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Design, structure–activity relationship, and pharmacokinetic profile of pyrazole-based indoline factor Xa inhibitors

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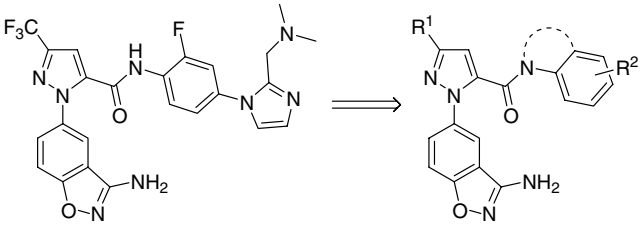
Abstract—A new series of pyrazole-based factor Xa inhibitors have been identified as part of our ongoing efforts to optimize previously reported clinical candidate razaxaban. Concern over the possible formation of primary aniline metabolites via amide hydrolysis led to the replacement of the primary amide linker between the pyrazole and phenyl moieties with secondary amides. This was accomplished by replacing the aniline with a variety of heterobicycles, of which indolines were the most potent. The indoline series demonstrated subnanomolar factor Xa binding K_is, modest to high selectivity versus other serine proteases, and good in vitro clotting activity. A small number of indoline fXa inhibitors were profiled in a dog pharmacokinetic model, one of which demonstrated pharmacokinetic parameters similar to that of clinical candidate razaxaban.

The trypsin-like serine protease fXa is an attractive target for the development of new anticoagulant drugs.[1] As a key enzyme in the coagulation cascade, fXa combines with fVa and calcium to form the prothrombinase complex responsible for the conversion of prothrombin to thrombin. Thrombin plays a critical role in clot formation by catalyzing the conversion of fibrinogen to fibrin and by activating platelets.[2] Due to the nature of the coagulation cascade, small quantities of fXa can produce large amounts of thrombin. Therefore, fXa inhibition is expected to be more efficient than direct inhibition of thrombin, and in vivo studies support a lower risk of bleeding with fXa inhibitors.[3,4]

We have described several fXa clinical candidates with excellent potency, selectivity, and oral efficacy in vivo.[5,6] Herein we describe a new series of factor Xa inhibitors developed as part of our overall optimization strategy. This series evolved from the P1-amino-benzisoxazole pyrazole-based scaffold of the previously reported clinical candidate razaxaban through modification of the carboxamido linker that connects the pyrazole and proximal phenyl moieties. While the biarylaniline P4 moiety of razaxaban tested negative in the Ames assay and was not observed in vivo,[6] we considered it advantageous to eliminate possible formation of a primary aniline altogether. In practice, the carboxamido linker was converted to a heterobicyclic moiety. Hydrolysis, if it should occur, would then yield a secondary aniline, which is less likely to be mutagenic. It was hoped that this modification would provide anticoagulants with both potency and selectivity for factor Xa and acceptable pharmacokinetic profiles for in vivo testing.



razaxaban (BMS-561389, DPC906)
FXa Ki = 0.19 nM (PT IC_{2x} = 1.3 μM)
Thrombin K_i = 540 nM
Trypsin K_i >10,000 nM

Initial leads for the heterobicyclic series are disclosed in Table 1. The most potent heterobicycles were indolines **2** and **3**, which were 16- and 30-fold less active, respec-

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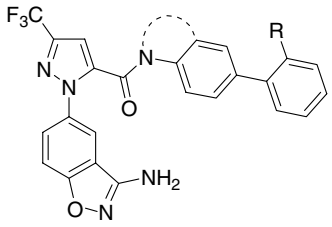
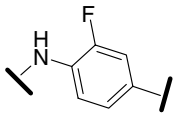
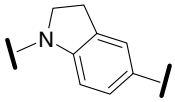
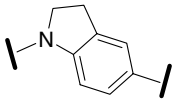
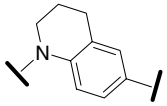
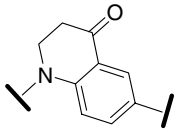
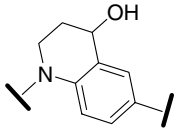
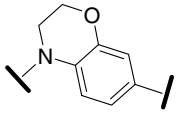
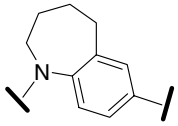
Table 1. Factor Xa, thrombin, and trypsin binding affinities for heterobicyclic scaffolds[a]



