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Bioorganic & Medicinal Chemistry Letters
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Bioorganic & Medicinal Chemistry Letters 14 (2004) 1221–1227

1-(2-Naphthyl)-1*H*-pyrazole-5-carboxylamides as potent factor Xa inhibitors. Part 2: A survey of P4 motifs

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Received 19 June 2003; revised 5 December 2003; accepted 12 December 2003

Abstract—A variety of P4 motifs have been examined to increase the binding affinity and in vitro anticoagulant potency of our biphenyl 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide-based fXa inhibitors. Highly potent 2-naphthyl-P1 fXa inhibitors ($K_i \leq 2$ nM) with improved in vitro anticoagulant activity ($2\times TG \leq 1$ μM) and respectable pharmacokinetic properties have been discovered.

1. Introduction

Human factor Xa (fXa), a trypsin-like serine protease, serves a pivotal role in the blood coagulation cascade. FXa inhibitors have demonstrated potent anticoagulant activity in vitro as well as antithrombotic efficacy in preclinical and clinical models in vivo.[1] The design and discovery of orally active small molecule competitive fXa inhibitors as novel therapies for thromboembolic disorders have been a major focus within the pharmaceutical industry.[2] We recently reported a series of biphenyl 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides as potent and highly selective fXa inhibitors.[3] They were designed based on DuPont's monobenzamidine lead SN429,[5] but using a substituted non-basic 2-naphthyl as the P1 binding element. We discovered that strong fXa binding affinity could be achieved without ionic interaction between the P1 motif and Asp189 in the fXa S1 pocket. We also discovered that the non-basic P1 motif could significantly increase the inhibitors oral bioavailability and enzyme selectivity (>10 μM IC_{50} values for thrombin, trypsin, tissue plasminogen activator (t-PA), activated protein C (aPC), plasmin and kallikrein).

2. Results and discussion

To increase the potency of this class of fXa inhibitors, we decided to examine a variety of known P4 motifs for binding optimization in the S4 pocket of the fXa active site.[4] We selected the 6-chloro-2-naphthyl containing analogues to initiate this SAR investigation because of their relatively higher fXa activity. To predict the in vivo anticoagulant efficacy of our fXa inhibitors, we have established an in vitro thrombin generation (TG) assay in human plasma to measure their in vitro anticoagulant potency.[6–8] Besides fXa binding affinity, the in vivo anticoagulant activity is dependent on the inhibitors hydrophilicity, plasma protein binding, fXa binding kinetics, inhibition of fXa on prothrombinase complex in vivo, and other unknown factors.[2a,7] The results of the TG and blood clotting assays (PT, aPTT, etc.) are much more predictive for a fXa inhibitors in vivo anticoagulant efficacy than its fXa binding potency. As the human plasma TG assay sometimes is more sensitive than the blood clotting assays in our hands, we have adopted the 2×TG results to compare our fXa inhibitors in vitro anticoagulant activity.

The P4 SAR results for the 1-(6-chloro-2-naphthyl)-1*H*-pyrazole-5-carboxylamides are shown in Table 1. Despite more potent than compound **1**, the biphenyl sulfonamide[5,9] analogue **2** and the biphenyl methylsulfone[5,9] analogues (**3**,**4**) exhibit very disappointing 2×TG results (>5 μM). The pyridinylphenyl sulfon-

Keywords: Factor Xa inhibitors.
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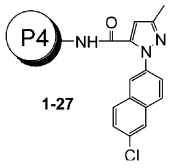
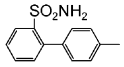
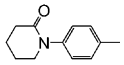
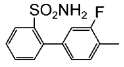
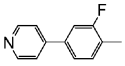
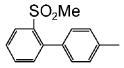
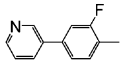
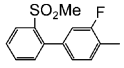
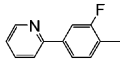
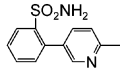
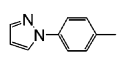
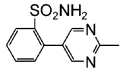
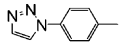
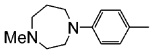
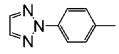
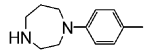
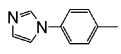
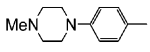
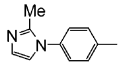
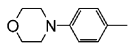
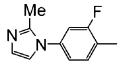
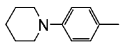
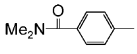
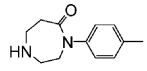
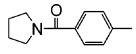
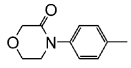
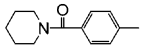
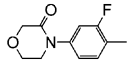
doi:10.1016/j.bmcl.2003.12.053

