Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1203–1208

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Non-Covalent Thrombin Inhibitors Featuring P_3-Heterocycles with P_1-Monocyclic Arginine Surrogates

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Received 17 December 2001; accepted 1 February 2002

Abstract—Investigations on P_2–P_3-heterocyclic dipeptide surrogates directed towards identification of an orally bioavailable thrombin inhibitor led us to pursue novel classes of achiral, non-covalent P_1-arginine derivatives. The design, synthesis, and biological activity of inhibitors **NC1**–**NC30** that feature three classes of monocyclic P_1-arginine surrogates will be disclosed: (1) (hetero)aromatic amidines, amines and hydroxyamidines, (2) 2-aminopyrazines, and (3) 2-aminopyrimidines and 2-aminotetrahydropyrimidines.

Thrombosis, or excessive blood clotting, is a significant factor in cardiovascular and related diseases, accounting for nearly half of US and European deaths annually. Although thrombus formation normally occurs in blood vessels to repair minor internal injuries, major vessel injury or other pathophysiological conditions can cause the thrombus to become very large. Acute myocardial infarction (MI, heart attack), unstable angina (serious chest pain preceding MI), ischemic stroke, deep vein thrombosis (DVT), pulmonary embolism and disseminated intravascular coagulation (DIC) all result from such aberrant thrombosis.[1]

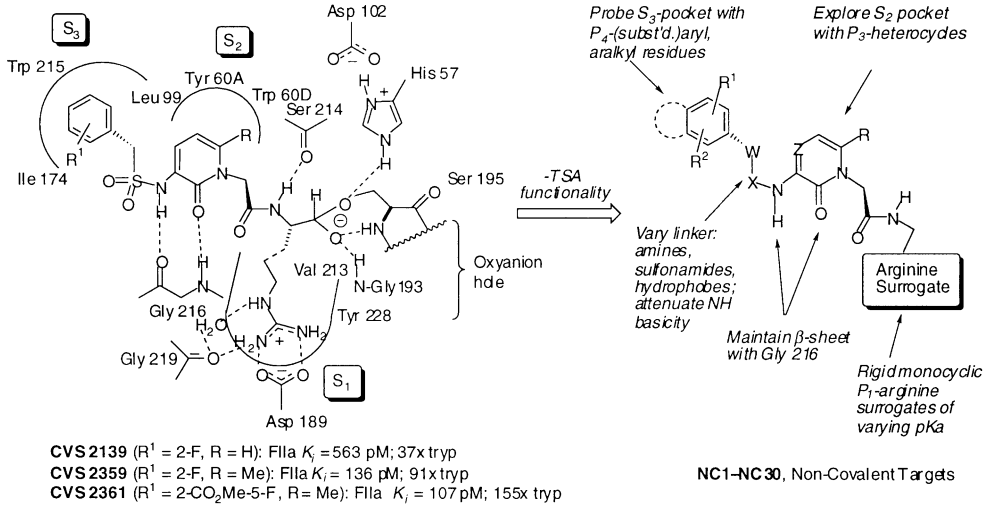

Figure 1. Design of P_3-heterocyclic thrombin inhibitors **NC1**–**NC30**.

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0960-894X/02/$ - see front matter
PII: S0960-894X(02)00129-4

Thrombin (fIIa), a multifunctional serine protease with trypsin-like specificity, plays a central role in thrombosis and hemostasis by regulating the blood coagulation cascade and platelet activation processes. Serving as the terminal enzyme of the cascade, thrombin cleaves the zymogen fibrinogen to fibrin, which ultimately combines with platelets and other components to form a blood clot.[2] Limited efficacy and side effects of established antithrombotics including heparin, warfarin and aspirin have provided the impetus for development of alternate drug classes.[3] Thrombin, along with procoagulant congeners factor Xa (fXa) and prothrombinase (PTase), are deemed as top targets for therapeutic intervention and continue to attract enormous attention in the pharmaceutical industry.[4] In this letter, we disclose the design, synthesis, and biological profiles of novel non-covalent P_3-heterocyclic thrombin inhibitors **NC1**–**NC30** that feature three different classes of P_1-monocyclic arginine mimics.[5]

