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Pyridine and pyridinone-based factor XIa inhibitors

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ABSTRACT

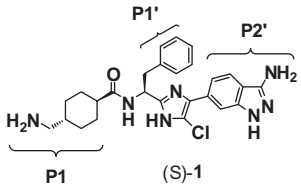
The structure–activity relationships (SAR) of six-membered ring replacements for the imidazole ring scaffold is described. This work led to the discovery of the potent and selective pyridine (*S*)-**23** and pyridinone (±)-**24** factor XIa inhibitors. SAR and X-ray crystal structure data highlight the key differences between imidazole and six-membered ring analogs.

Factor XIa (FXIa), a trypsin-like serine protease, functions early in the intrinsic pathway of the blood coagulation cascade. It has been demonstrated to play a key role in the amplification of thrombin production which leads to the growth and maturation of thrombi.[1] Based on the preclinical and genetic evidence, FXIa is a potential target for anticoagulant therapy. FXI deficient mice are protected in venous and arterial thrombosis models. Moreover, they do not show an increase in bleeding relative to wild-type mice.[2] Therapeutic inhibition of FXIa by neutralizing antibodies, antisense oligonucleotides, or small molecule inhibitors was found to be effective in a number of animal thrombosis models with minimal effects on bleeding time.[3–5,11]

Individuals deficient in FXI have a condition known as hemophilia C. In contrast to the severe bleeding observed with hemophilia A and B, individuals with hemophilia C do not experience spontaneous bleeding but rather injury-related bleeding which is generally characterized as mild to moderate.[6] Moreover, individuals with a severe FXI deficiency have shown a reduced incidence of ischemic stroke, however they were not found to be protected against acute myocardial infarction.[7] Elevated levels of FXI are a risk factor for acute myocardial infarction and deep vein thrombosis.[8] Selective FXIa inhibitors may offer an improved safety profile by preventing thrombus formation without causing a significant increase in bleeding.[9]

Several FXIa inhibitors, such as α-ketothiazole peptidomimetics, boronic acid peptidomimetics, clavatadine A, and macrocyclic indole derivatives, as well as, allosteric inhibitors have been reported.[5c,10] We have previously disclosed potent and reversible FXIa inhibitors based on tetrahydroquinoline and indole chemotypes.[11] Recently, work from our laboratories led to the discovery of imidazole (*S*)-**1**, a picomolar FXIa inhibitor having potent in vivo antithrombotic efficacy in a rabbit AV-Shunt thrombosis model (Fig. 1).[12] As part of our research program to explore structurally diverse FXIa inhibitors, we searched for replacements for the imidazole ring. In this communication, we describe the SAR of six-membered ring replacements for the imidazole ring resulting in the discovery of pyridine and pyridinone FXIa inhibitors.

Since one of the annular nitrogens of the imidazole ring resembles the nitrogen of a pyridine ring,[13] our initial ring replacements



(S)-1
FXIa Ki = 0.31 nM
aPTT EC_{2x} = 1.0 μM

Figure 1. Imidazole (*S*)-**1**.

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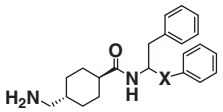
Table 1
Imidazole ring replacements



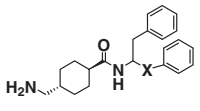
Entry	X	FXIa K_i[a] (nM)
(*S*)-**2**		120
(±)-**3**		30,207
(±)-**4**		377
(±)-**5**		330
(±)-**6**		433
(±)-**7**		1,690
(±)-**8**		1,063
(±)-**9**		2,530
(*S*)-**10**		11,423
(±)-**11**		331
(±)-**12**		936

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11b.

