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Design, synthesis, and biological evaluation of 1,5-benzothiazepine-4-one derivatives targeting factor VIIa/tissue factor

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ABSTRACT

The 1,5-benzothiazepine-4-one scaffold was earlier shown to provide efficient protease inhibitors. In this contribution, we describe its use in the design of factor VIIa/tissue factor inhibitors. A series containing a scaffold non-substituted on its aryl part led to compound **20** with an IC_{50} of 2.16 μM. Following molecular modelling studies of this compound, a second series was prepared, which necessitated the synthesis of protected 7- or 8-substituted 1,5-benzothiazepine-4-one derivatives.

Thrombosis related disorders such as deep vein thrombosis, and thromboembolic stroke, remain a major cause of morbidity worldwide. The drawbacks associated with current therapies such as parenteral administration of low molecular weight heparin or intense patient monitoring required with warfarin, limit their chronic utility and have driven the search for small molecule inhibitors of specific enzymes involved in the coagulation cascade with improved pharmacokinetics and pharmacodynamics parameters.[1] In this regard, the past decade has seen major progress in the development of thrombin and factor Xa inhibitors as potentially valuable therapeutic agents for thrombotic diseases.[2] Very recently, a thrombin inhibitor, dabigatran, was approved as its etexilate prodrug derivative,[3] while rivaroxaban, a factor Xa inhibitor,[4] will be soon marketed. However, due to their situation at the end of both extrinsic and intrinsic pathways, targeting these enzymes presents significant bleeding risk. More recently, the pharmaceutical industry has moved efforts toward the development of selective factor VIIa/tissue factor (FVIIa/TF) inhibitors as it was shown that inhibiting only the extrinsic pathway presented higher safety due to potentially lower bleeding risks.[5] Several series of small molecule inhibitors have been published these last years, some of them being highly selective with nanomolar affinities and others possessing satisfying oral bioavailability.[6] However, no inhibitor combining high potency, high selectivity, and good oral activity has been discovered yet and no clinical development has been successful to date.

In this communication, we disclose our own efforts in this field of research. Small molecule inhibitors, which incorporate the 1,5-benzothiazepin-4(5*H*)-one moiety (Fig. 1), recognized as a privileged scaffold for drug design,[7] were designed. Its derivatives have been successfully used in the design of biologically active com-

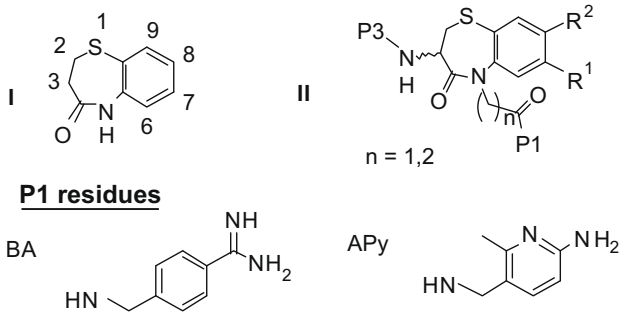

Figure 1. 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-one (**I**), and general structure of synthesized compounds based on (3*S* or 3*R*)-3-amino-5-carboxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**II**, *n* = 1, D-BT or L-BT) and (3*S* or 3*R*)-3-amino-5-carboxyethyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**II**, *n* = 2). BA, 4-aminomethylbenzamidine; Apy, 5-aminomethyl-6-methyl-pyridin-2-ylamine.