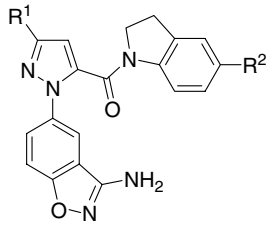
Compound	Scaffold	R	fXa K_i, nM	Thrombin K_i, nM	Trypsin K_i, nM	PT IC_{2x} μM
1		SO_2CH_3	0.09	6300	>5200	—
2		SO_2CH_3	1.5	>21,000	>2500	26
3		SO_2NH_2	2.7	>21,000	>2500	28
4		SO_2CH_3	2000	>6300	>4200	—
5		SO_2CH_3	500	>21,000	>4200	—
6[b]		SO_2CH_3	1400	>6300	>4200	—
7		SO_2CH_3	71	>21,000	—	—
8		SO_2NH_2	3400	>6300	>4200	—

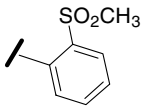
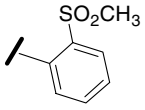
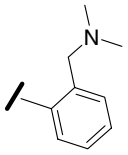
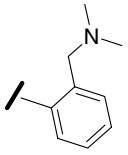
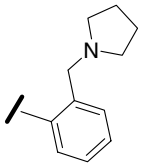
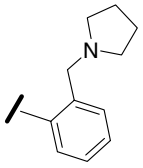
[a] K_is were obtained from purified human enzymes. K_is and PT values were measured according to Ref. 5a–c.
[b] Racemic.

tively, than **1**, the P4-phenylmethylsulfone analog of razaxaban. Both compounds also had relatively weak in vitro clotting activity in the prothrombin time (PT) assay. Modest to high selectivity for factor Xa over thrombin and trypsin was observed for all compounds. Increases in ring size (**4**, **8**), oxidation (**5**, **6**), or incorporation of a heteroatom (**7**) decreased fXa binding affinity by 50-fold or more compared to **2** and **3**.

To improve fXa binding affinity and in vitro clotting activity of the indoline series, the structure–activity relationships of the pyrazole substitutent (Table 2) and the indoline P4 group (Tables 2–4) were explored. Replacement of the 3-trifluoromethyl group of the pyrazole functionality with a C-linked primary amide increased binding affinity for fXa (Table 2). Compounds that also contained P4 benzylic amines were very potent in the PT assay, likely due to decreased protein binding as seen previously with P4 alkyl amines and 3-amidopyrazole analogs by our group.[5c,7,8] For example, replacing the 3-trifluoro-methylpyrazole of **2** with a 3-amidopyrazole (**9**) afforded a modest increase in fXa binding but decreased in vitro clotting activity. Making the same change to *N*,*N*-dimethylbenzylamine **10** to give **11** resulted in a 19-fold increase in binding affinity. Compared to sulfone **9**, benzylamine **11** was approximately 14-fold

Table 2. Amide and trifluoromethyl pyrazole substitutents[a]



Compound	R^1	R^2	fXa K_i, nM	Thrombin K_i, nM	Trypsin K_i, nM	PT IC_{2x} μM
2	CF_3		1.5	>21,000	>2500	28
9	$CONH_2$		0.82	>20,000	—	41
10	CF_3		19	19,200	—	—
11	$CONH_2$		1.0	—	>20,000	3.0
12	CF_3		4.9	15,000	>40,000	—
13	$CONH_2$		0.63	—	—	2.1

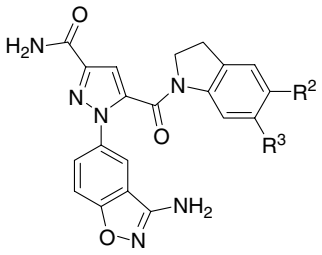
[a] K_is were obtained from purified human enzymes. K_is and PT values were measured according to Ref. 5a–c.