Table 1. Effects of P4 modification on fXa potency and in vitro anticoagulant activity



Compd	P4	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)	Compd	P4	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)
1		11	—	>5	**15**		3	1.1	>5
2		3	3.4	>5	**16**		40	—	—
3		4	1.4	>5	**17**		92	—	—
4		6	1.8	>5	**18**		94	—	—
5		5	1.9	2.0	**19**		215	—	—
6		7	2.5	2.0	**20**		112	—	—
7		22	—	5.0	**21**		2100	—	—
8		36	—	—	**22**		108	—	—
9		166	—	—	**23**		8	2.9	>5
10		88	—	—	**24**		15	—	—
11		131	—	—	**25**		13	—	>5
12		130	—	—	**26**		6	1.8	>5
13		1	0.3	3.0	**27**		66	—	—
14		1	0.5	5.0					

amide analogue **5** and the pyrimidylphenyl sulfonamide analogue **6** have displayed promising in vitro anticoagulant activity with a 2×TG value of 2.0 μM. Judged by their retention time on reverse-phase HPLC and calculated LogP,[10] inhibitors **5** and **6** should have better hydrophilicity than analogues **1**–**4**. Clearly, hydrophilicity plays a critical role for this class of non-basic fXa inhibitors in vitro anticoagulant activity.

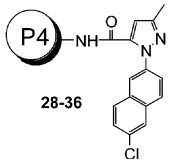
Incorporated a cyclic amine motif[11] as the P4 binding ligand, compounds **7**–**11** exhibit good hydrophilicity, but their fXa activity is weak. Featuring Baeyer's lactam-P4 motifs,[12] analogues **13** (IC_{50} 1 nM; K_i 0.3 nM; 2×TG 3.0 μM), **14** (IC_{50} 1 nM; K_i 0.5 nM; 2×TG 5.0 μM) and **15** (IC_{50} 3 nM; K_i 1.1 nM; 2×TG >5 μM) are highly potent fXa inhibitors. Morpholin-3-one (**13**,**14**) is superior to piperidinone (**15**) and homopiperazinone (**12**) for binding affinity. However, the in vitro anti-

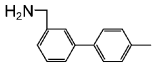
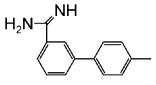
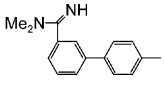
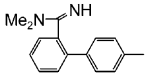
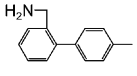
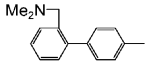
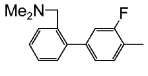
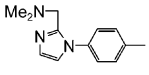
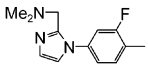
coagulant activity of compounds **13** and **14** are still disappointing.

Analogues **16–24** have examined a variety of nitrogen-containing heteocycles as the distal P4 element.[13,14] The unsubstituted pyridine (**16–18**), pyrazole (**19**), triazole (**20** and **21**) and imidazole (**22**) are not potent. Interestingly, the 2-methylimidazole analogues **23** (IC_{50} 8 nM; K_i 2.9 nM; 2×TG >5 μM) and **24** (IC_{50} 15 nM) are about 10-fold more potent than the unsubstituted imidazole analogue **22** (IC_{50} 108 nM), inviting more SAR exploration on the substituted imidazole moiety. Analogues **25–27** have probed three *N*,*N*-substituted benzamides[2] for P4 binding. Among them, the pyrrolidine-containing analogue **26** (IC_{50} 6 nM; K_i 1.8 nM; 2×TG >5 μM) is the most potent, but it does not possess any in vitro anticoagulant activity.