Our investigations on covalent thrombin[6] and fXa[7] inhibitors incorporating P_3-pyridones, -benzazepinones, -lactams and related heterocyclic P_2–P_3 dipeptide surrogates resulted in the identification of several potent, selective and orally bioavailable inhibitors. Evolution of these scaffolds coupled with a desire to overcome the limitations imposed by the P_1-argininal functionality (high basicity of the guanidine moiety impacting OBA/PK profiles, chiral lability, scale-up issues) led us to pursue novel classes of non-covalent thrombin inhibitors.[8] SAR and modeling considerations from the prototypical P_3-pyridone–P_1-argininals **CVS 2139**, **CVS 2359**, and **CVS 2361** (Fig. 1)[9] along with reference inhibitors **L374,087**[10] and **L375,378**[11] (Table 1) suggested the novel, achiral heterocyclic targets **NC1**–**NC30**. Deletion of the covalent aldehyde handle (~5–6 kcal/mol binding energy) was expected a priori to result in decreased inhibitor potency, which necessitated the identification of alternate active–site interactions so as to restore the desired activity levels.[12]

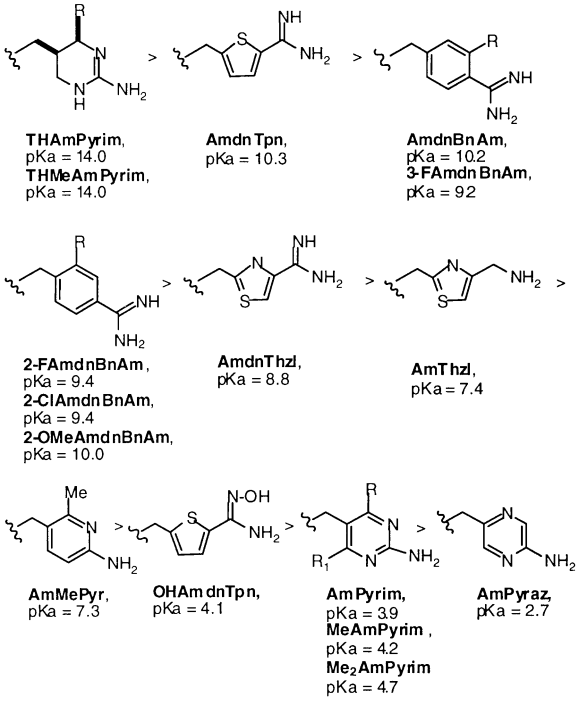


Figure 2. Acronyms and calculated pK_a values for representative rigidified P_1-arginine surrogates.

As summarized in Figure 1, our strategy was to explore the S_3 specificity pocket of thrombin with tethered, optimally substituted P_4-aromatics (increase potency, selectivity) and to survey S_1 with diverse P_1-monocyclic arginine surrogates[13] while maintaining the P_3-heterocycle (intrinsic potency via β-sheet H-bond with Gly216 plus interaction at 60's loop of S_2). Ideally, our rigid P_1-arginine surrogates would encompass a range of basicity (pK_a ~3–14), participate in hydrogen bonding and/or salt bridge interactions with Asp189, and benefit from hydrophobic interactions at the S_1 binding pocket.

Arginine mimics investigated are collected in Figure 2 in order of decreasing basicity and are identified by the indicated acronyms (see SAR, Table 1). The calculated pK_a values[14] for several prototypical P_1 arginine surrogates are listed and range from highly basic cyclic guanidines (THAmPyrim, THMeAmPyrim, calcd pK_a ~14) through the weakly basic aminopyrazine (AmPyraz, calcd pK_a ~2.7). The targets **NC1**–**NC30** are comprised by three novel sub-classes of P_1-arginine mimics: (1) (hetero)aromatic amidines, amines and hydroxyamidines, (2) 2-aminopyrazines, and (3) 2-aminopyrimidines and 2-aminotetrahydropyrimidines. Several potent, selective, and orally bioavailable thrombin inhibitors resulted from this exercise.

