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Benzimidazoles and Isosteric Compounds as Potent and Selective Factor Xa Inhibitors

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Abstract—Benzimidazoles and their isosteric compounds as factor Xa inhibitors are discussed

Efforts in searching for small molecular inhibitors of serine protease factor Xa have greatly intensified in recent years. Consequently, many novel compounds as factor Xa inhibitors have been identified.[1–7] In a preceding paper,[8] we have disclosed that the exploration of the benzamidine replacement of a novel series of factor Xa inhibitors led to the discovery of several non-benzamidine compounds as potent factor Xa inhibitors. Imidazole analogue **2**, derived from the initial lead **1**, was identified as a potent factor Xa inhibitor with a K_i of 12 nM. In addition, compound **2** is also very selective and essentially inactive against other serine proteases evaluated. Meanwhile, aminoquinazoline analogue **3** was recently reported by our colleagues to be a very potent and selective inhibitor with a K_i of 0.8 nM.[7,9] In an ongoing effort to discover novel factor Xa inhibitors, we have undertaken another approach to examine the structural diversity of compounds **1** and **3** as well as the tolerance of replacement/substitution of the chlorobenzothiophene pharmacophore in compounds **1**, **2**, and **3**. New advances in the structure–activity relationships in the piperazine-2-one series of factor Xa inhibitors is reported herein.

Benzimidazole and its isosteric functional groups were chosen to replace the benzothiophene group with the rationale presented hereafter. Conformation restriction via potential hydrogen bonding through N or NH of benzimidazoles with factor Xa might improve potency. Secondly, benzimidazoles have very different chemical and physical properties from benzothiophenes and thus such derivatives will possess quite different PK/PD profiles. For example, the *c*Log (3.18) of the parent benzimidazole is more than one log unit lower than that of the corresponding benzothiophene analogue. Thirdly, SAR can be established rapidly due to ease of synthesis to assess the tolerance for structural diversity.

The synthesis of aminoquinazoline analogues such as inhibitor **8** is exemplified in Scheme 1. A variety of diamines **5** were converted to the corresponding chloromethyl-benzimidazoles **6** with chloroacetic acid according to published procedures.[10] Alkylation of piperizin-2-one template **7**,[11] with chloromethyl compound **6** was achieved in the presence of sodium hydride in DMF to afford inhibitor **8**.

The synthesis of benzamidine analogues is outlined in Scheme 2. Alkylation of commercially available piperazine-one **9** with *para*-cyanobenzylbromide was straightforward to give compound **10**, which was then deprotected with HBr/AcOH[12] to give the corresponding HBr salt **11**. Alkylation of this salt with benzimidazole **6** produced nitrile **12**. Subsequent conversion of the nitrile to benzamidine **13** was achieved with previously described Pinner reaction conditions.[13]

The factor Xa and other serine protease assays were performed as previously described.[14] The results of benzimidazoles and their isosteric compounds as factor Xa inhibitors are included in Table 1. Compound **15** was founded to be a potent factor Xa inhibitor with a K_i of 3 nM, although 3-fold less potent than the corresponding benzothiophene analogue **3**. Replacement of the SO_2 linker of inhibitor **15** with a CH_2 group