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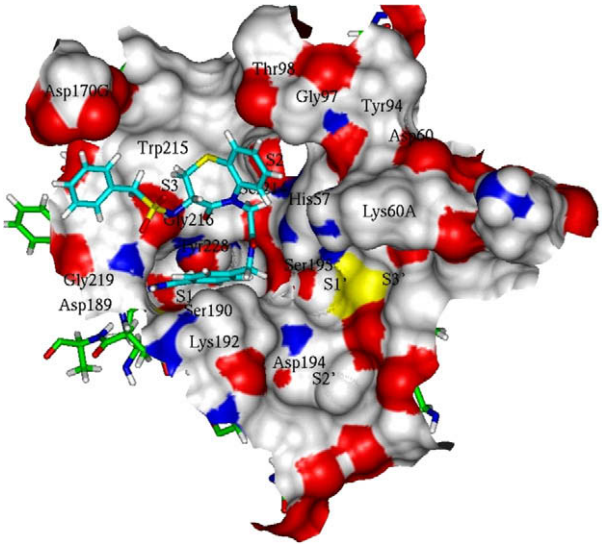
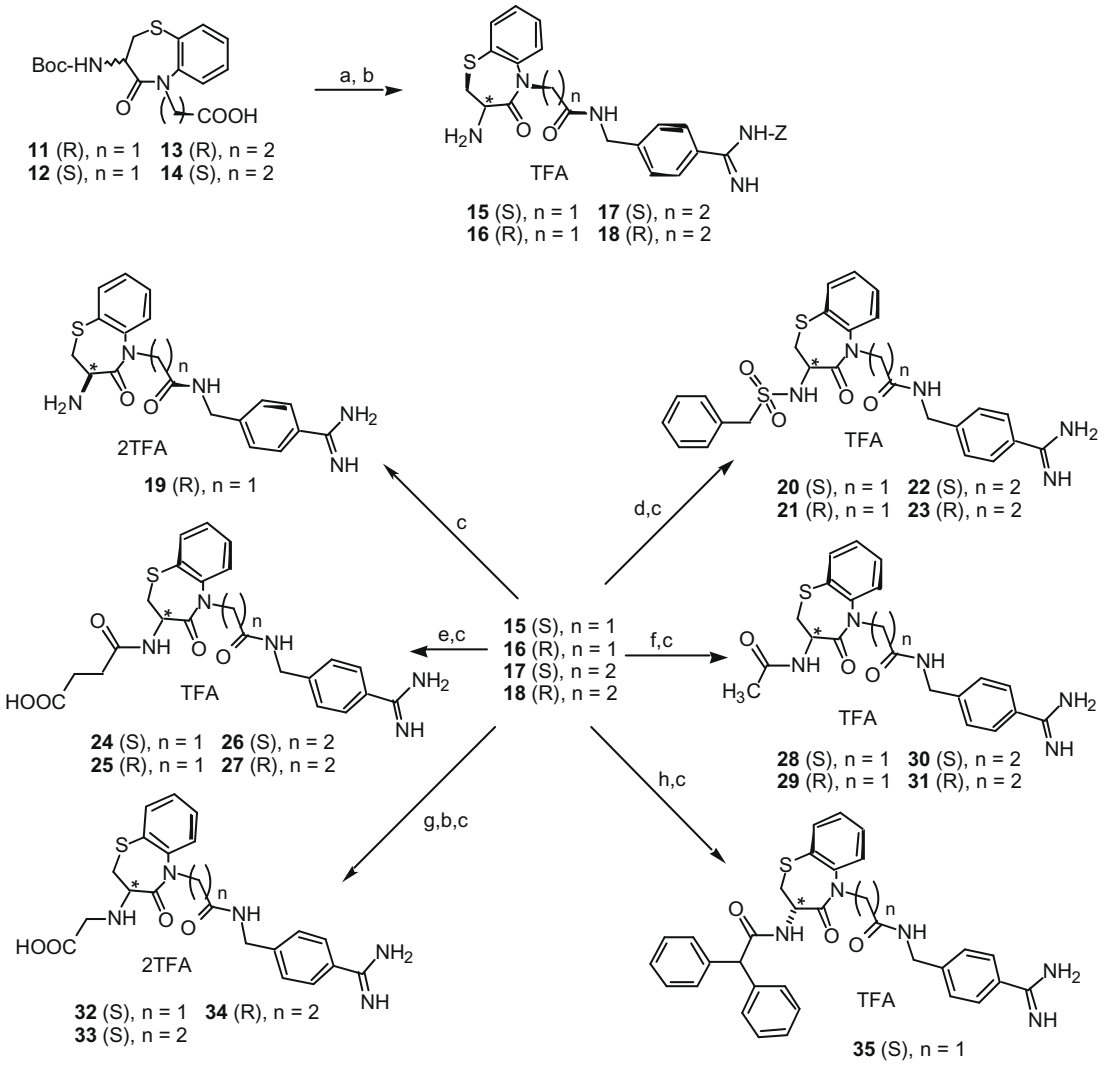


Figure 2. Molecular modelling of compound **20** in the binding site of FVIIa/TF complex.

pounds, the most famous example being diltiazem, a calcium channel blocker used in the treatment of several cardiovascular disorders.[8,9] It is also contained in the structure of agonists or antagonists of peptide hormone receptors (bradykinin,[10] cholecystokinin,[11] angiotensin II receptors[12]), growth hormone secretagogues,[13] and inhibitors of peptidases (elastase,[14] neprilysin,[15] ACE,[16,17] kallikrein[18]).