Synthetic routes to the P_1-arylamidine precursors 4-amidinobenzylamine, 2-fluoro-4-amidinobenzylamine, 2-azidomethyl-5-cyanothiophene **3**, 2-hydroxyamidinothiophene-5-methylamine and 2-amidinothiophene-5-methylamine were recently disclosed.[8] Preparation of 2-chloro-4-amidinobenzylamine paralleled the route to the 2-fluoro-analogue. Scheme 1 summarizes our routes to the (hetero)aromatic P_1-precursors **2**, **4**, **5a**–**c**, and **6a**,**b**.[15] Using classical aromatic substitution protocols, *p*-tolunitrile was elaborated over five steps to the substituted benzyl bromide **1**, which in turn led to the protected amidine precursor **2** after four additional steps. Azide **3**[8] was converted to the protected silyl ether **4** in three steps. Three commercially available 2-aminopyrimidines underwent nucleophilic aromatic substitution with cyanide under thermal conditions. The resultant 4-cyanopyrimidines were treated with Boc_2O/DMAP and then hydrogenated to provide the bis-*N*-Boc-protected amines **5a**–**c** in satisfactory overall yields. Further hydrogenation of **5a**,**b** in the presence of stoichiometric HCl effected smooth reduction of the heteroaromatic ring and produced the corresponding cyclic guanidines (tetrahydropyrimidines) **6a**,**b** in very high yield.

Scheme 2 outlines general approaches to the advanced heteroaromatic intermediates **8**, **10**, and **12**. Curtius rearrangement of commercial 5-methyl-2-pyrazinecarboxylic acid followed by radical bromination afforded **7**. Azide displacement of **7** and reduction delivered protected pyrazine **8**. Thiazole **9** was obtained from bromopyruvate and thioacetamide components via a four-step

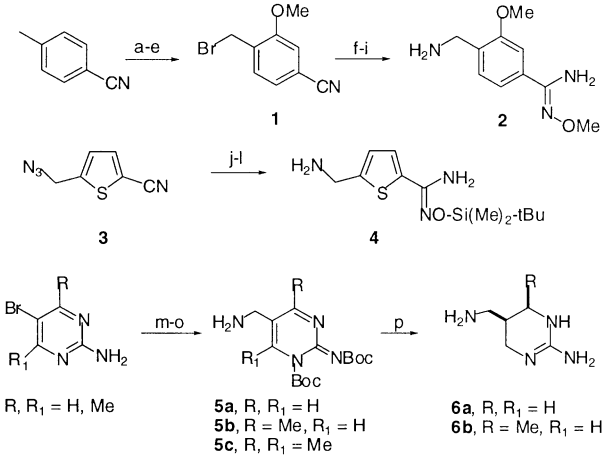
Table 1. In vitro and in vivo activity of non-covalent P_3-heterocyclic–P_1-arginine surrogate-type thrombin inhibitors **NC1–NC30**