To enhance hydrophilicity, aminomethyl[14,15] or amidine tethered biaryl-P4 compounds **28–36** were designed. As shown in Table 2, the 3′-substituted biphenyl-P4 compounds (**28–30**) are less active than the corresponding 2′-substituted analogues (**31**,**32**). The novel amidine-tethered biphenyl-P4 analogues (**29–31**) exhibit good hydrophilicity, but relatively weak fXa activity. The *N*,*N*-dimethylation of the 2′-aminomethyl group results in an order of magnitude increase of fXa potency. Moreover, the 2′-(*N*,*N*-dimethylaminomethyl)-biphenyl analogues **33** (IC_{50} 5 nM; K_i 1.8 nM; 2×TG 2.0 μM) and **34** (IC_{50} 2 nM; K_i 1.5 nM; 2×TG 1.7 μM) have also displayed promising in vitro anticoagulant activity. However, with higher hydrophilicity and about equal fXa affinity, the corresponding 2-(*N*,*N*-dimethylaminomethyl)-imidazole analogues (**35**: IC_{50} 8 nM; K_i 2.8 nM; 2×TG >5 μM; **36**: IC_{50} 4 nM; K_i 1.1 nM; 2×TG >5 μM) are weaker in vitro anticoagulants than **33** and **34**. We then conducted a systematic SAR exploration to examine other *N*,*N*-dialkyl and *N*-alkyl substituted aminomethyl groups as the 2′ substituent in the biphenyl and imidazolylbenzene P4 motifs. We have found that the *N*,*N*-dimethylaminomethyl group is optimal for fXa binding affinity and in vitro anticoagulant potency.

Table 2. Effects of P4 modification on fXa potency and in vitro anticoagulant activity



Compd	P4	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)
28		70	—	—
29		75	—	—
30		380	—	—
31		26	—	—
32		39	—	—
33		5	1.8	2.0
34		2	1.5	1.7
35		8	2.8	>5
36		4	1.1	3.0

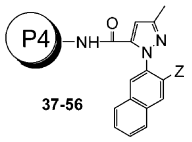
From the above SAR study, we identified the P4 motifs in compounds **2**, **4–6**, **13**, **14** and **33–36** as the optimal binding elements in the fXa S4 pocket for this class of 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide-based fXa inhibitors. As the 3-fluoro-2-naphthyl and 3-methylsulfonyl-2-naphthyl groups are potent fXa P1 ligands and are more hydrophilic than the 6-chloro-2-naphthyl, their corresponding analogues **37–50** were prepared to investigate the resulted fXa binding affinity and in vitro anticoagulant activity.

As shown in Table 3, the 3-fluoro-2-naphthyl analogues **37–40** and **42** are not highly active. As expected, 2′-(*N*,*N*-dimethylaminomethyl)-biphenyl analogue **41** (IC_{50} 2 nM; K_i 2.4 nM; 2×TG 2.2 μM) and morpholin-3-one analogue **43** (IC_{50} 2 nM; K_i 0.5 nM; 2×TG >5 μM) are potent fXa inhibitors, but are still not good in vitro anticoagulants. The more hydrophilic 3-methylsulfonyl-2-naphthyl analogues (**44–45** and **48–50**) have displayed strong fXa activity as well as excellent in vitro anticoagulant potency, judged by our human plasma TG assay. Compounds **45** (IC_{50} 9 nM; K_i 1.7 nM; 2×TG 1.0 μM), **48** (IC_{50} 7 nM; K_i 2.4 nM; 2×TG 0.64 μM), **49** (IC_{50} 8 nM; K_i 3.2 nM; 2×TG 1.7 μM) and **50** (IC_{50} 2 nM; K_i 0.8 nM; 2×TG 0.44 μM) all are potent fXa inhibitors and in vitro anticoagulants. The significant enhancement on their anticoagulant activity could be substantially contributed by the increased hydrophilicity. Interestingly, the 2-(*N*,*N*-dimethylaminomethyl)-imidazole compound **49** is a weaker in vitro anticoagulant than the corresponding 2′-(*N*,*N*-dimethylaminomethyl)-biphenyl compound **45**, following the same trend of compound **36** versus **34**.