The designed compounds are based on (3*S* or 3*R*)-3-amino-5-carboxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one ($n = 1$, L- or D-BT, Fig. 1), but also on the homologated analogues ($n = 2$). BT is a dipeptide mimetic, which was shown to be a β-turn mimetic.[19] Modelling experiments in the active site of FVIIa/TF suggested favourable positioning of L- and D-BT in the S2–S3 area of the binding site (not shown, the positioning of modelled BT alone resembles that in compound **20**, see Fig. 2). According to these studies, the P1 and P3 residues were tethered on the carboxyl and amino moieties of BT, respectively (Fig. 1).

A first series of compounds ($R^1 = R^2 = H$) was synthesized, in which stereochemistry (L- or D-BT) and nature of the P1 and P3 residues were modified. P1 was mainly a benzamidine (BA) group, a frequently used arginine mimetic allowing strong interaction in the S1 pocket through ionic bond with the protease residue



Scheme 1. Reagents and conditions: (a) 1.1 equiv BA-Z, 1.1 equiv BOP, 2.2 equiv DIEA, DMF; (b) TFA/DCM (1:1); (c) HF/anisole (5:0.1), 0 °C; (d) 1 equiv benzylsulfonyl chloride, 2.2 equiv Et_3 N, DCM; (e) 1 equiv succinic anhydride, 2.2 equiv DIEA, DCM; (f) 1.1 equiv acetyl chloride, 3 equiv DIEA, DMF; (g) 1 equiv *tert*-butyl-2-bromoacetate, 2.2 equiv DIEA, DMF; (h) 1.1 equiv diphenylacetyl chloride, 3 equiv NMM, DCM.

Asp189 (chymotrypsin numbering). As the highly basic amidine group is known to limit oral absorption (however, in this case, a prodrug strategy similar to that followed for melagatran, dabigatran or other amidine-containing compounds could be considered[3,20,21]), we also introduced the less basic mimetic 5-(aminomethyl)-6-methylpyridin-2-ylamine (APy), which has been successfully used for thrombin inhibition.[22] Various substituents differing in size, charge, and hydrophobicity were introduced as the P3 residue. Some were chosen according to modelling hypotheses. In particular, a carboxylic group present at this position (carboxymethyl, succinyl) might establish ionic interaction with the side-chain of Lys192 or Lys60A in the binding site, which should improve inhibitory potency and selectivity against thrombin and FXa.

The synthesis of this first series of compounds (**19**–**44**) was performed in three or four steps from the Boc-protected L-/D-BT **11**, **12**, or homo-L-/D-BT **13**, **14** (Schemes 1 and 2S in the online Supplementary data part; see also Scheme 1S for the preparation of intermediates **11**–**14**[23]). These precursors were first coupled to Z-protected BA (Scheme 1) or Boc-protected APy (Scheme 2S) in the presence of HBTU or BOP and DIEA, followed by removal of the Boc group(s) in acidic conditions, to give **15**–**18** and **36**–**38**, respectively. In the case of APy-containing intermediates **36**–**38** (Scheme 2S), the resulting free and poorly reactive aromatic amine of Apy did not interfere during the following step. Introduction of the P3 residues was then performed and, in the case of BA derivatives, the Z protecting group was finally removed by HF. Benzylsulfonyl was introduced by reaction with benzylsulfonylchloride, leading to compounds **20**–**23** (BA) and **39**, **40** (Apy). Treatment of one or several of the intermediates **15**–**18** (BA) and **36**–**38** (Apy) with succinic anhydride, acetyl chloride, or diphenylacetyl chloride gave **24**–**27** (BA), **28**–**31** (BA) and **41**, **42** (Apy), and **35** (BA), respectively. Reaction with *tert*-butyl bromoacetate followed by TFA treatment afforded the carboxymethyl derivatives **32**–**34** (BA) and **43**, **44** (Apy).