Compd	P_4	P_3	P_1	≈K_i Values (nM)[a]			Dog PK dosed @ 1 mg/kg		
				K_i FIIa	K_i FXa	K_i Trypn	AUC (μg* min/mL)	C_{max} (μg/mL)	$t_{1/2}$ (min)
Reference compounds:									
CVS 2139	(2F)$BnSO_2$	Pdn	Arg-al	0.56	192.0	20.8	198	2.0	50
CVS2359	(2F)$BnSO_2$	Pdn(6Me)	Arg-al	0.14	674.0	12.4			
CVS2361	(2CO2Me,5F)$BnSO_2$	Pdn(6Me)	Arg-al	0.10	1810	16.6			
L374,087	$BnSO_2$	Pdn(6Me)	AmMePyr	0.68	Inactive	Inactive	160±28	0.79±0.12	107±7
L375,378	3PhEtAm	Pdn[4aza](6Me)	AmMePyr	1.0	Inactive	Inactive	275±17	0.90±0.05	199±11
New non-covalent targets:									
NC1	(3OMe)$PhSO_2$	Pdn	AmdnBnAm	5.3	152.7	18.7	9.9±4.5	0.14±0.05	53±6
NC2	(3OMe)$PhSO_2$	Pdn	2ClAmdnBnAm	20.8	Inactive	76.5		No test	
NC3	(3OMe)$PhSO_2$	Pdn	3-FAmdnBnAm	6.0	248.6	31.3		Not absorbed	
NC4	(3OMe)$PhSO_2$	Pdn	2-OMeAmdn BnAm	1.6	76.8	11.9	1.3±0.5	0.4±0.01	62±25
NC5	(3OMe)$PhSO_2$	Pdn	AmdnThzl	5.9	178.6	>168		No test	
NC6	$BnSO_2$	Pdn(6Me)	AmdnBnAm	0.37	Inactive	49.3		No test	
NC7	$BnSO_2$	Pdn(6Me)	3-FAmdnBnAm	3.6	Inactive	Inactive		Not absorbed	
NC8	$BnSO_2$	Pdn(6Me)	AmdnTpn	0.10	96.4	13.6	1.1±0.5	0.4±0.01	ND
NC9	$BnSO_2$	Pdn(6Me)	AmThzl	136.0	>338	>168		No test	
NC10	PhEtAm	Pdn[4aza](6Me)	AmdnBnAm	0.57	Inactive	19.7	2.3±1.0	0.6±0.01	ND
NC11	PhEtAm	Pdn[4aza](6Me)	AmdnTpn	0.12	Inactive	4.4		No test	
NC12	PhEtAm	Pdn[4aza](6Me)	OHAmdnTpn	30.8	Inactive	Inactive	9.2±2.0	0.29±0.04	38±26
NC13	PhEtAm	Pdn[4aza](6Me)	OHAmdnTpn-TBDMS	13.2	Inactive	Inactive		No test	
NC14	$BnSO_2$	Pdn(6Me)	AmPyraz	157.9	Inactive	Inactive	176±29	0.70±0.08	157±4
NC15	PhEtAm	Pdn[4aza](6Me)	AmPyraz	276.2	Inactive	Inactive	293±36	2.01±0.13	84±10.6
NC16	Ph(2,2-diF)EtAm	Pdn[4aza](6Me)	AmPyraz	9.8	Inactive	Inactive	69±10	0.88±0.07	43±5
NC17	(4Cl)Ph(2,2-cycloBu)EtAm	Pdn[4aza](6Me)	AmPyraz	5.5	Inactive	Inactive	104±50	0.83±0.15	96±22
NC18	(4F)Ph(2,2-diF)EtAm	Pdn[4aza](6Me)	AmPyraz	5.9	Inactive	Inactive	55±10	0.81±0.18	35±3
NC19	$BnSO_2$	Pdn(6Me)	Me_2AmPyrim	281.0	Inactive	Inactive	43±7	0.24±0.02	112±7
NC20	$BnSO_2$	Pdn(6Me)	AmPyrim	461.9	Inactive	Inactive	390±75	1.57±0.26	139±22
NC21	PhEtAm	Pdn[4aza](6Me)	AmPyrim	357.1	Inactive	Inactive	801±141	1.95±0.16	248±39
NC22	$BnSO_2$	Pdn(6Me)	MeAmPyrim	85.2	Inactive	Inactive	97±6	0.6±0.1	74±12
NC23	Benzodioxan-SO_2	Pdn(6Me)	MeAmPyrim	103.2	Inactive	Inactive		Not absorbed	
NC24	PhEtAm	Pdn[4aza](6Me)	MeAmPyrim	196.8	Inactive	Inactive	387±90	1.2±0.2	240±75
NC25	2,3-Dihydro-benzofuran-5-EtAm	Pdn[4aza](6Me)	MeAmPyrim	323.8	Inactive	Inactive		Poor absorption	
NC26	Ph(2,2-diF)EtAm	Pdn[4aza](6Me)	MeAmPyrim	140.8	Inactive	Inactive		No test	
NC27	$BnSO_2$	Pdn(6Me)	THAmPyrim	1.0	Inactive	Inactive		Not absorbed @ 0.6 mg/kg	
NC28	PhEtAm	Pdn[4aza](6Me)	THAmPyrim	1.9	Inactive	Inactive		Not absorbed @ 0.4 mg/kg	
NC29	$BnSO_2$	Pdn(6Me)	THMeAmPyrim	1.1	Inactive	Inactive		No test	
NC30	PhEtAm	Pdn[4aza](6Me)	THMeAmPyrim	3.2	Inactive	Inactive		No test	

