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Novel thrombin inhibitors incorporating weakly basic heterobicyclic P_1-arginine mimetics: optimization via modification of P_1 and P_3 moieties

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Abstract—Optimization of lead compounds **1** and **2** resulted in novel, selective, and potent thrombin inhibitors incorporating weakly basic heterobicyclic P_1-arginine mimetics. The design, synthesis, and biological activity of racemic thrombin inhibitors **17**–**29** and enantiomerically pure thrombin inhibitors **30**–**33** are described. The arginine side-chain mimetics used in this study are 4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine, 4,5,6,7-tetrahydro-2*H*-indazole, and 2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3(2*H*)-yl-amine.

The development of an orally active thrombin inhibitor as an anticoagulant is one of the major focuses of the current pharmaceutical research.[1] Thrombin is the last enzyme in a cascade of trypsine-like plasma serine proteases that are involved in blood coagulation and plays a pivotal role in both fibrin generation penultimate to clot formation and platelet activation.[2] Although the currently available anticoagulant agents, including heparin, warfarin, and acetylsalicylic acid, have provided remarkable achievements in the treatment of thromboembolic diseases, these drugs have considerable limitations associated with a risk of bleeding and the inconvenience posed by the need for routine coagulation monitoring and/or parenteral administration. A key strategy to overcome these limitations has been directed toward the discovery of small-molecule inhibitors of the coagulation cascade enzymes, which possess the pharmacokinetic properties required for oral administration once or twice daily.[3] Due to its central role in thrombosis and hemostasis, thrombin is a prominent target in the development of new anticoagulants with desired properties.

The typical feature of the variety of small-molecule direct thrombin inhibitors is the presence of a highly basic guanidine or amidine moiety. However, strongly basic P_1 groups will tend to hinder absorption across the gut wall and may be associated with high plasma clearance and unwanted side effects.[4] In the effort to produce orally bioavailable thrombin inhibitors we have focused on design and synthesis of compounds that incorporate weakly basic S_1 binding moieties.[5] Toward this goal we previously reported on series of proline-based thrombin inhibitors[6] and 3-amino-2-pyridinone acetamide thrombin inhibitors[7] incorporating weakly basic partially saturated heterobicyclic P_1-arginine mimetics. In the last series inhibitors with 4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine and 6-aminomethyl-4,5,6,7-tetrahydroindazole P_1 moieties exhibited the best binding affinities for thrombin and excellent selectivity against trypsin (Fig. 1). Based on the X-ray structures of complexes of thrombin inhibitors **1** and **2** with human thrombin,[7] our effort was directed toward optimization of the binding affinity of lead structures **1** and **2**.

In this article, as a part of optimization strategy of leads **1** and **2**, we disclose the design, synthesis and biological profiles of novel pyridinone acetamide thrombin inhibitors **17**–**33** incorporating weakly basic P_1-heterobicyclic

Keywords: Thrombin; Thrombin inhibitors; Arginine mimetics.
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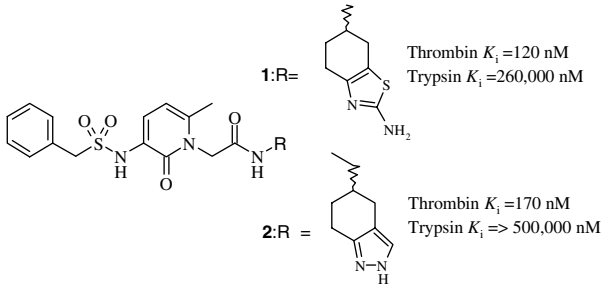
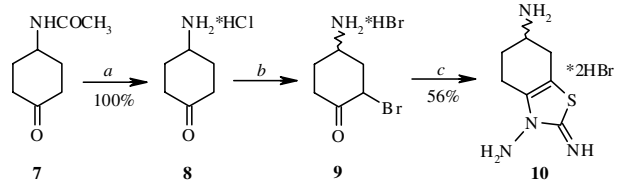
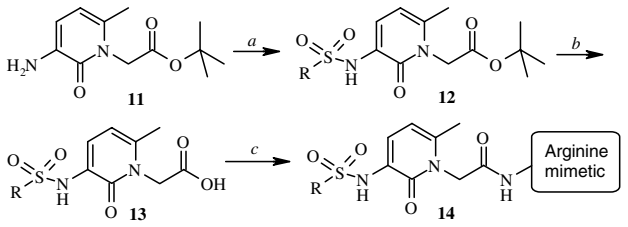


Figure 1. Structure of lead compounds **1** and **2**.



