Design, Synthesis and Discovery of 1-(2-(6-Chloro-3-methylsulfonyl)-naphthyl)-1*H*-pyrazole-5-carboxylamides as Highly Potent Factor Xa Inhibitors

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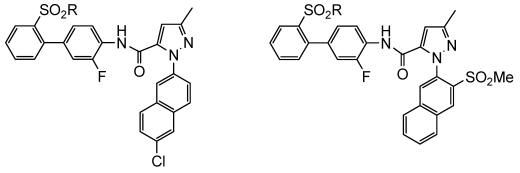
Based upon the biphenyl 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides reported in our previous communications, we designed and discovered 2-(6-chloro-3-methylsulfonyl)-naphthyl as an optimal factor Xa S1 binding element. Employing a key Diels–Alder reaction of 1,4-dihydro-2,3-benzoxathiin-3-oxide with maleic anhydride and a key Cu(I)-mediated methylsulfonylation, we prepared two biphenyl 1-(2-(6-chloro-3-methylsulfonyl)-naphthyl)-1*H*-pyrazole-5-carboxylamides as highly potent factor Xa inhibitors with K_i values of 0.065 nM and 0.045 nM respectively, and demonstrated the synergistically enhanced binding interaction in the factor Xa S1 site.

Key words factor Xa inhibitor; 1-naphthyl-1*H*-pyrazole; 6-chloro-3-iodonaphthyl-2-amine; 1,4-dihydro-2,3-benzoxathiin-3-oxide; sodium methanesulfinate

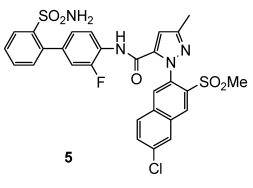
Serine protease factor Xa (fXa), positioned at the juncture of the intrinsic and the extrinsic pathways, plays a pivotal role in the blood coagulation cascade.[1] Selective inhibition of fXa without affecting the existing thrombin levels may cause less impairment of primary hemostasis and thus should be a safer anticoagulant therapy than direct inhibition of thrombin. Clinical findings have confirmed the potential of fXa inhibition for producing excellent antithrombotic efficacy with minimal bleeding risk when compared to direct thrombin inhibitors.[2—6]

Our previous communications have reported a series of 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides as potent and selective fXa inhibitors with good oral bioavailability and half-life.[7—9] This class of fXa inhibitors, as represented by compounds **1**—**4**, possesses a substituent either at the 6-position (chloro) or at the 3-position (methylsulfonyl, aminosulfonyl, aminocarbonyl, fluoro or cyano) on the P1 naphthalene moiety. The individual fXa affinity enhancing effect of the 6-chloro and the 3-methylsulfonyl substituents prompted us to wonder if the two substituents could be synergetic to each other for further fXa binding potency improvement. To answer this question, we designed compounds **5** and **6** that bear a tri-β-substituted 6-chloro-3-methylsulfonyl naphthalene moiety as the fXa S1 binding element.



1 (R=NH_2, fXa K_i 3.4 nM)
2 (R=Me, fXa K_i 1.8 nM)

3 (R=NH_2, fXa K_i 1.1 nM)
4 (R=Me, fXa K_i 1.7 nM)



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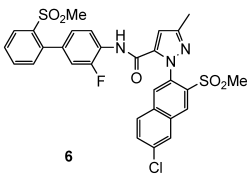