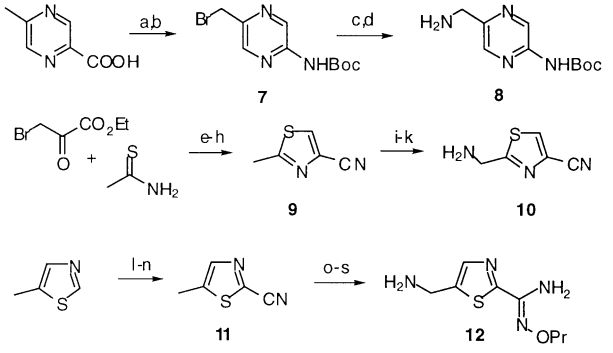
[a]Inhibition constants (K_i) of compounds **1a–w** are derived from the corresponding IC_{50} values necessary to inhibit human thrombin (FIIa), factor Xa (FXa) and trypsin cleavage of the chromogenic substrates described in ref 8 by 50%. Reported values for each compound are from a single IC_{50} determination that confirmed the initial range values.

process and was further functionalized to the P_1-amine **10** in three additional steps. The regioisomeric thiazole **11** was secured in three steps from commercial 5-methylthiazole. Subjection of intermediate **11** to a five-step sequence provided the requisite thiazole methylamine **12** in good overall yield.

Construction of the advanced P_4-sulfonamido-/aralkyl-amino–P_3-heterocyclic–P_2-acetic acid intermediates **14**, **16** and **18** is summarized in Scheme 3. Multigram quantities of P_3-pyridone intermediates **14** and **16** were secured via modification of our recent methods.[6f,9]



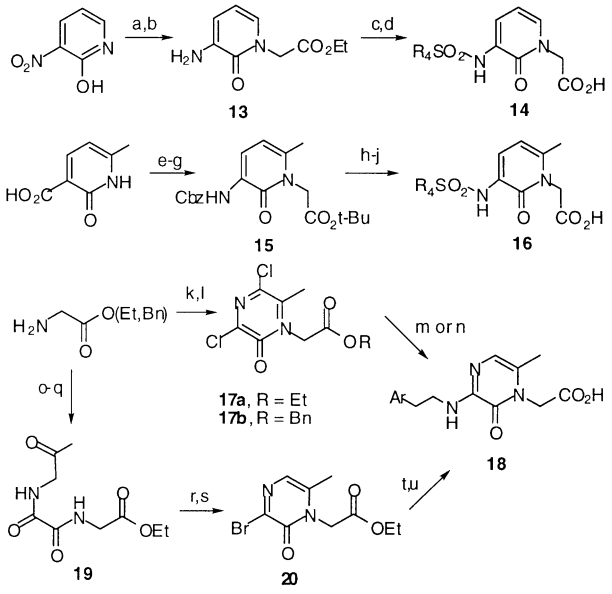
Scheme 1. (Hetero)aromatic P_1-arginine mimic precursors. Reagents and conditions: (a) HNO_3, −10 °C, 30%; (b) Pd/C, H_2 (1 atm), EtOH, 95%; (c) HNO_2, 0–100 °C, 48%; (d) NaH, MeI, DMF, 95%; (e) NBS, CCl_4, 80 °C, 48%; (f) NaN_3, DMF, rt, 20 h, 90%; (g) $HONH_2$·HCl, NMM, MeOH, rt to reflux, 55%; (h) MeI, Cs_2CO_3, DMF, 20 h, 72%; (i) Ph_3P, THF, H_2O, rt, 20 h, 73%; (j) H_2NOH·HCl, NMM, MeOH, rt, 65%; (k) TBDMSCl, Et_3N, CH_2Cl_2, ~quant; (l) 1,3-propanedithiol, Et_3N, MeOH, rt, 18 h, 21%; (m) CuCN, DMF, reflux, 18–20 h, 64% quant; (n) Boc_2O, DMAP, THF, rt, 2 h, 60–77%; (o) H_2, Pd/C, HCl (cat.), EtOH, 40–50 psi, 16 h, 43–93%; (p) H_2, Pd/C, 1 N HCl, EtOH, THF, 20 psi, 16 h, 94% ~quant.