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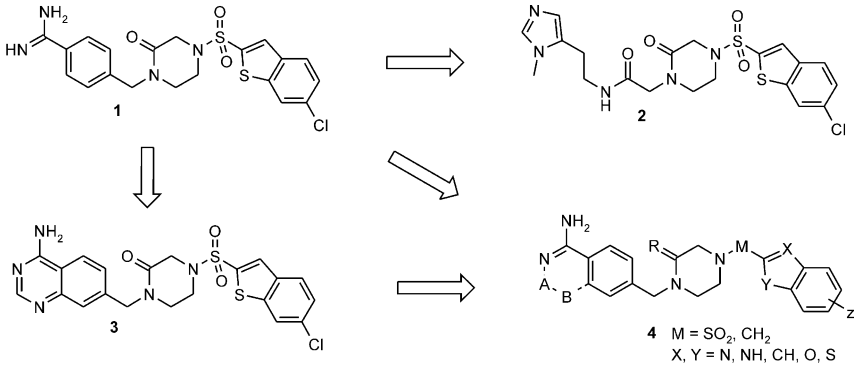
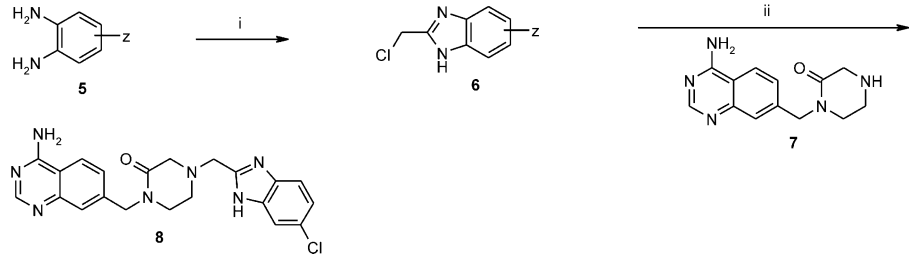
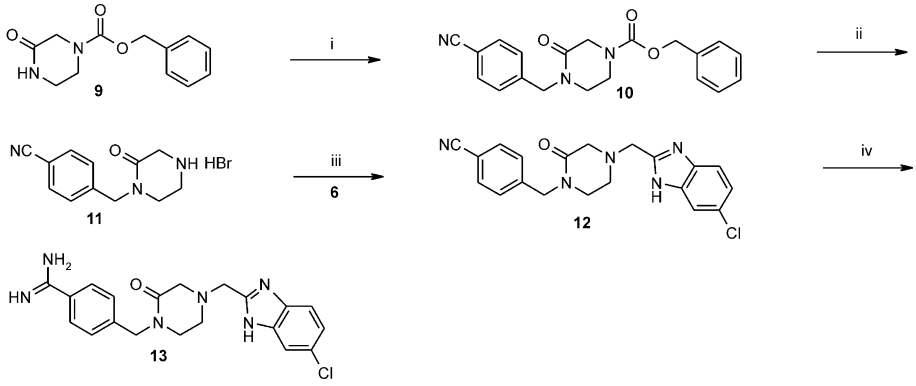


afforded the corresponding alkylamino analogue **8**. Only 3-fold loss of activity was observed between alkylamine **8** and sulfonamide analogue **15** within the benzimidazole series of factor Xa inhibitors, which is much less dramatic than the corresponding comparison among the benzothiophene analogues. Furthermore, both alkylamine **8** and sulfonamide **15** are also very selective against other serine proteases as shown in Table 2. Replacement of the chlorine atom with a methyl group resulted in 10-fold loss of activity (**18** vs **8**). However, substitution with methoxy, trifluoromethyl or dichloro groups abolished anti-factor Xa activities for benzimidazoles **19**, **20**, and **21**. Such results are not surprising in light of the unusual binding mode of a chlorobenzothiophene analogue with factor Xa (interaction of the chlorine atom with the aromatic ring of tyrosine 228 in S1 site) as revealed by protein X-ray crystallography studies.[8,10] Co-crystallization of benzimidazolyl inhibitors with factor Xa was not successful, but it is very likely that benzimidazolyl inhibitors also adopt the similar reverse binding mode to that of benzothiophene analogues considering the structural similarity between them and the strong preference for the chlorine atom. However, these two series of inhibitors do possess subtle differences in terms of SAR. In addition to the difference of alkylamino versus sulfonamide inhibitors discussed above, the fact that even the non-substituted compound **17** (Cl replaced by H) showed a weakly inhibitory activity seemed to support our rationale that conformation constrain and hydrogen bonding can improve potency. For comparison, the corresponding non-substituted benzothiophene analogue was inactive against factor Xa.

Methylation of benzimidazole **8**, to remove the hydrogen bond donor potential and to explore simple *N*-substitutions, resulted in an inseparable mixture of two isomers **23**, which were 30-fold less potent than the non-methylated parent compound. Replacement of the chlorine atom with a bromine atom did not offer any advantage (**22** vs **8**). Finally, reduction of the amide group of piperazin-2-one **8** produced the inactive piper-

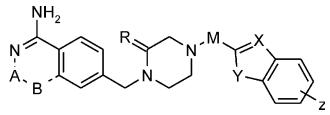


Scheme 1. Synthesis of aminoquinazoline analogues of factor Xa inhibitors: (i) $HCl/ClCH_2CO_2H$; (ii) K_2CO_3/DMF.