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Ethyl 1-(6-chloro-3-(methylsulfonyl)naphthalen-2-yl)-3-methyl-1*H*-pyrazole-5-carboxylate **7** was the key building block needed for the synthesis of compounds **5** and **6**, and the tri-β-substituted naphthalene **8** would be the precursor for its preparation, as analyzed in Chart 1. The amino group would lead to the pyrazole *via* condensation of the corresponding hydrazine, and the iodo group would serve as a handle to install the methylsulfonyl substituent through a copper-mediated C–S cross coupling with sodium methanesulfinate.[10] 6-Chloro-3-iodo-2-naphthylamine **8** could be synthesized from methyl 3-amino-2-naphthoate **9** *via* iodo-de-diazoniation followed by Curtius rearrangement. Based upon Levy's precedent work,[11] compounds **9**—**11** could be prepared from the Diels–Alder product **12** of 4-chloro-*o*-quinodimethane (**13**) and maleic anhydride. To produce the *o*-quinodimethane *in situ*, Levy forced the cheletropic elimination of sulfur dioxide from 1,3-dihydrobenzo[*c*]thiophene-*S*,*S*-dioxide using strong heat at 230 °C. In direct contrast, the 1,4-dihydro-2,3-benzoxathiin-3-oxide (also known as sulfinate or sultine) undergoes the sulfur dioxide cheletropic elimination smoothly around 80 °C.[12—17] Hoey and Dittmer[13] have developed a convenient one-step synthesis of 1,4-dihydro-2,3-benzoxathiin-3-oxide in high yield from α,α'-dihalo-*o*-xylene and sodium hydroxymethanesulfinate (rongalite). Townsend and co-workers[12] have elegantly applied this methodology in the preparation of tetra-β-substituted naphthalenes. We thus chose sulfinate **15** over sulfone **14** as the precursor for 4-chloro-*o*-quinodimethane **13**.

The synthesis of ethyl 1-(6-chloro-3-(methylsulfonyl)-naphthalen-2-yl)-3-methyl-1*H*-pyrazole-5-carboxylate **7** and its corresponding 2-(7-chloro-3-methylsulfonyl)-naphthyl isomer **7B** is illustrated in Chart 2. Diol **18** was readily prepared from commercially available 4-chlorophthalic anhydride **16** using lithium aluminum hydride (LAH) (>80%

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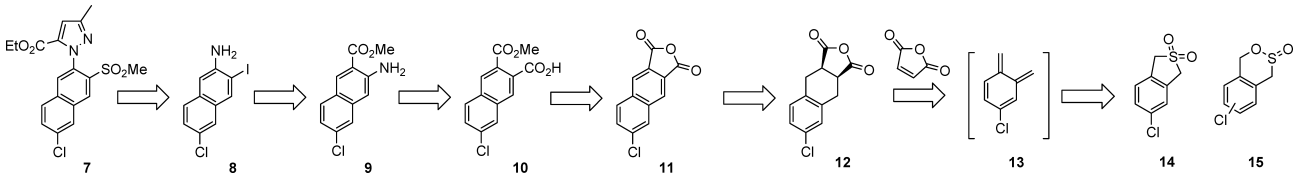
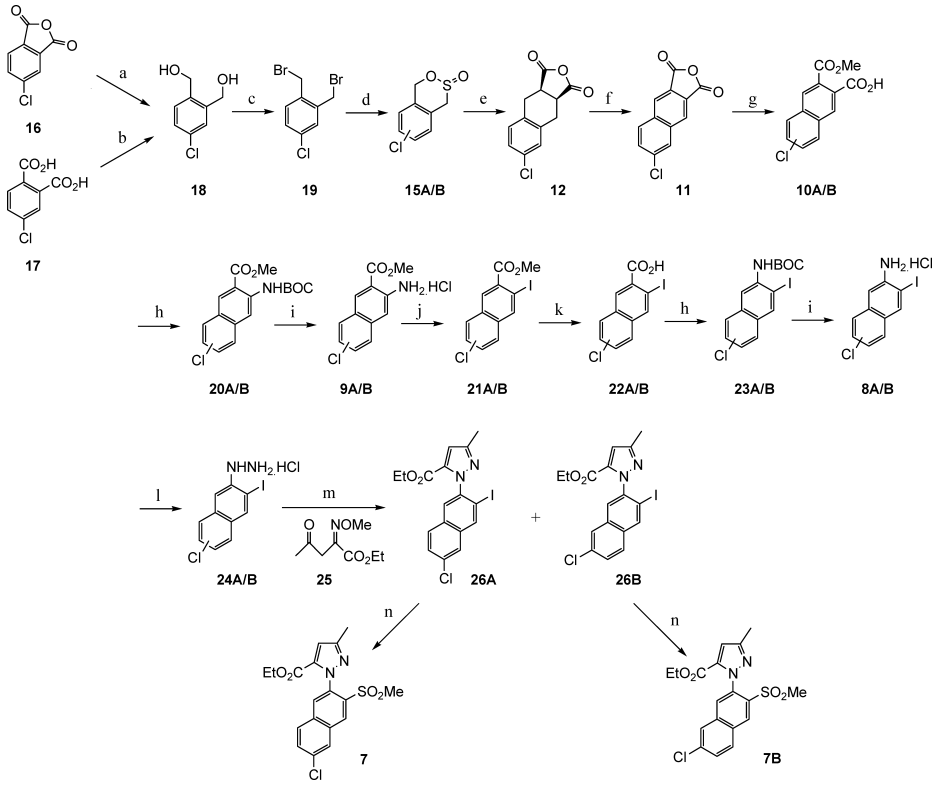