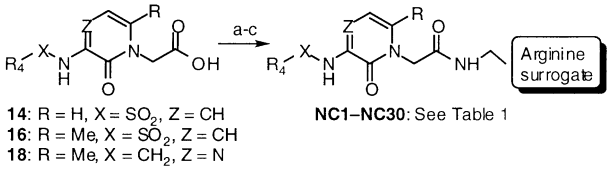
Scheme 2. Synthesis of heteroaromatic P_1-arginine mimics. Reagents and conditions: (a) DPPA, Et_3N, dioxane, 100 °C; *t*-BuOH, 25 h, 70%; (b) NBS, $(PhCO_2)_2$, CCl_4, $NaHCO_3$, reflux, 54%; (c) NaN_3, DMF, rt, 5 h, 98%; (d) H_2, Pd/C, 1 atm, MeOH, 98%; (e) Et_3N, CH_3CN, rt –90 °C, 1 h; (f) CSA (cat.), toluene, reflux, Dean–Stark, -H_2O, 12 h, 88% for two steps; (g) NH_4OH, MeOH, rt, 16 h, 89%; (h) $SOCl_2$, NMM, DMF, 0 °C rt, 5 h, 56%; (i) NBS, CCl_4, 80 °C, 39%; (j) NaN_3, DMF, rt, 20 h; (k) Ph_3P, THF, H_2O, rt, 20 h, 80%; (l) *n*-BuLi, THF, −78 °C, 30 min; DMF, −78 °C to rt; (m) $HONH_2$·HCl, NMM, MeOH, rt, 22 h, 91% over two steps; (n) CDI, CH_2Cl_2, rt, 1 h, 92%; (o) NBS, CCl_4, 80 °C, 48%; (p) NaN_3, DMF, rt, 20 h, 90%; (q) $HONH_2$·HCl, NMM, MeOH, rt, 55%; (r) *n*-PrI, Cs_2CO_3, DMF, 50 °C, 20 h, 42%; (s) Ph_3P, THF, H_2O, rt, 20 h, 73%.

P_3-pyrazinone intermediate **18** was prepared by two complimentary multistep routes using modifications of literature protocols.[11a,b]

The final coupling and elaboration reactions between **14**, **16**, and **18** and the various P_1-arginine precursors are outlined in Scheme 4. Coupling reactions generally employed EDC, HOBt or HOAt with added Et_3N or NMM bases at ambient temperature in dry acetonitrile, THF, or DMF solvents or mixtures thereof. In cases where such couplings afforded P_1-nitrile intermediates, further reaction with hydroxylamine installed the appropriate hydroxyamidine functionality. Optional final deprotections were effected by either TFA-cleavage