Scheme 1. Reagents and conditions: (a) 6 M HCl, reflux, 6 h; (b) Br_2, 47% HBr, 0 °C, 15 min, then rt, 30 min; (c) thiosemicarbazide, 47% HBr, rt, 30 min, then reflux, 1.5 h.



Scheme 2. Reagents and conditions: (a) RSO_2Cl,[9] CH_2Cl_2, Et_3N, 0 °C to rt, 2 h; (b) HCl_g, EtOAc, 0 °C, 20 min; (c) arginine mimetics **3**–**6**, EDC, HOBt, NMM, DMF, rt, 12 h.

arginine side-chain mimetics and different lipophilic P_3 residues. The arginine side-chain mimetics of low basicity used in this study are 4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine derivatives **3** and **4**, 4,5,6,7-tetrahydroindazole **5** and 2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3(2*H*)-ylamine (**6**) (Fig. 2). Their calculated pK_a values[8] range from 3.17 [2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3(2*H*)-yl-amine (**6**)] to 6.5 [4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (**4**)].

A convenient synthetic approach to conformationally restricted arginine side chain mimetics **3**–**5** has been reported by us previously.[5a–e,6] The synthetic route to 3-amino-2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-6(2*H*)-ylamine (**6**) based on a general synthesis of 2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3-ylamines[5f] is summarized in Scheme 1. Acidic hydrolysis of *N*-(4-oxocyclohexyl)acetamide (**7**)[5b] gave 4-aminocyclohexanone (**8**), which provided 3-bromo derivative **9** after bromination with bromine. In the next step a classical Hantzsch thiazole synthesis applying thiosemicarbazide as an S–C–N synthon afforded compound **10**. Scheme 2 outlines the synthetic route to P_3–P_2 pyridinone synthons **13** and the ultimate coupling reactions between P_3–P_2 synthons **13** and the P_1-arginine mimetics, which afforded final inhibitors **14**. The coupling reactions were performed using EDC, HOBt, and *N*-methylmorpholine in dry DMF at room temperature.

As the crystal structures of thrombin inhibitors **1** and **2** complexed with human thrombin revealed a preferential binding of *R* enantiomers of inhibitors **1** and **2** to the active site of thrombin,[7] we prepared also the pure enantiomers **30**–**33** of the inhibitors **1** and **20** and measured their in vitro inhibitory potency (Table 2). In the synthesis of the pure enantiomers, optical resolution of (±)2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (**3**) with L- and D-tartaric acid was employed affording (*S*)-2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (**15**) and (*R*)-2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (**16**).[10]

The ability of new thrombin inhibitors to inhibit the enzymatic action of thrombin, trypsin, and factor Xa was measured with the amidolytic enzyme assays using chromogenic substrates.[11a] Values of K_i were calculated according to Cheng and Prusoff,[11b] based on IC_{50} values or from a relation between reaction velocity equations in the absence and presence of inhibitor, using the relevant

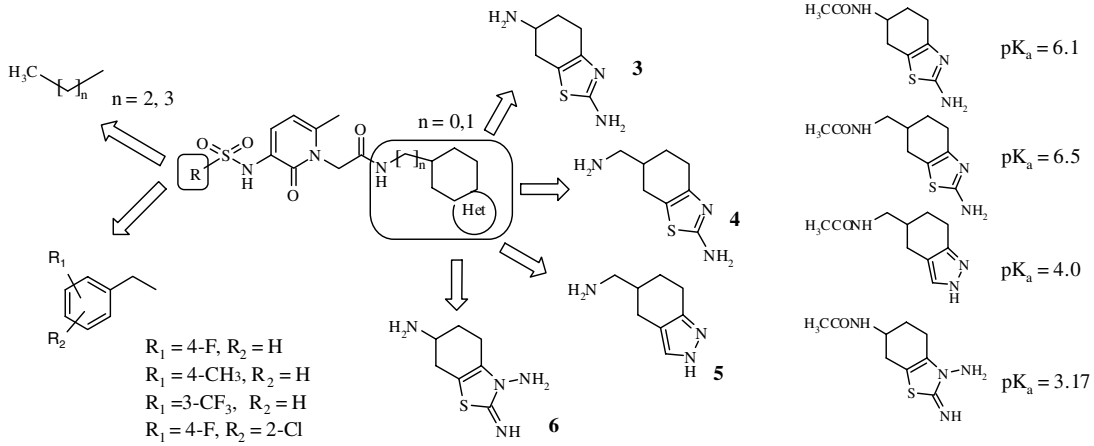
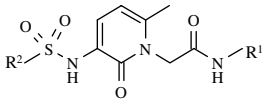
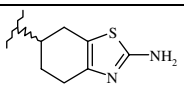
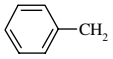
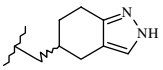
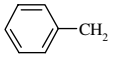
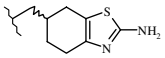
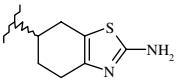
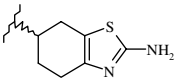
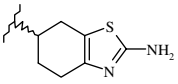
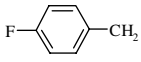
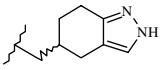
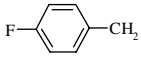
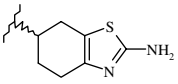
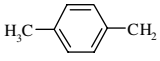
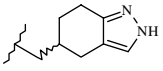
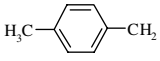
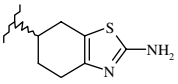
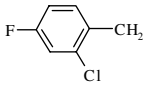
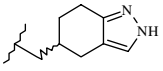
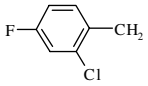
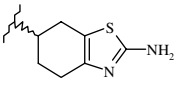
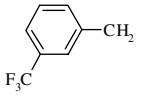
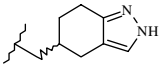
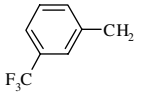
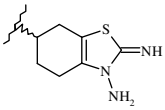
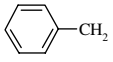
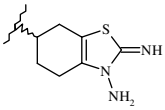
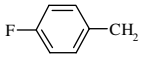