Chart 1. Retrosynthesis of Key Pyrazole Intermediate **7**



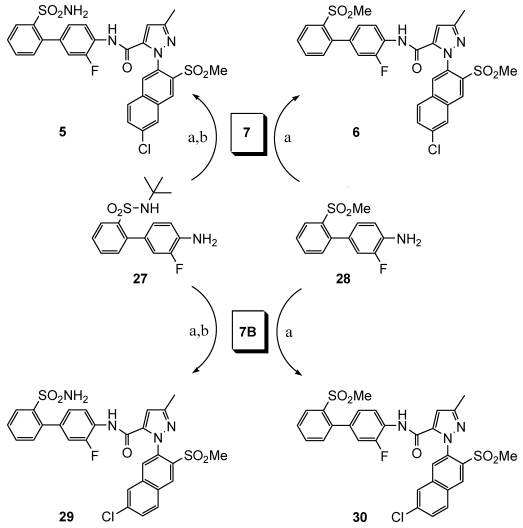
(a) LAH (1 M at THF, 2.5 eq), THF, room temperature (RT), 2 h, >80%; (b) $BH_3 \cdot THF$ (1 M in THF, 10 eq), dioxane, 0 °C to RT, 1 h, >70%; (c) 48% HBr, reflux, 4 h, 95%; (d) sodium hydroxymethanesulfinate dihydrate (2 eq), Bu_4NBr (0.2 eq), DMF, 0 °C to RT, overnight, 60%; (e) maleic anhydride (1 eq), PhH, reflux, overnight; (f) NBS (2 eq), AIBN (cat.), Ac_2O, 120 °C, 4 h; (g) (1) NaOMe (50 eq), MeOH, reflux, 3 h; (2) conc. HCl; (h) DPPA (1.1 eq), Et_3N (1.1 eq), *t*BuOH, reflux, overnight; flash column purification with 10% EtOAc in hexane; (i) HCl (4 N in dioxane), 2 h; (j) (1) $NaNO_2$ (1 eq), conc. HCl, 0 °C, 40 min; (2) NaI (4 eq in water), overnight, 0 °C to RT; (k) (1) $LiOH \cdot H_2O$ (2 eq), MeOH, THF, water, RT, 90 min; (2) conc. HCl; (l) (1) $NaNO_2$ (1 eq), conc. HCl, 0 °C, 30 min; (2) $SnCl_2 \cdot 2H_2O$ (3 eq), conc. HCl, 0 °C, 30 min; cold filtration to isolate solid product; (m) **25** (1 eq), THF/HOAc (2 : 1), reflux, 3 h; silica flash column purification with 5% EtOAc in hexane to separate **26A** and **26B**; (n) $MeSO_2Na$ (4 eq), $(CuOTf)_2 \cdot PhH$ (0.5 eq), $MeNHCH_2CH_2NHMe$ (0.5 eq), DMSO, 115 °C, 3 h; flash column purification with 10—20% EtOAc in hexane; 50%.