Scheme 3. Assembly of P_2–P_3 heterocyclic acetic acids. Reagents and conditions: (a) $LiN(TMS)_2$, THF, $BrCH_2CO_2Et$, 0 °C to rt; (b) H_2, Pd/C, 16 h; (c) R_4SO_2Cl, CH_3CN, collidine, 0 °C to rt; (d) LiOH, MeOH, H_2O, 0 °C to rt, ~70–85% over four steps; (e) $BrCH_2CO_2t$-Bu, K_2CO_3, DMF, 75%; (f) LiOH, EtOH, ~quant; (g) DPPA, Et_3N, dioxane, reflux; BnOH, reflux, 78%; (h) H_2, Pd/C, EtOH, 82%; (i) R_4SO_2Cl, NMM or collidine, 60–90%; (j) TFA, CH_2Cl_2, 0 °C to rt, 95% quant; (k) TMSCN, MeCHO, Et_3N, CH_2Cl_2, rt, 18 h, 87%; (l) $(COCl)_2$, *o*-DCB, 100 °C, 18 h, 82%; (m) for R = Et: 1. $Ar(CH_2)_2NH_2$, solvent; 2. LiOH, THF, H_2O; 3. H_2, Pd/C, 65–87% for 3 steps; (n) for R = Bn: 1. $Ar(CH_2)_2NH_2$, dioxane; 2. $Pd(OH)_2$/C, NH_4O_2CH, ~60–80% over two steps; (o) diethyl oxalate, Et_3N, EtOH, 50 °C, 91%; (p) amino-2-propanol, EtOH, rt to reflux, 97%; (q) $RuCl_3$, H_2O, $NaBrO_3$, 62%; (r) $(CF_3CO)_2O$, 80 °C; (s) $POBr_3$, reflux; NH_4OH, ~76% for 2 steps; (t) $Ar(CH_2)_2NH_2$, dioxane, Et_3N, 65–100 °C, 12–48 h; or toluene, reflux, ~12 h; 90–94%; (u) LiOH, H_2O, THF or EtOH, rt, 12–40 h, 60–88% over 2 steps.



Scheme 4. Coupling and elaboration to targets **NC1**–**NC30**. Reagents and conditions: (a) couple protected P_1-amine precursors **2**, **4**, **5a**–**c**, **6a**,**b**, **8**, **10**, and **12**: EDC, HOBt or HOAt, Et_3N or NMM, CH_3CN, THF, or DMF; rt, 12–15 h, 27%–quant; (b) for nitrile intermediates: NH_2OH·HCl, NMM, MeOH, rt to reflux, 31–80%; (c) optional deprotection of P_1-group: for **NC1**–**11**: Zn, HOAc, H_2O, RP-HPLC, 20–70%; for **NC14**–**26**: TFA, CH_2Cl_2, 0 °C to rt, RP-HPLC, 33–90%.

or Zn–HOAc reduction and were followed by RP-HPLC purification to deliver the targets **NC1**–**NC30**.

The in vitro and in vivo biological activity for targets **NC1**–**NC30** along with the standards **CVS 2139**, **CVS 2359**, **CVS 2361** ($F \sim 37$–70%, absolute oral bioavailability in dogs),[9] **L374**,**087**[10] and **L375**,**378**[11] is summarized in Table 1 [Pdn(6Me) = 6-methylpyridone and Pdn[4aza](6Me) = 6-methylpyrazinone]. In vivo pharmacokinetic (PK) data from cassette oral dosing studies in fasted dogs at 1 mg/kg is included for reference compounds and for several new targets. **L374**,**087** and **L375**,**378** demonstrated impressive PK profiles in dogs when dosed po at 1 mg/kg due to the presence of the well-engineered P_1-AmMePyr moiety (efficacious in $FeCl_3$ thrombosis model, $F \sim 44$–91%).[10,11] Moderate to excellent levels of thrombin inhibition were observed in vitro, with K_i's = 0.1–141 nM for our top candidates. All new targets were selective against the thrombolytic enzymes plasmin, tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) as well as activated protein C (PCa). Most new targets demonstrated moderate to excellent levels of selectivity against the digestive enzyme trypsin (trypn).