The inhibitory potency of this first series of compounds toward FVIIa/TF complex and thrombin (for some of them) was assessed (Table 1). They generally showed low (10^{-5} M) to very low ($>0.3 \times 10^{-3}$ M) inhibitory activities. In particular, the replacement of BA by APy as the P1 substituent abolished the activity. As a matter of fact, although the introduction of low basic or even neutral substituents at this position was often successful in the context of thrombin or FXa inhibition, loss in activity was generally reported in the case of FVIIa/TF.[6c,24] To our knowledge, only one series of potent inhibitors containing a less basic P1 residue (based on 5-azaindole) was recently reported by Celera Genomics,[25] while the use of a neutral P1 ligand by Astellas Pharma afforded moderately potent inhibitors (submicromolar range).[6j] In the BA series, no structural feature seemed to significantly influence the inhibitory potency of the compounds. The only exception could be the distance between BT and BA, with $n = 2$ being often less favourable than $n = 1$ (compounds **22**, **27**, **30**, **31**, **33** vs **20**, **25**, **28**, **29**, **32**, respectively). Otherwise, whatever the stereochemistry of BT and the nature of P3 residue, low potencies were generally measured, indicating that all the chosen P3 residues might be located outside the binding site and thus be unable to efficiently interact with the enzyme. Low inhibitory potencies were also obtained against thrombin. A notable exception was compound **20**, which possesses the *S* configuration and a benzylsulfonyl group in P3. It showed micromolar inhibitory potency toward FVIIa/TF ($IC_{50} = 2.16$ μM, a 10 times improvement compared to the activity of the *R* analogue **21**). An even higher improvement in activity (100 times) was observed for thrombin inhibition ($IC_{50} = 0.37$ μM).

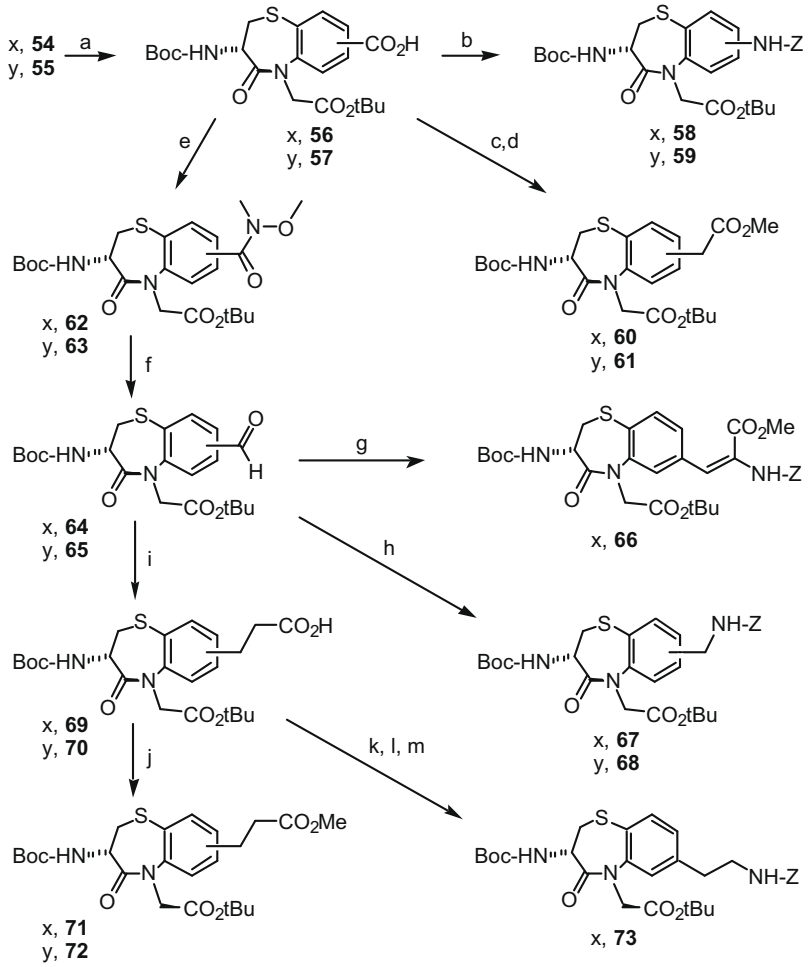
Table 1
In vitro inhibitory activities of 1,5-benzothiazepine-4-one derivatives