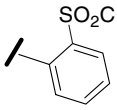
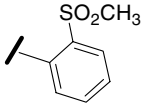
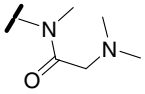
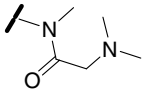
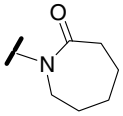
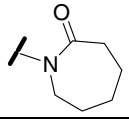
more efficacious in the clotting assay. Similarly, pyrrolidine **13** was 8-fold more potent than **12** and showed activity in the PT assay comparable to that of **11**.

Several indolines with P4 substituents at either the R^2 or R^3 position are shown in Table 3. Comparing the fXa binding affinities of **9** and **14** shows a marked preference (>1700-fold) for the P4 group to be in the R^2 position. While there is also a decrease in binding affinity in going from glycinamide **15** to **16**, the effect is significantly less pronounced, possibly because the P4 moiety of **16** has a greater degree of flexibility than that of **14**. Comparing the regioisomers of the moderately rigid ε-lactam P4-analogs (**17** and **18**) also indicates a preference for R^2 substitution by approximately 70-fold. This trend was found to hold for every pair of R^2 and R^3 isomers prepared and is thought to be due to a preferred orientation of the P4 group when bound in the aryl S4 binding pocket of the fXa enzyme.

The P4 substitutent of the aminobenzisoxazole-3-amido-pyrazole indoline scaffold was diversified to further improve the efficacy of our anticoagulants (Table 4). These substituents were selected because they have historically provided improved in vitro potency, better protein binding, and favorable pharmacokinetic properties.[5–8] Replacement of the dimethylbenzylamine of **11** with the dimethylamino-methyl imidazole of razaxaban decreased fXa binding affinity by approximately twofold (compound **19**). This decrease was more pronounced upon conversion of the dimethylamine to either the *N*-methylacetamide (**20**) or *N*-methylsulfonamide (**21**).

Table 3. Effect of indoline substitution on fXa binding affinity[a]



Compound	R^2	R^3	fXa K_i, nM
9		H	0.82
14	H		1400
15		H	6.8
16	H		350
17		H	15
18	H		1100

[a] K_is were obtained from purified human enzymes and were measured according to Ref. 5a–c.

Of the P4 N-linked moieties examined, lactam **17** (Table 3) was the least active, possibly due to the ring size exceeding the capacity of the S4 binding pocket. However, incorporation of the lactam P4 moiety found in apixaban (BMS-562247) afforded lactam **22** with binding affinity for fXa on par with that of imidazole **19** and a strong response in the PT assay. The corresponding aromatic analog of **22**, pyridone **23**, gratifyingly afforded an increase in fXa binding by approximately 10-fold compared to **22** and threefold compared to **13**. Pyridone **23** was also very active in the clotting assay, proving to be the most potent indoline prepared to date with activity comparable to that of razaxaban in vitro.

Poor Caco-2 permeability was observed for the most active compounds of Table 4 (**11**, **13**, **22**, and **23**). This raised the question of whether bioavailability would be problematic upon oral dosing. To determine the pharmacokinetic parameters of compounds from the indoline series and to assess how well the in vivo permeability correlated with that observed in vitro, four compounds were profiled in dog pharmacokinetic studies (Table 5). Pyrrolidines **12** and **13** had high rates of clearance that were partially offset by high to moderate volumes of distribution to afford modest intravenous half-lives ($t_{1/2(iv)}$ = 2.2 and 2.3 h, respectively). Regardless, neither **12** or **13** was detectable in plasma when dosed orally, most likely because of both poor absorption and significant first-pass metabolism. In contrast, lactam **22** was marginally bioavailable, which is partially attributable to a significantly lower rate of clearance (0.22 L/h/kg) than that of either **12** or **13**. Coupled with a low volume of distribution, tetrahydropyridone **22** was found to have a half-life of 1.6 h. The earlier lead, sulfonamide **3**, which was equipotent with **22** in terms of fXa binding affinity, exhibited a pharmacokinetic profile similar to that of razaxaban. Unfortunately, the sulfonamide had low activity in the clotting assay, suggesting a low free fraction in plasma, and was not further evaluated in in vivo models.

