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RATIONAL DESIGN AND SYNTHESIS OF A NOVEL, SELECTIVE CLASS OF THROMBIN INHIBITORS: P_1-ARGININAL DERIVATIVES INCORPORATING P_3-P_4 QUATERNARY LACTAM DIPEPTIDE SURROGATES[1]

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Abstract: SAR and molecular modeling investigations on the potent and selective thrombin inhibitor **1b** (CVS 1578) and related serine protease inhibitors led to the design of series **2a–g**, featuring quaternary α-amino-α-benzyl-lactam scaffolds that serve as novel P_3-P_4 dipeptide mimics. The design, synthesis, and biological activity of these targets are presented. © 1997 Elsevier Science Ltd.

Thrombin (FIIa) and Factor Xa (FXa) are trypsin-like serine proteases involved in the initiation and propagation of the coagulation response to vascular injury. They play key roles in the regulation of normal hemostasis and abnormal intravascular thrombus development. As evidenced by current literature activity, several laboratories are attempting to develop novel classes of safe, efficacious, and selective antithrombotic drugs.[2,3] The P_3–P_4 lactam sulfonamide **1b** (CVS 1578, n = 1, Figure 1) recently emerged from our laboratories as a representative of a new class of potent transition-state thrombin inhibitors that demonstrated good oral bioavailability and selectivity profiles.[4] Improved thrombin binding affinity relative to previous peptidic inhibitors led to enhanced selectivity against trypsin and was achieved in part by exploiting a unique lactam-S_2 interaction with thrombin's 60 insertion loop. X-ray structural information from the **1b**–thrombin complex combined with evolving SAR information led us to design a new series of novel P_1-argininals **2a–g**, which feature P_3–P_4 quaternary lactam moieties. Such quaternary α-amino-α-benzyl-lactam scaffolds serve as novel D-Phe-Pro dipeptide mimics.[5] The design, synthesis, and biological activity of these targets are presented herein.

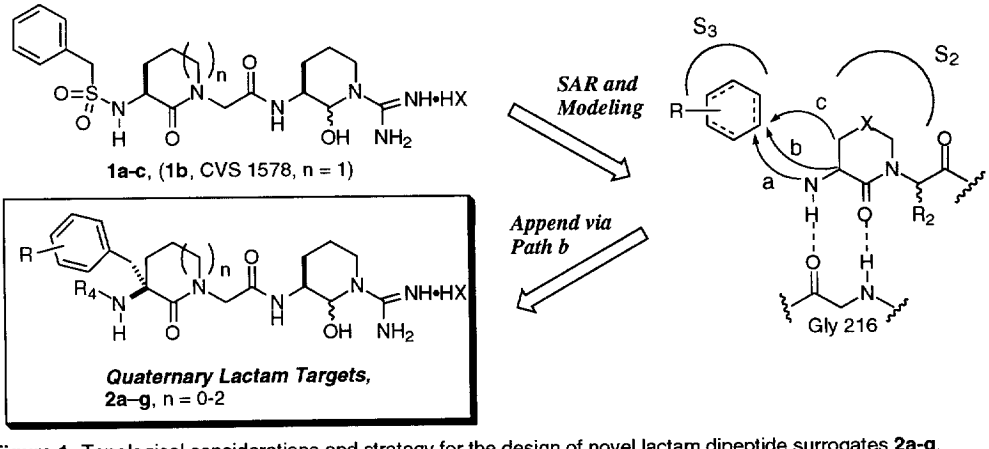


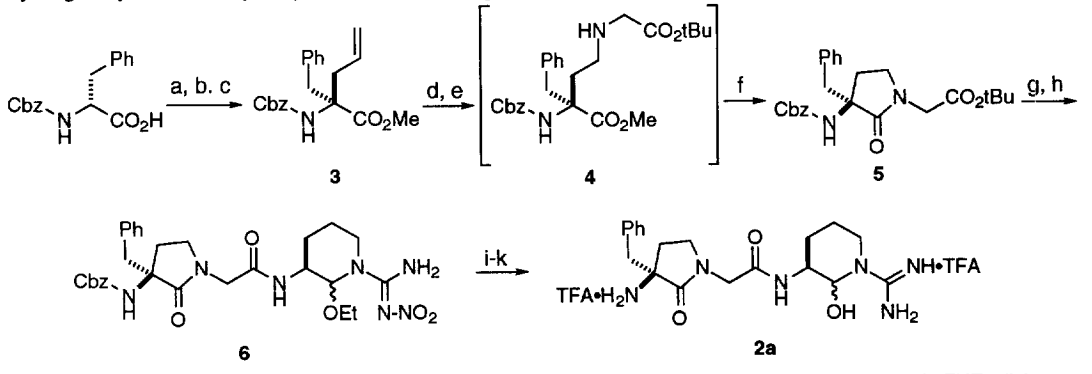
Figure 1: Topological considerations and strategy for the design of novel lactam dipeptide surrogates **2a-g**. Curved arrows denote tethering modes via paths a-c; X = O, S, $(CH_2)_n$.