focused on the pyridine ring system (Table 1). In order to quickly survey a variety of six-membered rings, racemic derivatives containing the simplified phenyl P2 prime group (replacing the amino indazole moiety in (*S*)-**1** with a phenyl) were prepared. The corresponding homochiral imidazole (*S*)-**2** is included for comparison. Though pyridine **3** was a very weak inhibitor of FXIa, we were pleased to discover racemic **4** had a FXIa K_i of 377 nM which was comparable to homochiral imidazole **2** (FXIa K_i = 120 nM). The pyridine nitrogen was important as oxidation to the corresponding N-oxide **7** led to a 4-fold decrease in activity. A similar trend was observed with the regioisomeric pyridine analogs. Pyridines **5** and **6** were equipotent to **4**, where as their corresponding N-oxides **8** and **9** showed a loss in activity. Interestingly, with pyrimidine (*S*)-**10**, containing both the nitrogens in **3** and **4**, a significant loss in activity was observed. Based on **3** and **10**, a nitrogen lone pair at the position between the substituents was deleterious for FXIa activity. Regioisomeric pyrimidine **11** was equipotent with the pyridine regioisomers **4**, **5**, and **6**. In order to elucidate the role of the nitrogen heteroatom on FXIa activity, the phenyl analog **12** was prepared. The phenyl ring showed a 2- to 3-fold loss in FXIa activity (FXIa K_i = 936 nM). The pyridine (**4**, **5**, and **6**) and pyrimidine (**11**) analogs proved to be good replacements for the imidazole ring. Since the pyridines and pyrimidine exhibited similar FXIa activity, the pyridine ring **4** was chosen for further SAR exploration with the goal of improving potency.

Our earlier work in the imidazole series revealed that halogenation (F or Cl) at the C5 position of the imidazole provided a 7.5- to 10-fold increase in FXIa activity.[12] It was postulated that the increase in activity was due to a lipophilic interaction with the aliphatic portion of the Lys 192 side chain of the FXIa active site. As a result, we investigated substitution at both the C5 (Table 2) and C6 positions (Table 3) on the pyridine ring. Imidazole (*S*)-**2** and chloro-imidazole (*S*)-**13** are included for comparison. Unfortunately,

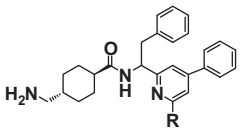
Table 2
C5-substitution on imidazole and pyridine rings

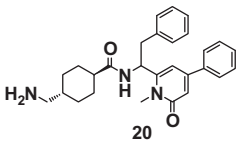


Entry	X	FXIa[a] K_i (nM)
(*S*)-**2**		120
(*S*)-**13**		12
(±)-**4**		377
(±)-**14**		320

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11b.

Table 3
C6-substitution on pyridine ring





Entry	R	FXIa[a] K_i (nM)
(±)-**4**	H	377
(±)-**15**	Cl	206
(±)-**16**	NH_2	227
(±)-**17**	NHMe	860
(±)-**18**	OH	113
(±)-**19**	OMe	949
(±)-**20**	*N*-Methyl pyridinone	479

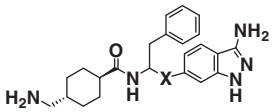
[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11b.

compound **14**, with fluorine incorporation at the C5 position of the pyridine, showed similar affinity as the unsubstituted pyridine **4**.

Next, we explored substitution at the C6-position on the pyridine ring (Table 3). The 6-chloro analog **15** showed a modest improvement in FXIa affinity, but not as much of an improvement as anticipated based on the chloro-imidazole (*S*)-**13**. The 2-amino pyridine **16** showed a similar modest improvement in FXIa activity. Methylation of the amino group (**17**) led to a 3.7-fold decrease in activity. Moving to the 2-hydroxy pyridine **18**, which is tautomeric with the pyridinone, provided a 3-fold increase in FXIa affinity and was equipotent to imidazole (*S*)-**2**. Methylation at oxygen (**19**) or nitrogen (**20**) decreased FXIa affinity.

A variety of six-membered rings proved to be good replacements for the imidazole and they are listed in order of decreasing FXIa activity: imidazole (*S*)-**2** ≃ pyridinone **18** < pyridine regioisomers (**4**, **5**, and **6**) ≃ pyrimidine **11** < phenyl **12**. We have shown in the imidazole series that a 40-fold increase in FXIa affinity could be achieved by replacing the P2 prime phenyl with the amino indazole moiety.[12] In order to improve the affinity with the six-membered ring scaffolds, we combined the amino indazole P2 prime moiety with the phenyl, pyridine, and pyridinone rings (Table 4). The imidazole (*S*)-**21** is included for comparison. Replacing the P2 prime phenyl in **12**, **4**, and **18** with the amino indazole moiety led to a >20-fold improvement in FXIa activity ((±)-**22** FXIa K_i = 42 nM; (±)-**23** FXIa K_i = 13 nM; (±)-**24** FXIa K_i = 3.7 nM). The chiral, nonracemic derivatives of **22** and **23** were prepared and FXIa activity was found to reside in one enantiomer (compare (*S*)-**22**