Scheme 2. Synthesis of benzamidine analogues of factor Xa inhibitors: (i) $NaH/DMF/4\text{-}NCPhCH_2Br$; (ii) HBr/AcOH; (iii) $K_2CO_3/DMF/ArCH_2Cl$; (iv) HCl/MeOH; $NH_3/MeOH$.

Table 1. Factor Xa inhibitory activity



Compd	A	B	M	R	X	Y	Z	K_i (nM)
1[7] (*para*)[a]	H	H	SO_2	O	CH	S	6-Cl	1
3[7]	CH	N	SO_2	O	CH	S	6-Cl	1
8	CH	N	SO_2	O	N	NH	Cl	10
13 (*para*)[a]	H	H	CH_2	O	N	NH	Cl	40
14 (*meta*)[b]	H	H	CH_2	O	N	NH	Cl	>1200
15	CH	N	SO_2	O	N	NH	Cl	3
16	CH	N	CH_2	H,H	N	NH	Cl	>>1200
17	CH	N	CH_2	O	N	NH	H	1200
18	CH	N	CH_2	O	N	NH	CH_3	120
19	CH	N	CH_2	O	N	NH	O CF_3	>>1200
20	CH	N	CH_2	O	N	NH	CF_3	>>1200
21	CH	N	CH_2	O	N	NH	5,6-di-Cl	>>1200
22	CH	N	CH_2	O	N	NH	Br	17
23	CH	N	CH_2	O	N	NMe	Cl	290
24	CH	N	CH_2	O	N	O	5-Cl	1200
25	CH	N	CH_2	O	N	O	6-Cl	>>1200
26	CH	N	CH_2	O	N	S	5-Cl	1200
27	CH	N	CH_2	O	N	S	6-Cl	>>1200
28	CH	N	CH_2	O	CH	NH	5-Cl	24
29	CH	N	CH_2	O	CH	NH	6-Cl	390

[a]*para*-Benzamidine analogue.
[b]*meta*-Benzamidine analogue.

Table 2. Selectivity profiles of factor Xa inhibitors

Compd	K_i (nM)					
	fXa	Thrombin	Trypsin	APC	Plasmin	*t*-PA
8	10	>4000	>2900	>18,000	>7300	>8700
15	3	>4000	>2900	>18,000	>7300	>8700
28	24	>4000	>2900	>18,000	>7300	>8700

azinyl compound **16**. This underscores the importance of the piperazin-2-one template to overall activity (conformational restriction and hydrogen bonding).

Since the methylated analogues **23** are not very active against factor Xa, it is not surprising that neither benzoxazoles (**24** and **25**) nor benzothiazoles (**26** and **27**) are good inhibitors of factor Xa. The weak activity or inactivity of these isosteric compounds of benzimidazole **8** might be due to lack of capability to act as hydrogen bonding donors. This hypothesis is further supported by the observation that the 5-chloroindole analogue **28**, having a relatively acidic proton, was only 2-fold less potent than the corresponding 6-chlorobenzimidazole **8**. The 6-chloroindole isomer **29** was much less active with a K_i of 390 nM probably due to its less optimal geometry to maintain both hydrogen bonding and chlorine/tyrosine interactions.

Replacement of the aminoquinazoline group of compound **8** with a benzamidine group afforded compounds **13** and **14**. The *para*-analogue **13** was 4-fold less potent than inhibitor **8** with a K_i of 42 nM while the *meta*-analogue **14** only showed 42% inhibition of factor Xa at a concentration of 3.9 μM.

In summary, we have explored the systematic replacement of a key chlorobenzothiophene group in a novel series of nanomolar factor Xa inhibitors with benzimidazole and its isosteres. This class of compounds is very selective against factor Xa over other serine proteases tested. This class of factors Xa inhibitors can be readily synthesized and might be useful in the further exploration of SAR. Optimization of these prototype compounds may lead to the discovery of novel anticoagulation drugs.

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