Compound	*n*	*R*/*S*	P1	P3	FVIIa IC_{50} (μM)	FIIa IC_{50} (μM)
19	1	*R*	BA	H–	24.4	87.0
20	1	*S*	BA	$BzSO_2$–	2.16	0.37
21	1	*R*	BA	$BzSO_2$–	27.9	48.0
22	2	*S*	BA	$BzSO_2$–	63.0	ND
23	2	*R*	BA	$BzSO_2$–	19.7	ND
24	1	*S*	BA	Succinyl	81.0	300
25	1	*R*	BA	Succinyl	27.7	>300
26	2	*S*	BA	Succinyl	61.0	ND
27	2	*R*	BA	Succinyl	166	>33
28	1	*S*	BA	Acetyl	90.0	ND
29	1	*R*	BA	Acetyl	37.3	100
30	2	*S*	BA	Acetyl	233	ND
31	2	*R*	BA	Acetyl	168	ND
32	1	*S*	BA	$HOOC\text{-}CH_2$–	15.9	ND
33	2	*S*	BA	$HOOC\text{-}CH_2$–	95	ND
34	2	*R*	BA	$HOOC\text{-}CH_2$–	>330	>33
35	1	*S*	BA	Ph_2CHCO–	33.0	ND
36	1	*S*	APy	H–	>300	88.0
37	1	*R*	APy	H–	>300	88.0
39	1	*S*	APy	$BzSO_2$–	>33	ND
40	2	*S*	APy	$BzSO_2$–	>33	ND
41	1	*S*	APy	Acetyl	>300	133.0
42	1	*R*	APy	Acetyl	>300	130.0
43	1	*S*	APy	$HOOC\text{-}CH_2$–	>33	ND
44	2	*S*	APy	$HOOC\text{-}CH_2$–	>33	ND

BA, benzamidine; APy, 2-aminopyridine.

Compound **20** was docked in the binding site of FVIIa to get insight into its binding mode and select modifications capable to improve potency and selectivity. Different protocols were elaborated and tested against various reported crystallized FVIIa/inhibitor complexes for validation. The retained protocol afforded the modelled complex shown in Figure 2 (see also Figure 1S in Supplementary data). The BA residue was located in the S1 subsite, with the amidine group making as expected four H-bonds with Asp189, Ser190, and Gly219. An additional one was observed between one amidine NH and the carbonyl oxygen of Trp215 through a bridging water molecule. Three more H-bonds were defined, between the side-chain oxygen of Ser214 and BA amide NH group, and between Gly216 NH and carbonyl and the corresponding carbonyl and NH groups of the BT moiety. The benzylsulfonyl group pointed outside S3 and was close to S4, making an hydrophobic interaction with the side-chain of Gln217. Finally, the BT phenyl ring appeared close to the S2 subsite and in particular Asp60, Tyr94, and Thr98 (Fig. 2). These residues were shown in several cases to be determinant for activity and selectivity.[6c,6d,6j,6k,26] Indeed, they can form an H-bond network with the inhibitor. Then, the physico-chemical properties and accessibility of S2 for FVIIa are significantly different from those of thrombin and FXa. Thus, it appeared that introducing substituents on the phenyl ring of BT in compound **20** might improve inhibitory potency and selectivity for FVIIa. According to the results obtained by Pharmacia with pyrazinone and 2-pyridone-based inhibitors,[6c] we chose to introduce amino and/or carboxylic groups at position 7 (R^1) or 8 (R^2) of D-BT. In the case of carboxylic groups, they might also interact with the side-chain of the close Lys60A. We also explored the presence of a phenyl ring at position 7.