Analogues **51–56** were synthesized to survey the lactam-P4 motifs in the 3-methylsulfonyl-2-naphthyl-P1 series of fXa inhibitors. Clearly morpholin-3-one is the optimal P4 binding element. Any modifications all resulted in significant loss in fXa activity.

The enzyme selectivity and rat PK profiles[16] of five leading fXa inhibitors (**34**, **41**, **45**, **48** and **50**) are summarized in Table 4. All of these compounds have excellent fXa selectivity (>1000-fold by IC_{50}) against thrombin, trypsin, t-PA, aPC, plasmin and kallikrein.

Table 3. Effects of P4 modification on fXa potency and in vitro anticoagulant activity



37-56

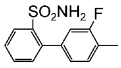
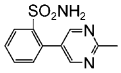
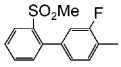
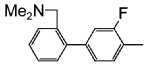
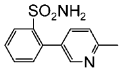
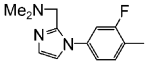
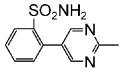
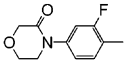
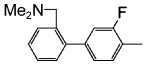
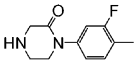
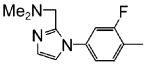
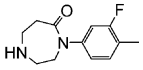
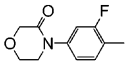
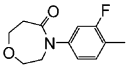
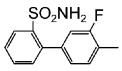
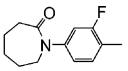
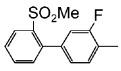
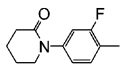
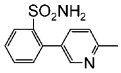
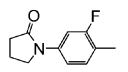
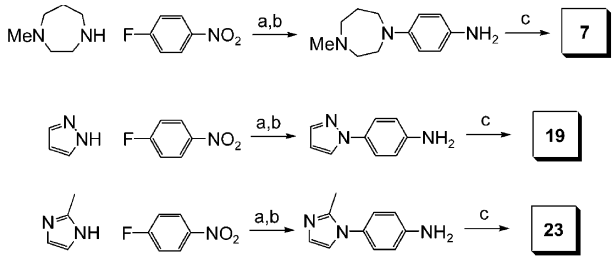
Compd	Z	P4	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)	Compd	Z	P4	fXa IC_{50} (nM)	fXa K_i (nM)	2×TG (μM)
37	F		29	—	—	**47**	SO_2Me		36	—	—
38	F		14	—	—	**48**	SO_2Me		7	2.4	0.64
39	F		81	—	—	**49**	SO_2Me		8	3.2	1.7
40	F		39	—	—	**50**	SO_2Me		2	0.8	0.44
41	F		2	2.4	2.2	**51**	SO_2Me		41	—	—
42	F		13	—	—	**52**	SO_2Me		680	—	—
43	F		2	0.5	>5	**53**	SO_2Me		23	—	—
44	SO_2Me		5	1.1	4.5	**54**	SO_2Me		47	—	—
45	SO_2Me		9	1.7	1.0	**55**	SO_2Me		27	—	—
46	SO_2Me		46	—	—	**56**	SO_2Me		58	—	—