Table 4
Amino indazole P2 prime with phenyl, pyridine, and pyridinone rings



Entry	X	FXIa K_i[a] (nM)	aPTT[b] EC_{2x} (μM)
(*S*)-**21**		3.2	3.0
(±)-**22**		42	>40
(*S*)-**22**		21	37
(*R*)-**22**		6160	NT[c]
(±)-**23**		13	6.0
(*S*)-**23**		8.4	4.5
(*R*)-**23**		1067	NT[c]
(±)-**24**		3.7	2.5

[a] K_i values were obtained from purified human enzyme and were averaged from multiple determinations ($n = 2$), as described in Ref. 11b.
[b] aPTT (activated partial thromboplastin time) in vitro clotting assay was performed in human plasma as described in Ref. 11b.
[c] NT = not tested.

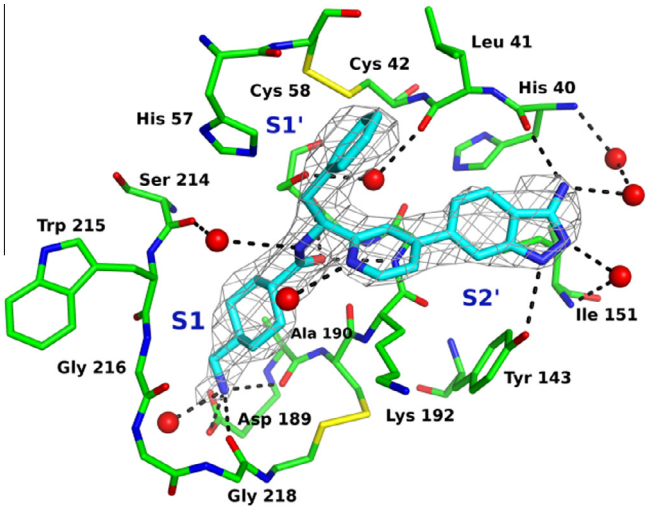


Figure 2. X-ray crystal of (*S*)-**23** in factor XIa.

with (*R*)-**22** and (*S*)-**23** with (*R*)-**23**). As in the imidazole series, the more active enantiomer was determined to possess the (*S*)-absolute stereochemistry.[12] Importantly, the pyridine and pyridinone were single-digit nanomolar FXIa inhibitors and they exhibited in vitro anticoagulant activity in the activated partial thromboplastin (aPTT) clotting assay[11b] ((*S*)-**23** aPTT $EC_{2x} = 4.5$ μM and (±)-**24** aPTT $EC_{2x} = 2.5$ μM). Both the pyridine (*S*)-**23** and the pyridinone (±)-**24** were comparable to the unsubstituted imidazole (*S*)-**21**.

An X-ray structure of (*S*)-**23** bound to human FXIa active site (2.6 Å resolution, *R*-work was 0.176 and *R*-free was 0.226, Figure 2) was obtained.[14] The overall binding mode is similar to that described previously for the imidazole (*S*)-**1**.[12] Compound (*S*)-**23** occupies the S1, S1 prime, and the S2 prime binding pockets and participates in a large number of hydrogen bonding interactions. The cyclohexyl methyl amine occupies the S1 pocket where the primary amine can interact with three of the four possible partners: a water molecule (2.7 Å), Asp189 (2.8 Å), Ala 190 (3.0 Å), or Gly 218 (3.1 Å). The NH of the amide forms an H-bond with a highly conserved water (3.4 Å). The carbonyl of the amide interacts with the oxyanion hole which consists of the backbone NH's of Ser 195 (3.3 Å), Asp 194 (3.1 Å) and Gly 193 (3.5 Å). The benzyl moiety occupies the S1 prime pocket with an edge-on hydrophobic interaction between the phenyl ring and the disulfide bridge, Cys 58–Cys 42. The pyridine nitrogen forms an H-bond to a conserved water molecule (3.0 Å). This H-bonding does not appear to be a key interaction for binding as the regioisomeric pyridines **5** and **6**, which lack the ability to participate with the water molecule, were equipotent to **4**. In addition, the phenyl analog **12**, which also lacks the ability to H-bond with the water molecule was only modestly less potent. The 3-amino indazole occupies the S2 prime pocket and engages in a number of key H-bonds which contributes to the 30-fold increase in FXIa activity. One of the NH bonds from the C3-amino group forms a H-bond with the backbone carbonyl of His 40 (3.0 Å) and the other NH forms an H-bond with the NH of His 40 via a network of water molecules. The indazole N(1)H forms an H-bond to Tyr 143 (3.0 Å) and the N(2) forms an H-bond through a conserved water to Ile 151 (3.1 Å). The dihedral angle between the pyridine scaffold and the amino indazole was 24.3°.