Modeling and Chemistry

Design and synthesis of peptidomimetic drug candidates that feature lactam,[4] pyridone, and related heterocyclic-based[6] scaffolds is currently an area of active investigation. The backbone structures of these interesting templates maintain or restrict biologically relevant dihedral angle, conformational, and stereochemical information derived from a parent peptide array. Furthermore, they can effectively mimic type II' β-turn conformations and incorporate critical hydrogen bond donor and acceptor elements such as amide NH and carbonyl groups. Scaffolds such as these can therefore possess useful structural features that help stabilize a potential inhibitor into the active site of a targeted enzyme.

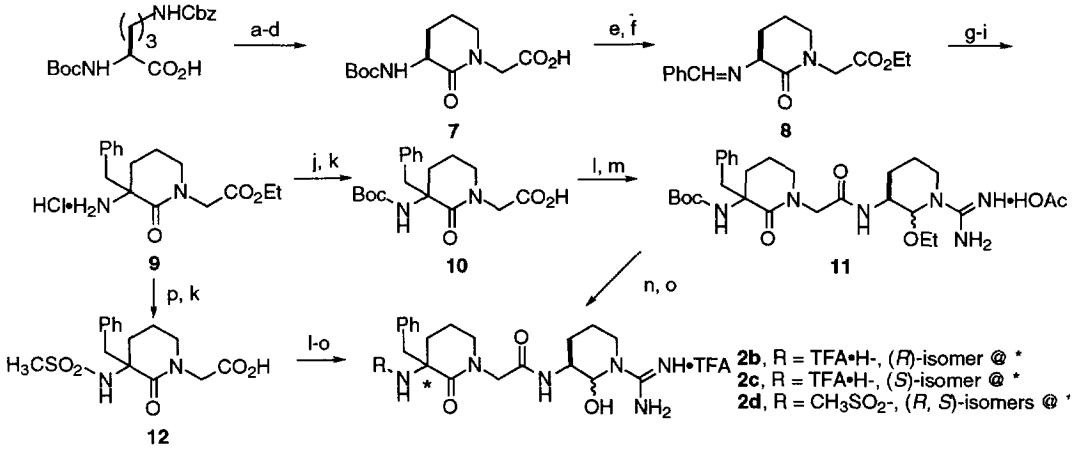
As summarized in Figure 1, molecular modeling considerations on the lead compound **1b** (FIIa IC_{50} = 6.2 nM) and related homologs suggested three potentially attractive tethering modes between the P_3 lactam residue and the P_4 aromatic ring. For retention of potency and selectivity in this general family of inhibitors, it is essential to maintain both β-antiparallel hydrogen bonds with the Gly 216 residue at the S_2 subsite.[4a,c] Trypsin selectivity is maintained via the lactam-S_2 interaction with thrombin's 60 insertion loop. Tethering via path "a" can be accomplished employing a variety of linkers, preferably of a tetrahedral nature. Exploring path "b" led to the design of the subject series **2a–g** which feature quaternary centers.[4b] Further considerations of the path "b" linkage suggested that although a range of sp^3-derived tethers should provide active inhibitors, an α-benzyl substituent would provide optimal edge to face interactions with Trp215 at the S_3-binding site. Appendage of P_4 moieties via path "c" has been successfully implemented and will form the basis of a forthcoming communication.[6b]

The 5-membered lactam target **2a** was obtained as outlined in Scheme 1.[7] Asymmetric alkylation of the chiral *cis*-oxazolidine derived from Cbz-d-Phe[8] followed by methanolysis provided the chiral quaternary ester **3** in good overall yield and with 24:1 diastereoselectivity. Ozonolysis and reductive amination[9] generated an intermediate amino-diester **4**, which underwent a smooth thermally-induced intramolecular ring closure to afford the 5-membered α-(*R*)-quaternary lactam **5** in 75% overall yield. Acid-catalyzed *t*-butyl ester cleavage, and EDC-HOBt mediated coupling with a convenient protected argininal precursor[10] delivered the advanced intermediate **6**. Hydrogenolysis, acidic hydrolysis, and RP HPLC purification produced the first target **2a**.



Scheme 1. *Reagents and conditions:* (a) $PhCH(OMe)_2$, BF_3•Et_2O, Et_2O, -78 °C to rt, 62%; (b) KHMDS, THF, allyl bromide, -78 °C; HOAc, -78 °C to rt, 89% (24:1); (c) NaOMe, MeOH, rt to reflux, 3 h, 93%-quant.; (d) O_3, CH_2Cl_2, -78 °C; Ph_3P, -78 °C to rt, ~quant; (e) HCl•Gly-Ot-Bu, Et_3N, $Na(OAc)_3BH$, 1,2-dichloroethane, 0 °C to rt, 8 h; (f) reflux, 10 h, 75%; (g) TFA,CH_2Cl_2, 0 °C to rt, 94%; (h) HCl•Arg(NO_2)-H Et aminal, EDC, HOBt, DIPEA, CH_3CN, rt, 45%; (i) H_2, Pd/C, EtOH, HOAc, H_2O, 55 psi, ~quant; (j) 3 N HCl, rt, 3 h; (k) RP HPLC purification, 17-34%.