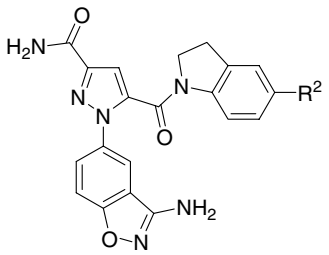
The general synthetic strategy for preparing compounds from the indoline series is shown in Scheme 1. Compounds containing 3-trifluoromethylpyrazoles were prepared from acid chloride **24**[5c] by treatment with the sodium salt of the appropriate heterobicycle. Compounds generated from 3-amidopyrazole **25** were similarly prepared upon treatment of indole and acid with 1,3-diisopropylcarbodiimide in 4:1 pyridine/*N*,*N*-dimethylformamide for 24 h. Conversion to the P1-aminobenzisoxazole was carried out using acetohydroxamic acid and potassium carbonate in DMF.[5c] At this stage, compounds containing P4-thioanisole moieties were oxidized to the sulfone using *m*-chloroperoxybenzoic acid in dichloromethane. Similarly, compounds containing P4-*tert*-butyl-sulfonamides were deprotected using trifluoroacetic acid in dichloromethane.

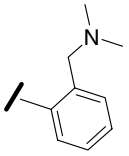
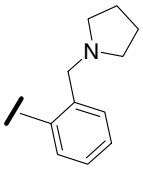
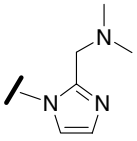
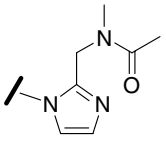
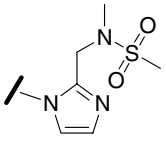
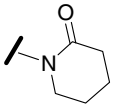
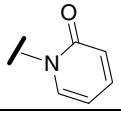
Amidopyrazole **25** was prepared as shown in Scheme 2 starting with a lithium hexamethyldisilazide-mediated addition of commercially available ethanedioic acid bis(1,1-dimethylethyl) ester (**26**) to 2-acetylfuran (**27**). The resulting lithium salt was then reacted with hydrazine **28**[5c] in situ to afford furan **29**. Ester hydrolysis under acidic conditions, conversion to the acid chloride, and treatment with 0.5 M ammonia in dioxane afforded the corresponding 3-amidopyrazole that was then oxidized with $KMnO_4$ to provide acid **25**.

The heterobicycles were generated according to Schemes 3–7.[5c,b,c,6] Representative chemistry for preparing the indoline moieties of compounds **2**–**3**, **9**–**14**, **19**–**21**, and **23** is shown in Scheme 3. Reduction and Boc-protection of commercially available 5-iodoindole (6-iodoindole in the case of **14**) afforded indoline **31**, which could then be reacted with boronic acid **32a**–**c** under Suzuki conditions to yield biaryls **33a**–**c**. Reductive amination of aldehyde **33c** with either pyrrolidine or dimethylamine afforded benzyl amines **33d** and **33e**, respectively. In an analogous manner, iodoindoline **31** was reacted under Ullman conditions with previously reported imidazoles **35a**–**b**[5c] to afford indolines **36a**–**b**. Treatment of **36b** with acetyl chloride or methanesulfonyl chloride under basic conditions resulted in amides **36c**–**d**. The indoline moiety of **23** was prepared by substituting 2-hydroxypyridine for imidazole **35**. Removal of the Boc-carbamate for all compounds of Scheme 3 was accomplished using trifluoroacetic acid followed by conversion to the free base upon workup using sodium bicarbonate.

The indoline moieties of compounds **15**–**18** and **22** were prepared according to the chemistry in Scheme 4 start-

Table 4. Data for indoline P4 analogs[a]



Compound	R^2	fXa K_i, nM	PT IC_{2x} μM	Caco-2 Papp × 10^{-6} cm/s
11		1.0	3.0	0.3 ± 0.1
13		0.63	2.1	0.7 ± 0.1
19		2.20	—	—
20		4.80	—	—
21		6.9	—	—
22		2.4	3.30	0.1
23		0.20	1.9	0.1

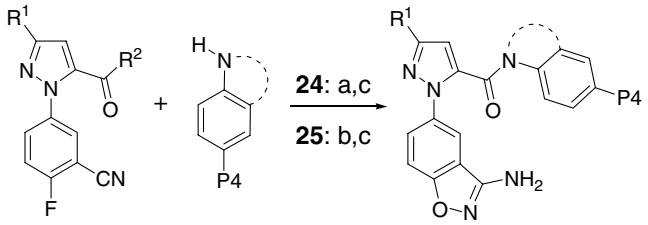
[a] K_is were obtained from purified human enzymes. K_is, PT, and Caco-2 values were measured according to Ref. 5a–c.