Table 4. The selectivity and PK profiles of five leading fXa inhibitors

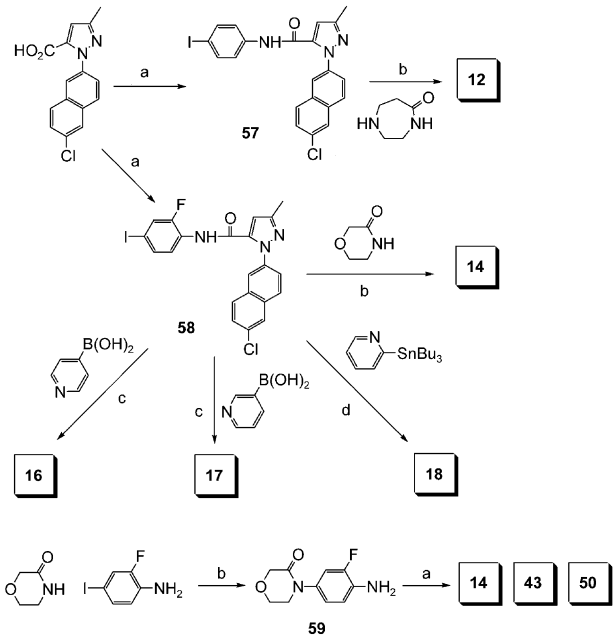
Compd	**34**	**41**	**45**	**48**	**50**
fXa IC_{50} (nM)	2	2	9	7	2
fXa K_i (nM)	1.5	2.4	1.7	2.4	0.8
2×TG (μM)	1.7	2.2	1.0	0.64	0.44
Thrombin IC_{50} (μM)	5.5	>10	>10	>10	>10
Trypsin IC_{50} (μM)	>10	>10	>10	>10	>10
t-PA IC_{50} (μM)	>10	>10	>10	>10	>10
aPC IC_{50} (μM)	>10	>10	>10	>10	>10
Plasmin (μM)	>10	>10	>10	>10	>10
Kallikrein IC_{50} (μM)	9.7	>10	>10	>10	>10
F (%)	35.2	22.8	18.0	18.0	19.3
$t_{1/2}$ (IV) (h)	7.2	2.5	0.7	2.8	0.5
Vd (L/kg)	22.1	11.0	2.6	27.3	0.8
CL (mL/min/kg)	35.7	51.8	41.2	114	16.8

The 2′-(*N*,*N*-dimethylaminomethyl)-biphenyl analogues **34**, **41** and **48** all have good bioavailability and long half-life. Despite respectable bioavailability, the biphenyl methylsulfone-P4 analogue **45** and morpholin-3-one-P4 analogue **50** suffer short half-life, unfortunately.

In summary, we have optimized the fXa binding affinity and in vitro anticoagulant activity of our 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamide fXa inhibitors by exploring a variety of P4 motifs and increasing hydrophilicity. Highly potent fXa inhibitors with respectable oral bioavailability, long half-life and ≤ 1 μM 2×TG results have been discovered. We have also discovered the *N*,*N*-disubstituted benzamidines as another highly potent as well as orally active fXa P4 motif in this class of fXa inhibitors, reported in the following communication. Our further optimization of the 2-naphthyl P1 moiety using two substitution groups will be described in a future publication.



Scheme 1. (a) Cs_2CO_3 (1.5 equiv), DMF or DMSO, 60–100 °C; (b) H_2 (1 atm), Pd/C, MeOH, rt; (c) $ArCO_2H$ (1 equiv), $POCl_3$ (1.5 equiv), pyr, 0 °C.



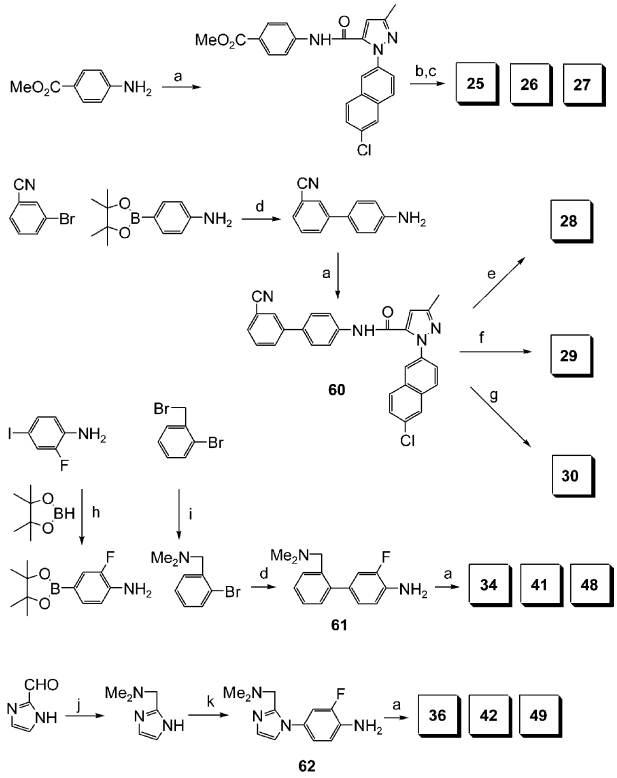
Scheme 2. (a) $ArNH_2$ (1 equiv), $POCl_3$ (1.5 equiv), pyr, 0 °C; (b) lactam (1.5 equiv), CuI (0.2 equiv), $MeNHCH_2CH_2NHMe$ (0.2 equiv), Cs_2CO_3 (2 equiv), dioxane, 120 °C, 16 h; (c) $ArB(OH)_2$ (1.5 equiv), $Pd(Ph_3P)_4$ (0.1 equiv), Cs_2CO_3 (3 equiv), *n*-BuOH/water/PhMe (1:2:4), 80 °C, 2 h; (d) $ArSnBu_3$ (1.2 equiv), $Pd(Ph_3P)_4$ (0.1 equiv), PhMe, reflux, 1 h.