Chart 2

yield) and also from commercially available 4-chlorophthalic acid **17** using borane-tetrahydrofuran (THF) (>70% yield). α,α'-Dibromo-*o*-xylene **19** was produced from diol **18** in refluxed 48% HBr quantitatively. Under Dittmer's condition,[12,13] compound **19** reacted smoothly with sodium hydroxymethanesulfinate to afford a mixture of 1,4-dihydro-2,3-benzoxathiin-3-oxides **15A**/**B** in 1 : 1 ratio in 60% yield. In refluxed benzene, mixture **15A**/**B** decomposed to 4-chloro-*o*-quinodimethane **13**, which then underwent Diels–Alder reaction with maleic anhydride to cleanly generate 6-chloro-1,2,3,4-tetrahydro-2,3-naphthalic anhydride **12**. Its aromatization to 6-chloro-2,3-naphthalic anhydride **11** was accomplished using NBS (*N*-bromosuccinimide) in boiling acetic anhydride.[11]

Naphthalic anhydride **11** was converted to its half esters **10A**/**B** (inseparable) with sodium methoxide and next to the corresponding *tert*-butoxycarbonyl (BOC)-protected naphthylamine derivatives **20A**/**B** (inseparable) *via* Curtius rearrangement using diphenylphosporyl azide (DPPA).[11,12] Compounds **20A**/**B** were purified by flash column and their overall yield from **15A**/**B** was 60%. The BOC protecting group was then cleaved by HCl, and the resulted naphthylamines **9A**/**B** (1 : 1 by HPLC, yet separable by challenging flash column work) were converted to iodonaphthalenes **21A**/**B** (inseparable) through iodo-de-diazoniation.[18] Methyl esters **21A**/**B** were hydrolyzed into naphthyl carboxylic acids **22A**/**B**, which were converted to the corresponding BOC-protected naphthylamines **23A**/**B** *via* another Curtius rearrangement. Compounds **23A**/**B** (inseparable) were purified by flash column, and their overall yield from **20A**/**B** was 37%. Treatment of **23A**/**B** with 4 N HCl in dioxane offered the HCl salt of 6-chloro-3-iodonaphthyl-2-amine **8A** and 7-chloro-3-iodonaphthyl-2-amine **8B**.

Naphthylamines **8A**/**B** were converted to hydrazines **24A**/**B** using the same procedure we had reported earlier.[7] It was then condensed with mono-protected diketone **25** to afford naphthyl pyrazoles **26A**/**B** (1 : 1 by HPLC; overall 12% yield from **23A**/**B**). 6-Chloro-3-iodo-2-naphthyl pyrazole



(a) Me_3Al (2 M in hexane, 5 eq), DCM, RT, 1 d; Rochelle's salt (aq.) quench; 40—60%; (b) TFA, 50 °C, 1 h, 90%.

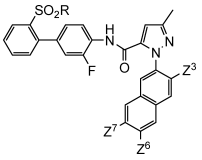
Chart 3

26A and its 7-chloro-3-iodo-2-naphthyl regioisomer **26B** were separated from each other by silica flash column using 5% EtOAc in hexane. Compound **26B** has a slightly higher *Rf* value than its regioisomer **26A**. Ethyl 1-(6-chloro-3-(methylsulfonyl)naphthalen-2-yl)-3-methyl-1*H*-pyrazole-5-carboxylate **7** was then successfully prepared from compound **26A** in about 50% yield by the Cu(I)-promoted C–S cross coupling reaction.[10,19] So was ethyl 1-(7-chloro-3-(methylsulfonyl)naphthalen-2-yl)-3-methyl-1*H*-pyrazole-5-carboxylate **7B** prepared from compound **26B**. The structures of **7** and **7B** were determined by proton NMR NOE study.[20]

Finally, the synthesis of 6-chloro-3-methylsulfonyl fXa inhibitors **5** and **6**, along with their corresponding 7-chloro-3-methylsulfonyl regioisomers **29** and **30**, was completed by the route shown in Chart 3.[21,22] Weinreb reactions[23] were used to couple the biphenylamines (**27**, **28**)[24] with ethyl esters **7** and **7B** in 40—60% yield. The amino-protecting *t*-butyl groups were cleaved using warm trifluoroacetic acid (TFA) to liberate the sulfonamide functionality in compounds **5** and **29**.