These modifications necessitated the synthesis of various 7- or 8-substituted D-BT derivatives, most of them having never been described. The protected 7- or 8-amino- and carboxylic-substituted D-BT derivatives were all prepared from the carboxylic acid derivatives **56** and **57**, respectively (Scheme 2; for the synthesis of the corresponding methyl esters **54** and **55**, see Scheme 3S in the online Supplementary data part). The Z-protected amino derivatives **58** and **59** were directly prepared from **56** and **57** by Curtius rearrangement using diphenylphosphorylazide (DPPA) in the presence of benzyl alcohol. The methyloxycarbonylmethyl analogues **60** and **61** were obtained by homologation of **56** and **57** using the Arndt–Eistert method. Intermediates **66** to **73** were prepared



Scheme 2. *x*, substitution in 7; *y*, in 8 of DBT. Reagents and conditions: (a) 1.1 equiv 1 N LiOH, dioxane; (b) 1.2 equiv DPPA, 1.1 equiv Et_3N, dioxane, 10 equiv benzyl alcohol, reflux; (c) 1 equiv IBCF, 1 equiv Et_3N, THF, −20 °C, 15 min, then 3 equiv diazomethane; (d) silver benzoate/Et_3N (1:9), MeOH, reflux; (e) 1.1 equiv BOP, 3.5 equiv Et_3N, 1.3 equiv *N,O*-dimethyl-hydroxylamine, HCl, DCM; (f) 2 equiv 1 M $LiAl(O^tBu)_3H$/THF, dry THF; (g) 1.05 equiv trimethyl *N*-(benzyloxycarbonyl)-α-phosphonoglycinate, 1.05 equiv tetramethylguanidine, dry DCM, −30 °C; (h) 3 equiv benzyl carbamate, 10 equiv Et_3SiH, 2 equiv TFA, MeCN, 30 °C, **4j**; (i) 1 equiv Meldrum acid, triethylammonium formate/DMF (1:1), 95 °C, 5 h; (j) 2 equiv MeI, 3 equiv K_2CO_3, dry DMF; (k) 1.2 equiv IBCF, 1.2 equiv NMM, DME, 0 °C, 30 min, then 5 equiv 28% NH_3/water; (l) 1.2 equiv BTIB, 2.4 equiv pyridine, DMF/H_2O (6:3); (m) 1.2 equiv benzyl chloroformate, 1.2 equiv Et_3N, DCM, 0 °C, 1 h.

Table 2
In vitro inhibitory activities of 7- or 8-substituted 1,5-benzothiazepine-4-one derivatives

Compound	R^1	R^2	FVIIa	FXa	FIIa
20	H	H	2.16	3.28	0.37
79	CO_2H	H	4.67	NT	NT
80	H	CO_2H	>33	NT	NT
81	NH_2	H	2.3	1.52	1.89
82	H	NH_2	4.86	1.63	7.05
83	CH_2CO_2H	H	2.98	0.21	33
84	H	CH_2CO_2H	14.3	NT	NT
85	CH_2NH_2	H	1.86	1.72	10
86	H	CH_2NH_2	5.6	0.80	10
87	$(CH_2)_2CO_2H$	H	2.64	2.03	33
88	H	$(CH_2)_2CO_2H$	13.1	NT	NT
89	$(CH_2)_2NH_2$	H	1.32	2.79	6.23
90	$CH_2CH(NH_2)CO_2H$	H	1.50	1.05	33
91	Ph	H	10.9	NT	NT
92	Ph-3′-NO_2	H	5.96	2.81	0.79
93	Ph-3′-NH_2	H	6.86	3.23	10

Values of IC_{50} are indicated in μM.
NT, not tested.

from the aldehydes **64** and **65**. The latter were classically obtained from **56** and **57** via Weinreb amides **62** and **63**, using $LiAl(O^tBu)_3H$ as a reducing agent to limit reaction with the *tert*-butyl ester.[27] The protected α-amino acid **66** was prepared from **64** by a Wittig–Horner reaction with protected glycine phosphonate in the presence of tetramethylguanidine. The Z-protected aminomethyl derivatives **67** and **68** were obtained by reductive amination of **64** and **65**, respectively, using benzylcarbamate in the presence of triethylsilane/TFA[28] in mild temperature conditions avoiding simultaneous Boc and *tert*-butyl removal. The carboxyethyl analogues **69** and **70** were, respectively, prepared by treating **64** and **65** with Meldrum acid in the presence of triethylammonium formate as a reducing agent.[29] They were then converted into the corresponding methyl esters, **71** and **72**, or, in the case of the 7-substituted analogue **69**, underwent Hoffman rearrangement to yield the Z-protected aminoethyl derivative **73**.