An overlay of pyridine (*S*)-**23** with the X-ray structure of the imidazole (*S*)-**1** bound to human FXIa active site (the resolution was 2.09 Å, the *R*-work was 0.179, and the *R*-free was 0.206) is shown in Figure 3.[12] Despite the similar binding mode, there are two major differences in SAR between the imidazole and the six-membered rings.[15] The first difference involves the role of the heteroatom between the ring substituents. It is interesting to note that the imidazole (*S*)-**2** possesses a nitrogen atom between the ring substituents and it was active. This was not the case for pyridine **3** or pyrimidine **10**. A nitrogen atom between the ring substituents led to a significant loss in activity. The explanation for this difference in activity may come from an interaction between the ring atom and a conserved water molecule (orange sphere in Fig. 3). Based on the residues of the enzyme that surround the water and subsequent H-bonding interactions, the water molecule is oriented so that the oxygen lone pair is pointing toward the ring atom. In the case of pyridine **3** or pyrimidine **10**, electrostatic repulsion arises between the nitrogen lone pair from the ring and the oxygen lone pair from the water, resulting in a destabilizing interaction and loss in FXIa activity.[16] The imidazole ring can avoid this electrostatic repulsion since a tautomeric form of the

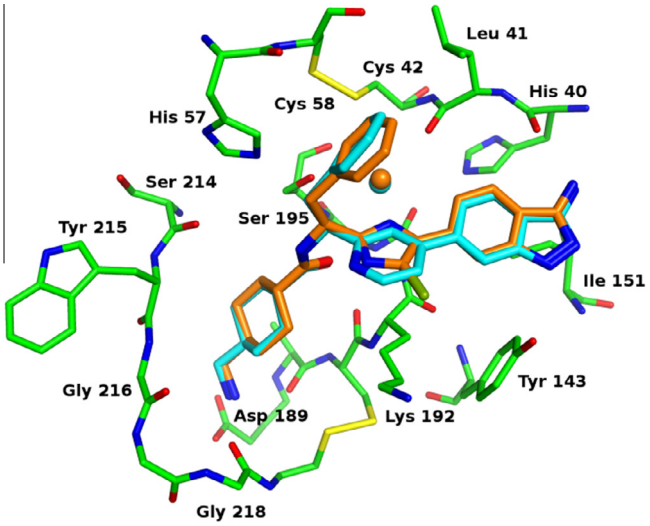


Figure 3. Overlay of X-ray crystals of (*S*)-**23** (cyan) and (*S*)-**1** (orange) in factor XIa.

Table 5
Human enzyme selectivity profile for pyridine (*S*)-**23** compared to imidazole (*S*)-**1**

Human enzyme K_i[a] (nM)	(*S*)-**23**	(*S*)-**1**
Factor XIa	8.4	0.31
Factor VIIa	>10,890	4540
Factor IXa	>34,860	>34,900
Factor Xa	>9000	>9000
Thrombin	>12,610	>12,610
Trypsin	64	23
Plasma kallikrein	24	4
Activated protein C	>21,400	>31,180
Plasmin	>22,100	8438
TPA	>21,900	>21,940
Urokinase	>14,060	15,180
Chymotrypsin	>20,780	>20,800

[a] All K_i values in nM were obtained using human purified enzymes.

imidazole can place the NH, rather than the nitrogen lone pair, between the substituents on the ring. The imidazole NH can then engage in a H-bond with the conserved water (2.9 Å).