The biological activity data for the biphenyl 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides are summarized in Table 1. It is clear that the 7-chloro (Z^7) substituent in compounds **29** and **30** is not tolerated in the fXa S1 pocket, due to its unfavorable geometrical orientation. We were delighted to learn that the 6-chloro-3-methylsulfonyl compounds **5** (fXa IC_{50} 0.5 nM; K_i 0.065 nM) and **6** (fXa IC_{50} 0.6 nM; K_i 0.045 nM) are highly potent fXa inhibitors.[25,26] Their fXa binding affinity is about 10-fold better than that of the corresponding 6-chloro analogs (**1**, **2**), and is also about 10-fold better than that of the corresponding 3-methylsulfonyl analogs (**3**, **4**). This observation confirms that the Z^3 (3-methylsulfonyl) and Z^6 (chloro) substituents are synergetic to each other for the 2-naphthyl's binding interaction in the fXa S1 pocket. Like inhibitors **1**—**4**, compounds **5** and **6** have displayed excellent enzyme selectivity toward fXa. Their IC_{50} values for thrombin, trypsin, tissue plasminogen activator, activated protein C and plasmin are all above 10 μM.

Table 1. Effects of Naphthalene Substituents on fXa Potency



Compound	R	Z^3	Z^6	Z^7	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)
1	NH_2	H	Cl	H	3	3.4	>5
2	Me	H	Cl	H	6	1.8	>5
3	NH_2	SO_2Me	H	H	5	1.1	4.5
4	Me	SO_2Me	H	H	9	1.7	1.0
5	NH_2	SO_2Me	Cl	H	0.5	0.065	2.5
6	Me	SO_2Me	Cl	H	0.6	0.045	4.6
29	NH_2	SO_2Me	H	Cl	56	19	nd
30	Me	SO_2Me	H	Cl	65	22	nd

The kallikrein IC_{50} values for compounds **5** and **6** are 1.6 μM and 1.9 μM, respectively. Unfortunately, fXa inhibitors **5** (2×maximum thrombin generation (TG) 2.5 μM) and **6** (2×TG 4.6 μM) have not displayed strong *in vitro* anticoagulant activity in our human plasma thrombin generation assay,[27] probably due to their poor hydrophilicity and the resulted high plasma protein binding. However, as we have reported previously, the fXa inhibitors' hydrophilicity and *in vitro* anticoagulant potency can be significantly improved by changing and optimizing the P4 moieties, without compromising the potent fXa binding affinity.[8,9] Hopefully, the optimal P4 motifs we have discovered can lead us to potent 1-(2-(6-chloro-3-methylsulfonyl)-naphthyl)-1*H*-pyrazole-5-carboxylamide-based fXa inhibitors with improved anticoagulant activity and desired pharmacokinetic properties.

In conclusion, we have designed and synthesized biphenyl 1-(2-(6-chloro-3-methylsulfonyl)-naphthyl)-1*H*-pyrazole-5-carboxylamides **5** and **6** as highly potent fXa inhibitors. We have discovered that the 2-(6-chloro-3-methylsulfonyl)-naphthyl is a more potent fXa S1 binding element than the 2-(6-chloro)-naphthyl and the 2-(3-methylsulfonyl)-naphthyl in the class of 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide-based fXa inhibitors, due to the synergetic effect of the 6-chloro and the 3-methylsulfonyl groups to the S1 binding interaction.