Table 5. Indoline pharmacokinetic profiles[a]

Compound	Caco-2 Papp × 10^{-6} cm/s	Cl L/h/kg	Vdss L/Kg	$t_{1/2}$ (po)	F% (po)
Razaxaban	5.56	1.1	3.4	5.3	84
3	6.8 ± 2.9	0.63	2.0	4.0	66
12	—	7.4	20	nd	bql
13	0.7 ± 0.1	3.57	6.2	nd	bql
22	0.1	0.22	0.2	1.6	6

[a] Compounds were dosed in an *N*-in-1 format at 0.5 mg/kg iv and 0.2 mg/kg po (n = 1).[5a–c]

ing from commercially available 5- or 6-nitroindole (**38**). Protection with di-*tert*-butyl dicarbonate and subsequent hydrogenation afforded aniline **39**. The aniline could then be converted to the lactam (**41a**–**b**) upon treatment with either **40a** or **40b** and two equivalents of potassium *t*-butoxide. Deprotection using 4 M hydrogen chloride in dioxane followed by basification upon workup gave indolines **42a**–**b**. Conversion of aniline **39**

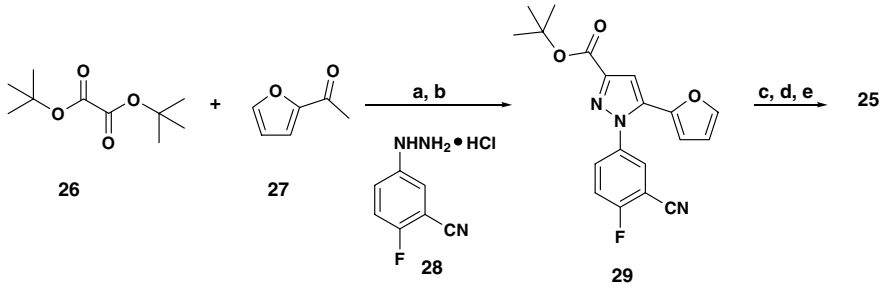


Scheme 1. Reagents and conditions: (a) NaH, CH_2Cl_2, 60–70%; (b) DIC, py/DMF, 20–80%; (c) Ac-NHOH, K_2CO_3, DMF, 50 °C, 20–50%.

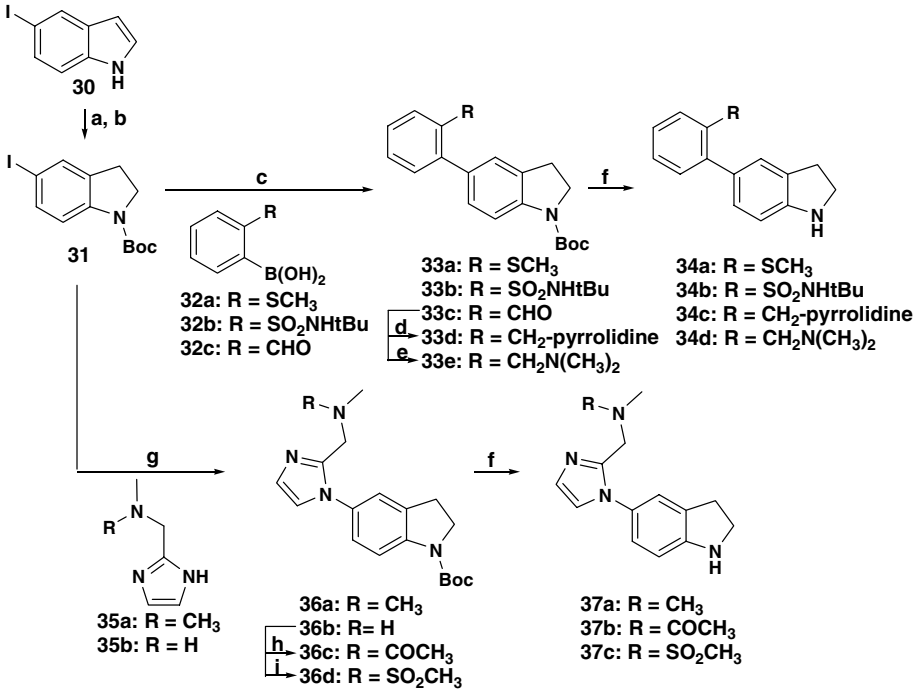
to glycinamide **43** was carried out via a pyBOP-mediated coupling with *N*-methylglycine and subsequent methylation. Deprotection and basification produced indoline **44**.