3. Chemistry

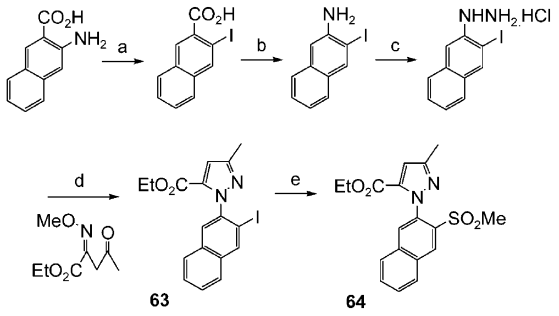
Compounds **2**–**6**, **37**–**40** and **44**–**47** were prepared by coupling of the biaryl amines[9] with the corresponding 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylic acids.[3] The synthesis of compounds **7**, **19** and **23** is shown in Scheme 1. The P4 building blocks were produced from 1-fluoro-4-nitrobenzne and the corresponding amines or heterocycles. Compounds **8**–**11** and **20**–**22** were similarly synthesized.

The preparation of compounds **12**, **14**, **16**, **17** and **18** is illustrated in Scheme 2. Intermediates **57** and **58** were the common synthetic precursors to yield these fXa inhibitors via Buchwald's Cu(I) promoted C–N coupling methodology (**12**,**14**),[17] Suzuki reaction (**16**,**17**) or Stille reaction (**18**). In the preparation of compound **12**, the lactam nitrogen coupled with the phenyl selectively. No amine nitrogen coupling product was observed. Compound **14** could also be prepared from P4 building block **59**, which had been synthesized using a Buchwald reaction. FXa inhibitors **13**, **15**, **43** and **50**–**56** were made using the same chemistry shown in Scheme 2.

Compounds **25**–**27** were synthesized according to Scheme 3. 3′-Cyanobiphenyl analogue **60** served as the



Scheme 3. (a) $ArCO_2H$ (1 equiv), $POCl_3$ (1.5 equiv), pyr, 0 °C; (b) LiOH, MeOH, water, rt; (c) HNR_1R_2 (1.5 equiv), PyBOP (2 equiv), DIEA (4 equiv), DMF, rt; (d) $Pd(Ph_3P)_4$ (0.1 equiv), Cs_2CO_3 (3 equiv), *n*-BuOH/water/PhMe (1:2:4), 80 °C; (e) $NaBH_4$ (8 equiv), $CoCl_2$ (2 equiv), DMF, 0 °C to rt; (f) $LiN(TMS)_2$ (1M in THF, 5 equiv), THF, 0 °C; (g) $LiNMe_2$ (5 wt% in hex, 5 equiv), THF, 0 °C; (h) $Pd(dppf)Cl_2{\cdot}CHCl_3$ (0.05 equiv), Et_3N (2 equiv), dioxane, reflux; (i) Me_2NH (3 equiv), Cs_2CO_3 (1 equiv), MeCN, rt; (j) Me_2NH (1.3 equiv), $NaBH_3CN$ (1.5 equiv), MeOH, HOAc, rt; (k) $ArNH_2$ (1 equiv), CuI (0.2 equiv), 8-hydroxyquinoline (0.2 equiv), K_2CO_3 (1.1 equiv), DMSO, 120 °C.