References and Notes

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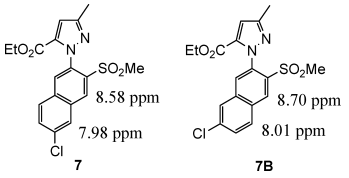
19) Preparation of compound **7**: To the solution of compound **26A** (430 mg, 1.0 mmol) in 10 ml DMSO were added sodium methanesulfinate (Aldrich #433063, 400 mg, 4.0 mmol), copper(I) trifluoromethanesulfonate benzene complex (Aldrich #407240, 250 mg, 0.5 mmol) and *N*,*N*′-dimethylethylenediamine (55 μl, 0.5 mmol). The mixture was stirred for 3 h in 115 °C bath. After cooling to RT, the mixture was treated with 10 ml 1N HCl solution for a few minutes. The mixture was diluted using 250 ml ethyl acetate and washed with brine three times. The organic phase was dried, concentrated and subjected to silica flash column using 20% ethyl acetate in hexane to isolate compound **7** (192 mg, 49% yield). Compound **7B** was prepared using compound **26B** by the same procedure.
20) Compound **7**: MS found for $C_{18}H_{17}ClN_2O_4S$ as $[M+H]^+$ 393.1 with pattern of 1 chlorine; ^{1}H-NMR ($CDCl_3$) δ: 8.58 (1H, s), 7.98 (1H, d, J=2.0 Hz), 7.86 (1H, s), 7.80 (1H, d, J=8.8 Hz), 7.58 (1H, dd, J=8.8, 2.0 Hz), 6.82 (1H, s), 4.08 (2H, q, J=7.0 Hz), 2.96 (3H, s), 2.33 (3H, s), 1.04 (3H, t, J=7.0 Hz) ppm; NOE: irradiation at 8.58 ppm caused positive response at 7.98 (d, J=2.0 Hz) ppm; irradiation at 7.98 ppm caused positive response at 8.58 (s) ppm. Compound **7B**: MS found for $C_{18}H_{17}ClN_2O_4S$ as $[M+H]^+$ 393.1 with pattern of 1 chlorine; ^{1}H-NMR ($CDCl_3$) δ: 8.70 (1H, s), 8.01 (1H, d, J=8.8 Hz), 7.90 (1H, d, J=1.6 Hz), 7.84 (1H, s), 7.63 (1H, dd, J=8.8, 1.6 Hz), 6.87 (1H, s), 3.01 (3H, s), 4.12 (2H, q, J=7.0 Hz), 2.38 (3H, s), 1.10 (3H, t, J=7.0 Hz) ppm; NOE: irradiation at 8.70 ppm caused positive response at 8.01 (d, J=8.8 Hz) ppm.



