti-fXa activity was realized by incorporation of the ortho-substituted phenyl group at P4 position, which had been known as the optimal scaffold for the S4 pocket.[13] Replacement of the isopropyl group by the 2-methanesulfonylphenyl group markedly increased anti-fXa activities (**48**, **49**). As in the case of compounds **43** and **46**, equivalent efficacy was seen in the carboxymethoxy derivative **48** and the carboxymethylamino derivative **49**, but the systemic clearance of **48** was threefold better than that of **49**.

Compound **48** exhibited high selectivity for fXa over thrombin and trypsin, and good anticoagulant activity in plasma (Fig. 6). An amidoxime/*n*-butyl ester double prodrug **50** demonstrated sufficient oral bioavailability in several animal species including primates.[14] On the basis of the oral bioavailability, and the in vitro potency and selectivity of its parent form (**48**), KFA-1982, a hydrochloride salt of **50**, was selected for clinical development.

Acknowledgments

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