The protected 7-phenyl substituted D-BT derivatives **77** ($R^1 = C_6H_5$) and **78** ($R^1 = m NO_2$-C_6H_4), precursors of **91**–**93**, were prepared from the 7-bromo-D-BT analogue **76** by Suzuki couplings with the corresponding phenylboronic acids (see Scheme 4S in Supplementary data).

The final compounds **79**–**93** (see Table 2) were then prepared from the protected 7- or 8-substituted D-BT derivatives following two general pathways (see Scheme 5S for more details). Compounds **91** and **92** were prepared from **77**, **78** similarly to that presented in Scheme 1. Compound **93** was then obtained by reduction of the nitro group of **92** with a mixture of Fe/NH_4Cl in $EtOH/H_2O$ at

80 °C. An inverse pathway was followed for the preparation of compounds **79**–**90**. Compounds **54**, **55**, **58**–**61**, **66**–**68,** and **71**–**73**, were first deprotected and reacted with benzylsulfonyl chloride before coupling with BA-Z. The Z protecting group was finally removed with a 33% HBr/AcOH solution. In the case of **90**, the ethylenic group (originating from intermediate **66**) was reduced by catalytic hydrogenation[30] with simultaneous Z removal.

Table 2 shows the inhibitory potencies of compounds **79**–**93** against FVIIa/TF and, for those with IC_{50} below 5 μM, FXa and thrombin. Compared to **20**, no significant improvement in potency against FVIIa was obtained, the best compounds (**79**, **81**, **83**, **85**, **87**, **89**, **90**) possessing similar IC_{50} values. A closer examination revealed that substitution of D-BT at position 8 caused steric hindrance as it was generally less well tolerated by FVIIa/TF compared to 7-substitution, in particular when the substituent contained a carboxylic group (**80** vs **79**, **84** vs **83**, **88** vs **87**, 5 to 10 times less active). No satisfying explanation of this behaviour was obtained by modelling studies. A similar result was obtained with a phenyl ring at position 7, which led to a three to five times drop in potency. Interestingly, as far as thrombin inhibition was concerned, we found that substitution of D-BT at position 7 or 8 led to a significant decrease in inhibitory potency (about 100 times for compounds **83**, **87**, **90**), especially when the substituent contained a carboxylic function. This resulted in a significant selectivity for factor VIIa/TF against thrombin, with a ratio of around 20 for the amino acid-containing compound **90**. Compounds **20** and **83** were modelled in the active site of thrombin (PDB code, 1DWD). Compound **20** occupied the same region as in Factor VIIa with the BT moiety present in the S2–S3 area, making H-bonds with Gly216 backbone. In particular, the aromatic part of BT bound in S2 and interacted with Tyr60A and Trp60D, while the benzylsulfonyl phenyl ring was staking with Arg221A side-chain. The acetic group in compound **83** made contact with Trp60D, resulting in the absence of interaction of the benzylsulfonyl phenyl ring with thrombin and in its staking with the BT moiety. This could explain the lower inhibitory potency of these compounds against thrombin. However, no selectivity against FXa was obtained, as all tested compounds (**20**, **81**–**83**, **85**–**87**, **89**, **90**, **92**, **93**) showed IC_{50} in the micromolar range, generally with small variations whatever the substitution. However, compound **83** possessing an acetic group at position 7 of D-BT presented a 15 times improvement in inhibitory potency against FXa (IC_{50} = 0.21 μM) compared to the unsubstituted analogue **20**, rather making it a relatively selective inhibitor of FXa (IC_{50}'s ratios FVIIa/FXa = 14; FIIa/FXa = 150).

In conclusion, several series of 1,5-benzothiazepine-4-one containing compounds were prepared as potential FVIIa/TF complex inhibitors. The best compounds presented micromolar IC_{50} against this coagulation factor. Derivatization of the D-BT moiety at positions 7 or 8 did not allow to improve significantly the potency compared to unsubstituted **20**. However, some structural features allowing to acquire significant selectivity against thrombin in these series were obtained. As other structural classes with high potency and high selectivity were reported, further studies are necessary to improve inhibitory potency and selectivity in this D-BT series.

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Supplementary data

Synthetic procedures and analysis data for compounds 45-78. Structural analysis data for compounds 20, 79-93. Schemes 1S to 5S. Figure 1S. In vitro Factor VIIa/TF, Factor Xa, Thrombin assay methods. Molecular modelling description. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.01.039.

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