21) Preparation of compound **5**: Ethyl ester **7** (60 mg, 0.15 mmol) and aniline **27** (100 mg, 0.31 mmol) were dissolved in 10 ml dichloromethane (DCM). To this solution was added trimethylaluminum (2.0 M solution in hexane, Aldrich #268569, 0.45 ml, 0.90 mmol), and the mixture was stirred for 1 d at RT. To it was carefully added 10 ml of a saturated solution of Rochelle's salt (potassium sodium tartrate tetrahydrate) in water to quench the reaction, followed by addition of 100 ml DCM. The mixture was stirred for 1 h. The organic phase was separated and washed with brine twice. The organic phase was dried and concentrated *in vacuo*. The residue was then treated with 10 ml TFA at 50 °C for 1 h. The mixture was concentrated *in vacuo* and directly subjected to reverse phase preparative HPLC to isolate compound **5** (47 mg, 51% yield). Compound **29** was prepared using the same procedure. Compounds **6** and **30** were prepared using the same procedure without the TFA treatment step.
22) Compound **5**: MS found for $C_{28}H_{22}ClFN_4O_5S_2$ as $[M+H]^+$ 613.2 with pattern of 1 chlorine; HR-MS (ESI) *m*/*z* calcd for $[M+H]^+$ 613.0782, found: 613.0782; ^{1}H-NMR (CD_3OD) δ: 8.59 (1H, s), 8.13 (1H, d, J=2.0 Hz), 7.97 (1H, s), 7.96—7.92 (2H, m), 7.61 (1H, dd, J=8.4, 2.0 Hz), 7.48—7.44 (2H, m), 7.39 (1H, td, J=7.6, 1.6 Hz), 7.17 (1H, dd, J=7.2, 1.2 Hz), 7.10 (1H, dd, J=11.2, 1.6 Hz), 7.01 (dd, J=8.8, 1.6 Hz), 6.92 (1H, s), 3.00 (3H, s), 2.32 (3H, s) ppm. Compound **6**: MS found for $C_{29}H_{23}ClFN_3O_5S_2$ as $[M+H]^+$ 612.2 with pattern of 1 chlorine; HR-MS (ESI) *m*/*z* calcd for $[M+H]^+$ 612.0830, found: 612.0830; ^{1}H-NMR (CD_3OD) δ: 8.71 (1H, s), 8.24 (1H, d, J=2.0 Hz), 8.12 (1H, dd, J=7.6, 1.6 Hz), 8.08 (1H, s), 8.04 (1H, d, J=8.8 Hz), 7.74—7.67 (2H, m), 7.61 (1H, td, J=8.0, 1.6 Hz), 7.36 (1H, dd, J=7.2, 1.6 Hz), 7.25 (1H, dd, J=11.2, 2.0 Hz), 7.13 (1H, dd, J=8.0, 2.4 Hz), 7.04 (1H, s), 3.12 (3H, s), 2.72 (3H, s), 2.43 (3H, s) ppm. Compound **29**: MS found for $C_{28}H_{22}ClFN_4O_5S_2$ as $[M+H]^+$ 613.3 with pattern of 1 chlorine; HR-MS (ESI) *m*/*z* calcd for $[M+H]^+$ 613.0782, found: 613.0782; ^{1}H-NMR (CD_3OD) δ: 8.63 (1H, s), 8.07 (1H, d, J=8.8 Hz), 7.99 (1H, d, J=2.4 Hz), 7.95 (1H, dd, J=8.0, 1.2 Hz), 7.92 (1H, s), 7.59 (1H, dd, J=9.2, 2.4 Hz), 7.48—7.44 (2H, m), 7.39 (1H, td, J=7.6, 1.6 Hz), 7.17 (1H, dd, J=7.2, 1.2 Hz), 7.10 (1H, dd, J=11.6, 2.0 Hz), 7.01 (dd, J=8.4, 1.2 Hz), 6.93 (1H, s), 3.00 (3H, s), 2.32 (3H, s) ppm. Compound **30**: MS found for $C_{29}H_{23}ClFN_3O_5S_2$ as $[M+H]^+$ 612.3 with pattern of 1 chlorine; HR-MS (ESI) *m*/*z* calcd for $[M+H]^+$ 612.0830, found: 612.0842; ^{1}H-NMR (CD_3OD) δ: 8.75 (1H, s), 8.17 (1H, d, J=8.4 Hz), 8.11 (1H, dd, J=8.0, 1.6 Hz), 8.08 (1H, d, J=2.0 Hz), 8.03 (1H, s), 7.72—7.66 (3H, m), 7.60 (1H, td, J=8.0, 1.6 Hz), 7.35 (1H, dd, J=7.6, 1.6 Hz), 7.25 (1H, dd, J=11.6, 2.0 Hz), 7.13 (1H, dd, J=8.0, 2.4 Hz), 7.04 (1H, s), 3.11 (3H, s), 2.71 (3H, s), 2.43 (3H, s) ppm. The ESI-HR-MS experiments were performed by HT Laboratories, Inc., 9823 Pacific Heights Blvd, Suite F, San Diego, CA 92121, U.S.A.
23) Basha A., Lipton M., Weinreb S. M., *Tetrahedron Lett.*, **18**, 4171—4172 (1977).
24) Quan M. L., Liauw A. Y., Ellis C. D., Pruitt J. R., Carini D. J., Bostrom L. L., Huang P. P., Harrison K., Knabb R. M., Thoolen M. J., Wong P. C., Wexler R. R., *J. Med. Chem.*, **42**, 2752—2759 (1999).
25) The fXa IC_{50} values were determined by the method described in: Sinha U., Ku P., Malinowski J., Zhu B. Y., Scarborough R. M., Marlowe C. K., Wong P. W., Lin P. H., Hollenbach S. J., *Eur. J. Pharmacol.*, **395**, 51—59 (2000).
26) The fXa K_i values were determined by the method described in: Betz A., Wong P. W., Sinha U., *Biochemistry*, **38**, 14582—14591 (1999).
27) For description of our human plasma-based thrombin generation assay, see: Sinha U., Lin P. H., Edwards S. T., Wong P. W., Zhu B., Scarborough R. M., Su T., Jia Z. J., Song Y., Zhang P., Clizbe L., Park G., Reed A., Hollenbach S. J., Malinowski J., Arfsten A. E., *Arterioscler. Thromb. Vasc. Biol.*, **23**, 1098—1104 (2003). This is an *in vitro* functional assay run in human plasma to measure the overall anticoagulant activity of a fXa inhibitor. The assay result (2×TG) is expressed by the required concentration of this inhibitor to extend the time for reaching the maximum thrombin generation point by one fold. The targeted 2×TG values for our fXa inhibitors were 1.0 μM or less.