The heterobicycles of compounds **4–6** were prepared from known 6-bromo-2,3-dihydro-4(1H)-quinolinone (**45**).[9] Suzuki coupling with 2-thioanisole boronic acid afforded ketone **46a**. To prepare the corresponding racemic alcohol, **46a** was treated with sodium borohydride in tetrahydrofuran after the coupling described in Scheme 1 but before aminobenzisoxazole formation. Alternatively, **45** was reduced with an aluminum trichloride/lithium aluminum hydride melt prior to coupling with 2-thioanisole boronic acid to generate **46b.**

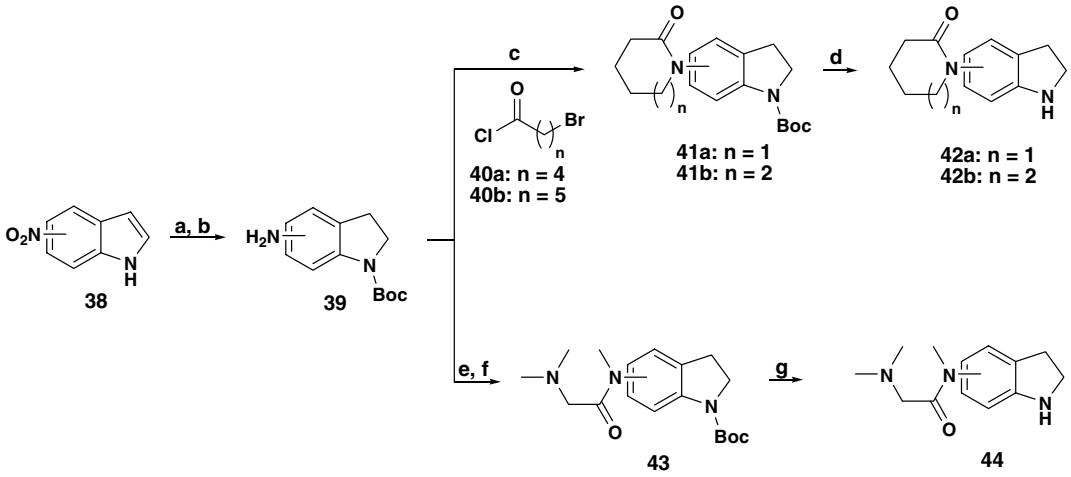
The heterobicycle of **7** was prepared from commercially available aniline **47**, which was converted to benzoxazinone **48** upon acylation with acetoxyacetylchloride and cyclization under basic conditions. Suzuki coupling with 2-thioanisoleboronic acid followed by reduction with lithium aluminum hydride afforded amine **49**.



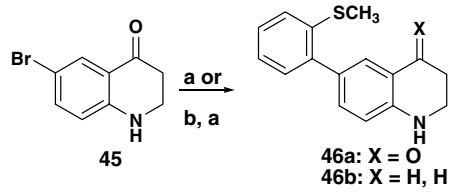
Scheme 2. Reagents and conditions: (a) LiHMDS, Et_2O, −78 to 25 °C, 83%; (b) **28**, HOAc, 50 °C, 93%; (c) TFA, CH_2Cl_2, 95%; (d) $(COCl)_2$, DMF, CH_2Cl_2 then NH_3, dioxane/CH_2Cl_2, 69%; (e) $KMnO_4$, *t*-BuOH, 5% NaH_2PO_4, H_2O, 60 °C, 71%.