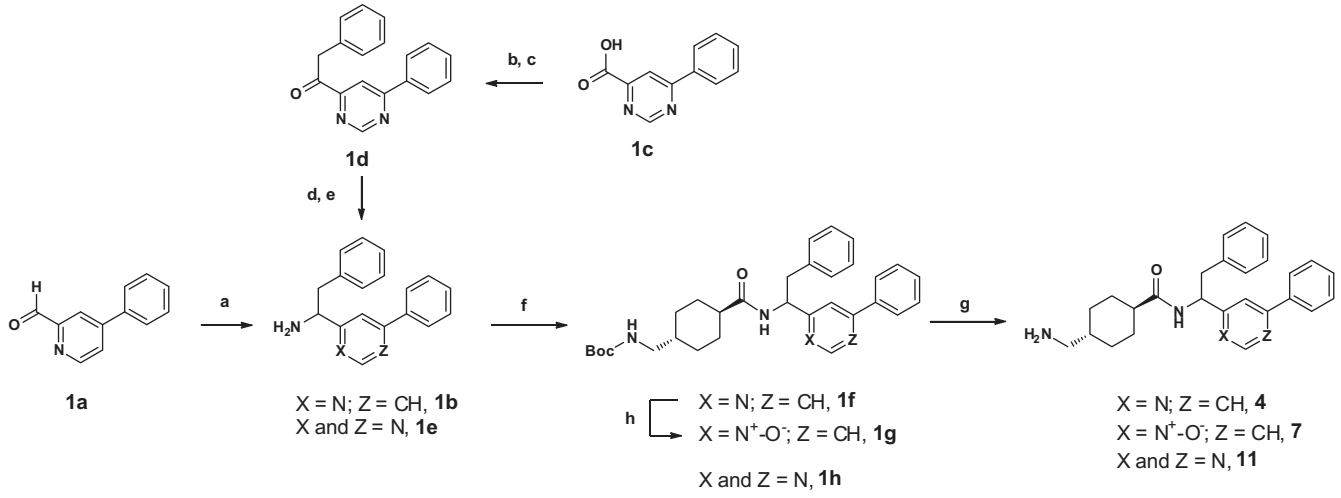
The second major difference between the SAR of the imidazole and the six-membered ring analogs involves the role of halogen on the heterocyclic scaffold. As described, halogenation of the imidazole led to a significant increase in FXIa binding. However, halogenation of the pyridine ring did not lead to this increase in activity. The increase in binding for the imidazole was originally attributed to a lipophilic interaction with the alkyl portion of the Lys 192 side chain.[12] Based on the overlay in Figure 3, a portion of the pyridine ring is occupying the region of the chloro group in the imidazole. It is possible that the pyridine ring is already picking up this lipophilic interaction which is accounted for in the observed FXIa K_i. An alternative explanation is that halogenation of the imidazole ring makes the imidazole NH a better H-bond donor resulting in a stronger interaction with the conserved water molecule and thus leading to an increase in binding for the imidazole. Since the pyridine cannot form an H-bond to the conserved water, halogenation does not significantly help the binding affinity.

The selectivity profile of pyridine (*S*)-**23** is compared to imidazole (*S*)-**1** in Table 5. These compounds have >1000-fold selectivity against many of the relevant serine proteases, except for plasma kallikrein and trypsin.