Figure 2. Evolution of 3-amino-2-pyridinone acetamide thrombin inhibitors incorporating weakly basic, partially saturated heterobicyclic P_1-arginine side chain mimetics with their calculated pK_a values[8] and different P_3 lipophilic residues.

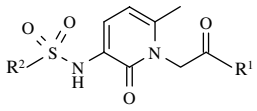
Table 1. Inhibitory potencies of lead compounds **1**, **2**, and thrombin inhibitors **17–29**

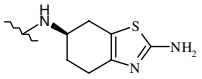
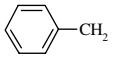
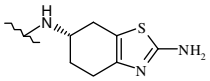
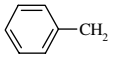
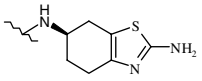
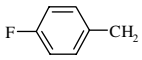
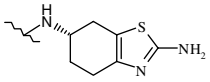
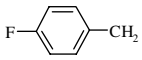


Compound	R^1	R^2	K_i (μM)			Selectivity thrombin/trypsin	2×APTT	PT	TT
			Thrombin	Trypsin	FXa		(μM)		
1			0.12	260	92	2166	36.5	41.4	6.6
2			0.17	>500	103	>2941	20.5	30.6	5.2
17		$H_3CCH_2CH_2$	3.8	ND	ND	ND	ND	ND	ND
18		$H_3CCH_2CH_2$	2.30	64.3	200	28	ND	ND	ND
19		$H_3CCH_2CH_2CH_2$	1.34	50.2	179	38	ND	ND	ND
20			0.100	>800	>300	>8000	28.7	57.7	5.1
21			0.149	258	314	1725	15.8	34	3.9
22			0.100	246	80	2460	31.3	56	12
23			0.102	>300	228	>2900	18.8	26.8	3.4
24			0.157	1923	69	1097	94	ND	93.8
25			0.157	>300	75	>1910	50	120	10.8
26			0.652	>200	81	>300	428	435	125
27			0.562	425	252	757	447	293	36.6
28			0.042	2.71	>200	65	2.4	ND	ND
29			0.022	8.06	131	201	22.6	ND	ND

APTT: concentration of inhibitor required to double the activated partial thromboplastin time in human plasma.
PT: concentration of inhibitor required to double the prothrombin time in human plasma.
TT: concentration of inhibitor required to double the thrombin time in human plasma.
ND: not determined.

Table 2. Inhibitory potencies of compounds **30–33**



Compound	R^1	R^2	K_i (μM)			Selectivity thrombin/trypsin	2×APTT (μM)
			Thrombin	Trypsin	FXa		
30			0.071	263	225.2	3704	9.52
31			1.16	294	370.6	253	ND
32			0.077	>700	>500	>9091	20.1
33			1.44	>700	176.4	>123	ND

K_m.[11c] The selectivity for thrombin over trypsin was compared on the basis of the ratios K_i(trypsin)/K_i (thrombin). In addition, the inhibitors were tested in standard clotting assays including the thrombin time (TT), activated partial thromboplastin time (2×APTT) and prothrombin time (PT) determinations, which were used as qualitative in vitro indicators of potential antithrombotic activity.