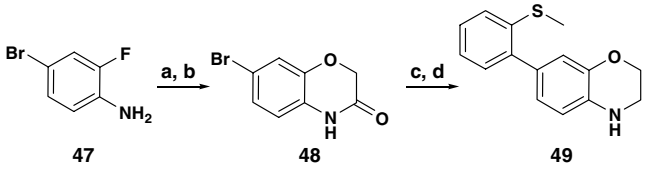
Scheme 3. Reagents and conditions: (a) HOAc, $NaBH_3CN$; (b) Boc_2O, $NaHCO_3$, H_2O/THF, 71% (two steps); (c) **32**, $Pd_2(dba)_3$, PPh_3, Na_2CO_3, tol, 110 °C, 65–80%; (d) pyrrolidine, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 63%; (e) H_2NCH_3, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 90%; (f) TFA, CH_2Cl_2 then $NaHCO_3$, 60–80%; (g) **35**, CuI, K_2CO_3, DMSO, 130 °C, 33–60%; (h) AcCl, py, CH_2Cl_2 99%; (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 99%.



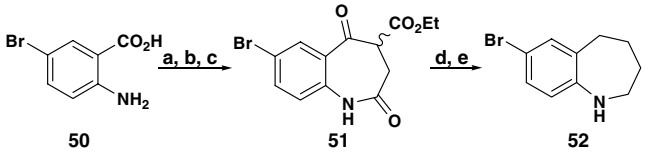
Scheme 4. Reagents and conditions: (a) Boc_2O, DMAP, THF, 60%; (b) Pd/C, H_2, MeOH, 90%; (c) **40**, *t*-BuOK, THF, 52–67%; (d) 4 M HCl/dioxane then $NaHCO_3$, 46–88%; (e) *N*-methylglycine pyBOP, Et_3N, DMF, 91%; (f) CH_3I, DMF, 55%; (g) TFA, CH_2Cl_2, then $NaHCO_3$, 85%.



Scheme 5. Reagents and conditions: (a) 2-Thioanisole boronic acid, $Pd(PPh_3)_4$, 2 M $NaHCO_3$, tol, 80 °C, 65%; (b) $AlCl_3$, LAH, THF, 60 °C, 30%.



Scheme 6. Reagents and conditions: (a) $ClCOCH_2OAc$, K_2CO_3, $CHCl_3$, 75%; (b) NaH, DMF, 55%; (c) 2-thioanisoleboronic acid, $Pd(PPh_3)_4$, 2 M Na_2NaCO_3, 80 °C, 72%; (d) LAH, $AlCl_3$, THF, 71%.



Scheme 7. Reagents and conditions: (a) H_2SO_4, EtOH, reflux, 13%; (b) $ClCO(CH_2)_2CO_2Et$, CH_2Cl_2, 60%; (c) KH, DMF, tol, 80 °C, 62%; (d) DMSO, H_2O, 150 °C, 70%; (e) $AlCl_3$, LAH, THF, 60 °C, 33%.

The heterobicycle of **8** was generated from commercially available aniline **50**. Esterification and acylation followed by base-induced ring closure gave benzazepine-2,5-dione **51**. Thermal decarboxylation and deoxygenation employing an aluminum trichloride/lithium aluminum hydride melt provided amine **52**. This amine was coupled as described in Scheme 1 with acid chloride **24** prior to a Suzuki coupling with boronic acid **32b** as described in Scheme 3.

In conclusion, we have prepared a series of potent and selective indoline fXa inhibitors designed to prevent the release of a primary aniline upon hydrolysis in vivo. The more potent compounds of this series demonstrate subnanomolar binding affinity and in vitro clotting activity under 5 μM. Conversion from a 3-trifluoromethyl to a 3-amidopyrazole improved binding affinity by approximately 2- to 19-fold, while substitution at the 5-position of the indoline was preferred over the 6-position. Incorporation of an *N*-substituted pyridone at the P4 position gave an indoline fXa inhibitor with potency comparable to that of razaxaban. Subsequent evaluation of a small number of indolines in a dog pharmacokinetic model indicated that phenylsulfonamide **3** (fXa $K_i = 2.7$ nM) had a pharmacokinetic profile similar to that of razaxaban. However, sulfonamide **3** also demonstrated reduced in vitro clotting activity. Permeability and oral bioavailability remain a significant issue for compounds with improved potency in the clotting assay.

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