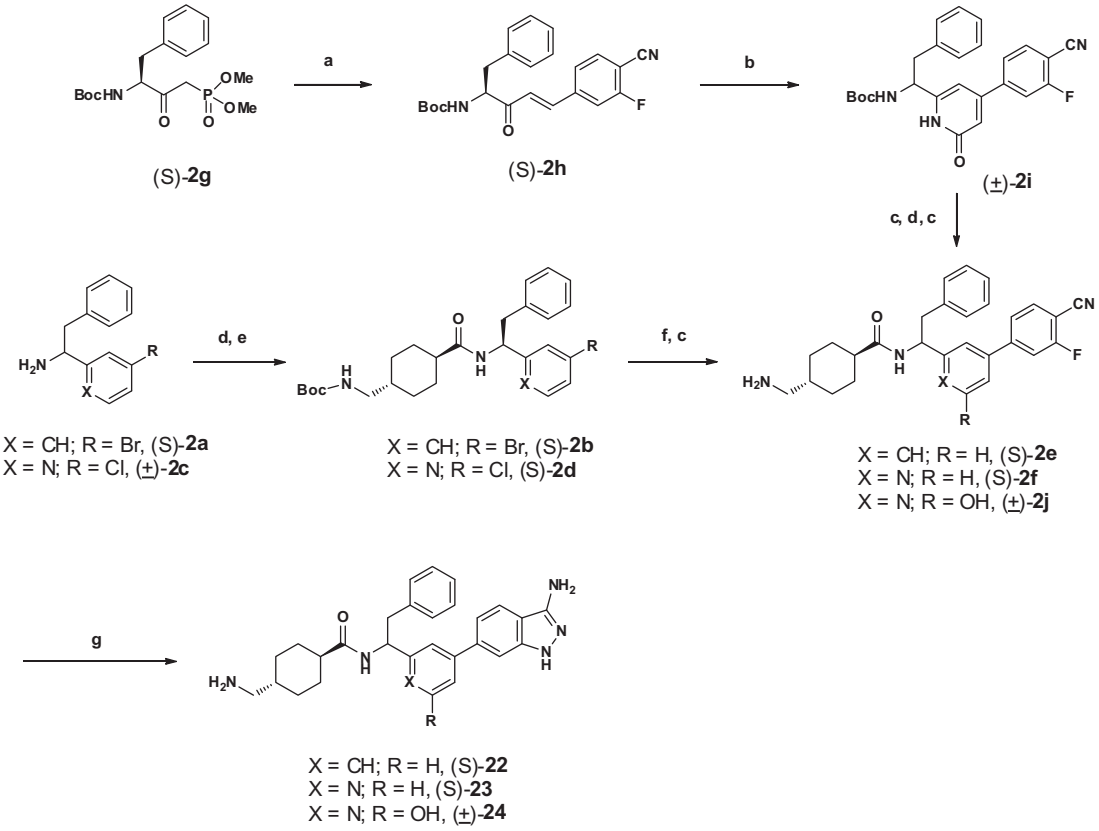
Representative examples of the synthesis of the compounds listed in Tables 1–3 are described in Scheme 1. The key amine intermediates **1b** and **1e** were prepared by two general methods. The first method, used to prepare **1b**, employed a modification of the procedure described by Hart.[17] In situ generation of *N*-trimethylsilylaldimine from **1a** and lithium bis(trimethylsilyl)amide, followed by the addition of benzyl magnesium bromide, gave after aqueous work up, the primary amine **1b**. The second approach, used to prepare **1e**, began with the carboxylic acid **1c**. Negishi coupling of the acid chloride, derived from **1c**, and benzyl zinc chloride afforded the ketone **1d**. Condensation of ketone **1d** with hydroxylamine hydrochloride generated the oxime, which was reduced to the primary amine **1e** with zinc dust and TFA.[18] Amide coupling of amines **1b** and **1e** with N-Boc tranexamic acid provided **1f** and **1h**. Boc-deprotection of **1f** and **1h** gave the final compounds **4** and **11**. The pyridine N-oxide **7** was prepared by oxidation of **1f** with *m*CPBA which gave **1g**, followed by Boc-deprotection.

The compounds in Table 4 were prepared according to Scheme 2. Acylation of the phenyl derivative (*S*)-**2a** provided (*S*)-**2b**.[19] Similarly, acylation of the pyridine (±)-**2c** followed by chiral preparatory hplc, gave (*S*)-**2d**.[20] Suzuki–Miyaura coupling of 3-bromophenyl (*S*)-**2b** or 4-chloropyridine (*S*)-**2d** with 4-cyano-3-fluorophenylboronic acid, followed by Boc-deprotection, gave (*S*)-**2e** and (*S*)-**2f**. An alternative method was used to prepare the pyridinone (±)-**2j**. Horner–Wadsworth–Emmons reaction of β-ketophosphonate (*S*)-**2g** and 2-fluoro-4-formyl benzonitrile gave α,β-unsaturated ketone (*S*)-**2h**.[21] Condensation of (*S*)-**2h** with 1-(ethoxycarbonylmethyl)-pyridinium chloride or 1-(carbamoylmethyl)-pyridinium chloride in the presence of ammonium acetate in ethanol at elevated temperature afforded the racemic pyridinone (±)-**2i**.[22] Boc-deprotection, amide coupling with Boc-tranexamic acid, followed by Boc-deprotection gave (±)-**2j**. Heating (*S*)-**2e**, (*S*)-**2f**, and (±)-**2j** with hydrazine monohydrate in butanol at 150 °C in a microwave afforded the aminoindazoles (*S*)-**22**, (*S*)-**23**, and (±)-**24**.