In general, in vitro potency decreased as a function of the P_1-arginine surrogate as follows: AmdnTpn ($pK_a = 10.3$) > THAmPyrim ($pK_a = 14.0$) ≥ 2/3-substd AmdnBnAm ($pK_a = 9.4$–10.2) > OHAmdnTpn ($pK_a = 4.1$) > AmdnThzl ($pK_a = 8.8$) > AmPyraz ($pK_a = 2.7$) > AmPyrim ($pK_a = 3.9$–4.7). In our series, oral PK ranking was essentially opposite to the potency ranking above, decreasing as a function of the P_1-arginine surrogate in the following order: AmPyrim ($pK_a = 3.9$–4.7) > AmPyraz ($pK_a = 2.7$) > OHAmdnTpn ($pK_a = 4.1$) ≥ 2/3-substd AmdnBnAm ($pK_a = 9.4$–10.2) > THAmPyrim ($pK_a = 14.0$) > AmdnTpn ($pK_a = 10.3$). Targets of greatest interest in terms of activity, selectivity, and/or PK profiles include **NC6**, **NC8**, **NC10**, **NC11** (subnanomolar FIIa K_i's); **NC5**, **NC7**, **NC12**, **NC13**, **NC16**–**18**, and **NC27**–**30** (high potency, excellent selectivity); **NC14**–**15**, **NC17**, **NC19**–**21**, and **NC24** (moderate potency, excellent selectivity, good to excellent PK profile). Notably, the P_1-aminopyrimidine derivatives **NC21** and **NC24**, albeit only moderately potent as thrombin inhibitors, showed impressive PK profiles in terms of conferring maximal AUC, C_{max} and $t_{1/2}$ values. Further details of in vivo oral bioavailability and efficacy will be reported elsewhere.

Potency and selectivity in the **NC1**–**NC30** series result from key binding interactions at each of the S_1–S_3 specificity pockets in the thrombin active site, including β-sheet (Gly216), hydrophobic, van der Waals and aromatic edge-to-face interactions (S_3 pocket plus 60 loop in S_2 pocket, Fig. 1). Binding to thrombin occurs in a canonical substrate-like mode, with the rigid P_1-arginine surrogates participating in salt bridge and/or water-mediated hydrogen-bonding interactions with Asp189 at the S_1 specificity pocket.[6,12] Other putative interactions of the P_1 residue at S_1 include van der Waals interaction with Val213 and hydrogen bonds with Gly219, Gly193 and Tyr228.[4,10,11] OBA and overall PK efficacy appears to be governed by a number of factors including choice of P_4-hydrophobe, P_3-heterocycle and especially the P_1-arginine mimic. Arginine surrogates with calculated pK_a's ~2.7–7.4 appear to confer the best OBA, however optimal inhibitor potency results from incorporation of the more highly basic functions.

In conclusion, a structure-based design strategy, which hybridized the prototypical P_3-pyridone P_1-argininals **CVS 2139**, **CVS 2359** and **CVS 2361** with **L374**,**087** and **L375**,**378**, was employed to generate a novel family of non-covalent thrombin inhibitors **NC1**–**NC30** featuring P_3-heterocyclic P_1-monocyclic arginine surrogates. Our series probed the S_3 specificity pocket with eight P_4-residues and the S_1 pocket with 15 rigid arginine surrogates of varying size, shape and basicity, while maintaining the intrinsically potent P_3-pyridone and pyrazinone pharmacophores at the S_2 pocket. Potent, selective and orally bioavailable thrombin inhibitors were identified which serve as attractive leads for further SAR/PK development. Numerous active-site interactions and optimal physical properties (net pK_a, log P) are deemed as critical factors for conferring high potency, specificity, and useful PK properties in this class of inhibitors.

Acknowledgements

We gratefully acknowledge L. Truong and P. W. Bergum for in vitro pharmacological studies, and T. K. Brunck and S. Y. Tamura for stimulating discussions regarding antithrombotic inhibitor targets.

References and Notes

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15. All new compounds were characterized by full spectroscopic (NMR, IR, MS) data. Yields refer to spectroscopically and chromatographically homogeneous ($\geqslant 95\%$ by ^{1}H NMR, HPLC, TLC) materials.