Scheme 4. (a) (1) $NaNO_2$ (1.05 equiv), concd HCl, 0 °C, 30 m; (2) KI (1.5 equiv, solution in water), 0 °C–rt, overnight; (b) (1) DPPA (1.5 equiv), Et_3N (1.5 equiv), DMF, rt, 3 h; (2) water, reflux, 1 h; (c) (1) $NaNO_2$ (1.05 equiv), concd HCl, 0 °C, 30 m; (2) $SnCl_2{\cdot}2H_2O$ (2.5 equiv), concd HCl, 0 °C, 1.5 h; (d) HOAc, dioxane, reflux, 2.5 h; (e) $MeSO_2Na$ (3 equiv), $MeNHCH_2CH_2NHMe$ (0.1 equiv), $(CuOTf)_2{\cdot}PhH$ (0.1 equiv), DMSO, 115 °C, overnight.

common precursor for compounds **28** and **29**. Reduction of the nitrile yielded the aminomethyl analogue **28**. Treatment of the nitrile using commercial lithium bis(trimethylsilyl)amide and lithium dimethylamide afforded the amidine analogues **29** and **30**, respectively. Compounds **31** and **32** were similarly prepared. The biphenylamine building block **61** for targets **34**, **41** and **48** was produced through Suzuki coupling,[18] while the imidazolylaniline building block **62** for fXa inhibitors **36**, **42** and **49** was prepared using Buchwald-type Cu(I)-promoted C–N cross coupling. Analogues **33** and **35** were prepared using the same chemistry approach for compounds **34** and **36**.

The synthesis of building block ethyl 1-(3-aminosulfonyl-2-naphthyl)-3-methyl-1*H*-pyrazole-5-carboxylate (**64**) has been improved from what we reported previously.[3] As shown in Scheme 4, commercial 3-amino-2-naphthoic acid was first converted to 3-iodo-2-naphthoic acid. The one-pot diphenylphosphoryl azide (DPPA) reaction[19] produced 3-iodo-2-naphthylamine, which was then used to build pyrazole **63**. Employing Wang's Cu(I)-promoted C–S cross coupling methodology,[20] compound **64** was smoothly produced in high yield from the iodonaphthyl precursor **63**.

Acknowledgements

We would like to thank Jaya Kothule, Sherin Halfon, Paul Wong, Brian Huang, Bridget May and Shannon Poole for performing the biological assays.

References and notes

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4. Part of the work described in this communication has been previously presented at the 223rd ACS National Meeting in April 2002 in Orlando, Florida (MEDI-27 and MEDI-126) and at the 226th ACS National Meeting in September 2003 in New York, New York (MEDI-32).
5. (a) Pinto, D. J.; Orwat, M. J.; Wang, S.; Amparo, E.; Pruitt, J. R.; Rossi, K. A.; Alexander, R. S.; Fevig, J. M.; Cacciola, J.; Lam, P. Y. S.; Knabb, R. M.; Wong, P. C.; Wexler, R. R. *Abstracts of Papers,* 217th ACS National Meeting, Anaheim, CA, 1999, MEDI-006. (b) Pinto, D. J.; Orwat, M. J.; Wang, S.; Fevig, J. M.; Quan, M. L.; Amparo, E. C.; Cacciola, J.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. S.; Luettgen, J. M.; Liang, L.; Aungst, B. J.; Wright, M. R.; Knabb, R. M.; Wong, P. C.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2001**, *44*, 566.
6. Thrombin generation (TG) assay in human plasma: 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. The 2×TG results for DuPont's SN429 and DPC423[5] are 0.16 μM and 1.2 μM, respectively.
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