In conclusion, the SAR of six-membered ring replacements for imidazole has been described. A variety of six-membered rings proved to be good replacements for the imidazole and they are listed in order of decreasing FXIa activity: imidazole (*S*)-**2** ≃ pyridinone **18** < pyridine regioisomers (**4**, **5**, and **6**) ≃ pyrimidine **11** < phenyl **12**. This work led to the discovery of the potent and selective pyridine (*S*)-**23** and pyridinone (±)-**24** factor XIa inhibitors. SAR and X-ray crystal structure data highlight the key differences between the imidazole and six-membered ring analogs. Further development on these six-membered ring replacements for the imidazole will be reported in due course.



Scheme 1. Reagents and conditions: (a) LiHMDS, THF, 0 °C, then BnMgCl, 47%; (b) thionyl chloride, cat. DMF, DCE, reflux; (c) $Pd(Ph_3P)_4$, BnZnCl, THF, −30 °C to 0 °C, 43% over two steps; (d) hydroxylamine hydrochloride, MeOH; (e) Zn, TFA, 0 °C, 63% over two steps; (f) N-Boc-tranexamic acid, EDC, HOBt, Hunig's base, DMF, 0 °C to rt; (g) 30% TFA (v/v), CH_2Cl_2, rt, 45–67% over two steps. (h) *m*CPBA, $CHCl_3$, rt.



Scheme 2. Reagents and conditions: (a) 2-fluoro-4-formyl benzonitrile, K_2CO_3, THF, 75%; (b) 1-(ethoxycarbonylmethyl)-pyridinium chloride or 1-(carbamoylmethyl)-pyridinium chloride, NH_4OAc, EtOH, 80 °C, 60%; (c) 30% TFA (v/v), CH_2Cl_2, rt; (d) N-Boc-tranexamic acid, EDC, HOBt, Hunig's base, DMF, 0 °C to rt; 66–80%; (e) chiral prep. hplc on (±)-**2d** to give (*S*)-**2d**; (f) 4-cyano-3-fluorophenylboronic acid, $Pd_2(dba)_3$, tBu$_3$PHBF$_4$, Cs_2CO_3, dioxane, 90 °C; or $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, K_3PO_4, DMSO, 85 °C; (g) hydrazine monohydrate, *n*-BuOH, microwave, 150 °C, 10 min, 18% over three steps for phenyl (*S*)-**22**; 16% over three steps for pyridine (*S*)-**23**; 33% over four steps for pyridinone (±)-**24**.

Acknowledgments

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14. PDB deposition number for (*S*)-**23** is 4WXI.
15. The dihedral angle between the chloro-imidazole and the amino indazole was 21.8°. Geometries were optimized using QChem at the B3LYP/6-31G** level of theory and RI-MP2/CC-PVTZ method. These studies indicated that the bioactive conformation of the biaryl systems do not differ significantly from the lowest energy conformation and therefore cannot explain the difference in potency.
16. A significant loss in FXIa activity is a general trend when a heteroatom, possessing a lone pair, occupies the position between the ring substituents. This is supported by SAR from the five-membered heterocycle ring replacements, please see Ref. 12.
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19. (*S*)-**2a** was prepared from 3-bromo benzaldehyde using the procedure of Hart (Ref. 17). The enantiomers were separated by chiral preparatory HPLC and the absolute stereochemistry was determined by reaction with (*S*)-(+)-α-methoxyphenyl acetic acid according to Trost, B. M. et al *J. Org. Chem.* **1994**, *59*, 4202.
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