The in vitro inhibitory potencies of inhibitors **17–33** along with those of the lead compounds **1** and **2** are summarized in Tables 1 and 2. Starting from the lead structure **1** we synthesized analogues **17–19** with *n*-propyl and *n*-butyl group in P_3 part of the molecules to examine the contribution of different lipophilic residues in P_3 part to binding affinity. The resulting compounds turned out to be of one order of magnitude less active than **1**, clearly demonstrating the importance of the interactions of the benzyl group in **1** with the lipophilic distal pocket of thrombin. This finding was not a surprise because the X-ray crystal structure of compounds **1** and **2** complexed with human thrombin revealed a good fit of the benzyl group in the distal pocket of the enzyme. A methylene linker between the cyclohexane ring and the amino group in R^1 substituent of compound **17** was not beneficial for the inhibitory potency as compound **18** with amino group bound directly to the cyclohexane ring had a slightly better binding affinity than compound **17**. On the contrary, in the tetrahydroindazole type of inhibitors lacking the terminal amino group the methylene linker between the heterocycle and amino group, which allows substantial rotation freedom of the P_1 part is favorable for inhibitory activity against thrombin.[7]

In a further step the attention was turned to substituted benzyl moieties in P_3 part of the inhibitors. In order to improve the binding affinity and retain selectivity we synthesized a series of compounds with different benzylsulfonamido P_3 parts substituted on phenyl ring bearing 2-amino-4,5,6,7-tetrahydrothiazole arginine mimetic **3** or 4,5,6,7-tetrahydroindazole arginine mimetic **5** in P_1 part of the inhibitors. From Table 1, it is clearly seen that *p*-fluoro- and *p*-methylbenzylsulfonamido derivatives **20–23** showed the best K_i values and excellent selectivity. It is also evident that both arginine mimetics used in the study contribute equally to the binding affinity in respect of K_i values for thrombin, although when comparing 2×APTT values of inhibitors **20–23** it can be concluded that tetrahydroindazole inhibitors **21** and **23** show a slightly superior anticoagulant activity in vitro. Introduction of *o*-chloro-*p*-fluorobenzyl moiety in inhibitors **24** and **25** led to a slight decrease in binding affinity. Additionally, the 2×APTT values increased significantly comparing to values for **20–23**, which is probably due to increased lipophilicity. Incorporation of trifluoromethylbenzyl R^2 substituent in both series afforded compounds **26** and **27** with a 5-fold loss in thrombin inhibition compared to the lead compounds **1** and **2**.

In an effort to obtain further improvement of K_i values modifications were performed also in P_1 part of the inhibitors. In compounds **28** and **29** 3-amino-2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-6(2*H*)-ylamine (**6**) was introduced as a new arginine mimetic. This modification resulted in an improved affinity for thrombin with K_i values for inhibitors **28** and **29** of 42 and 22 nM, respectively. Although **29** displayed the best K_i value, in vitro clot inhibition (2×APTT) was better with the compound **28**, which is likely due to the differences in physicochemical properties of **28** and **29** (e.g., increased lipophilicity in compound **29** and consequently a higher binding to plasma proteins[3b]). The new arginine mimetic

is weakly basic (calculated pK_a is 3.17), which is crucial in an effort to produce orally bioavailable thrombin inhibitors. Unfortunately, compounds **28** and **29** showed also better affinity for trypsin than compounds **17**–**27**. However, as their affinity for thrombin is much higher than for trypsin they still demonstrate a moderate level of selectivity.

Based on the crystal structure of **1** complexed to human thrombin, evidencing a preferential binding of *R* enantiomer to the active site of thrombin, we prepared the single enantiomers **30**–**33** of the existing racemates **1** and **20**. The K_i values confirmed that the *R* enantiomer binds with approximately 20-fold higher affinity to the thrombin active site than the *S* enantiomer. The selectivity of the *R* enantiomers **30** and **32** was also increased in comparison to racemates **1** and **20**. Thus, compounds **30** and **32** are potent and selective thrombin inhibitors with K_i values of 71 nM and 77 nM, respectively. The 2×APTT values for compound **30** is significantly lower than for compound **33**, which again could be explained on the basis of a higher lipophilicity of the inhibitor **33**.

In conclusion, optimization of lead compounds **1** and **2** led to novel noncovalent thrombin inhibitors **20**, **23**, and **29** in racemic form and inhibitors **30**–**33** as single enantiomers, which all incorporate weakly basic heterobicyclic P_1-arginine side-chain mimetics. This study confirmed a preferential binding of *R* enantiomer of inhibitor **1** in the thrombin active site, which was earlier proposed on the basis of a crystal structure.

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