Synthesis of the 6-membered targets **2b–d** are outlined in Scheme 2. Following a variation of Friedinger's protocol,[11] N-α-Boc-N-δ-Cbz-l-Ornithine was elaborated in four steps to the corresponding 2-piperidone intermediate **7**. Simultaneous esterification and deprotection followed by Schiff base formation produced **8**, which underwent a regioselective alkylation to deliver a racemic quaternary α-benzyllactam in excellent overall yield. Mild aqueous acidic hydrolysis and re-esterification of the partially (ca 3-5%) cleaved carboxylic acid moiety provided the advanced common intermediate **9**. α-Amino group protection as the N-Boc derivative and ester hydrolysis afforded intermediate carboxylic acid **10**. Coupling with the P_1-argininal precursor, hydrogenolysis, and final mild acid hydrolysis afforded crude **2b,c** as a ca. 1:1 mixture of diastereomers. Separation by preparative RP-HPLC, although quite tedious due to the existence of three distinct interconverting P_1-argininal forms[4a] for each diastereomer, provided pure samples of the biologically active



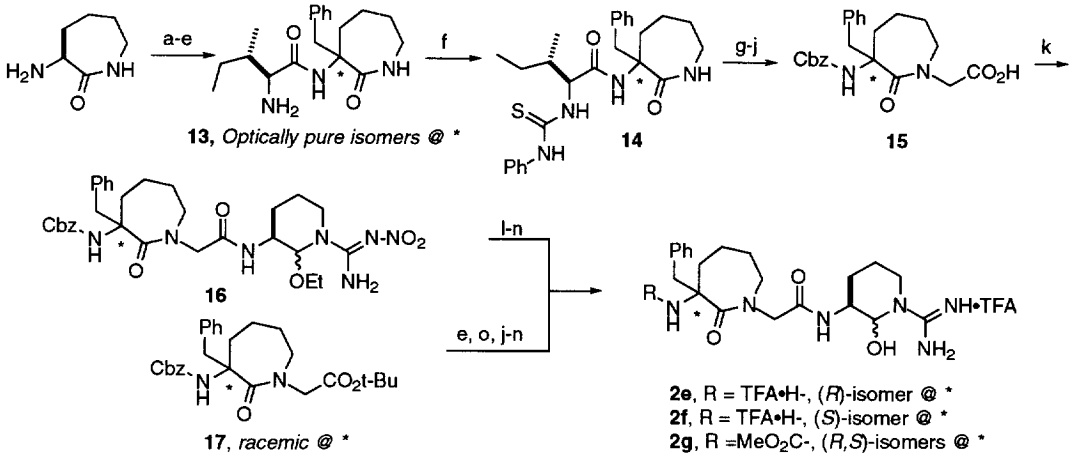
Scheme 2. *Reagents and conditions:* (a) H_2, Pd/C, 35 psi, MeOH, H_2O, HOAc, 2.5 h; (b) $OHCCO_2H$, rt, 20 h; (c) H_2, Pd/C, 40 psi, 37 h; (d) DMF, 50-60 °C, 2.5 h; 67% overall for 4 steps; (e) EtOH, HCl, 0 °C to rt, ~quant ; (f) PhCHO, Et_3N, $MgSO_4$, CH_2Cl_2, 0 °C to rt, 89%; (g) KOtBu, THF, BnBr, ~rt, 89%; (h)1 N HCl, rt, 2-4 h; (i) EtOH, HCl, 0 °C to rt, 96%; (j) Boc_2O, $NaHCO_3$, THF, H_2O, 77%; (k) LiOH, EtOH, H_2O, 0 °C to rt; Dowex H^+, 87-98%; (l) HCl•Arg(NO_2)-H Et aminal, EDC, HOBt, DIPEA, CH_3CN, rt, 58-67%; (m) H_2, Pd/C, 60 psi ~quant; (n) 3N HCl, rt, 3 h; (o) HPLC purification and diastereomer separation, **2b,c**: 32%;**2d**: 56% (p) MsCl, Et_3N, CH_3CN, 0 °C to rt, 91%.

α-(*R*)-quaternary 6-membered lactam **2b** as well as the less interesting α-(*S*)-quaternary 6-membered lactam **2c**. The lactam chirality assignments were determined by modeling considerations of the spacial requirements of inhibitor binding into the S_3 thrombin subsite and by the relative biological activity profiles. In turn, the observed activity in this new quaternary lactam series correlated well with results we obtained in our initial studies where both (*R*)- and (*S*)-P_3-P_4 lactam sulfonamide thrombin inhibitors were compared by in vitro evaluation.[4,12]

Treatment of the intermediate **9** with mesyl chloride and ester hydrolysis produced acid **12**. Processing via the three step procedure described above afforded target **2d** as a ca 1,1 mixture of α-(*R,S*)-lactam diastereomers in good overall yield.

Synthesis of the 7-membered targets **2e–g** are outlined in Scheme 3. Commercially available l-α-amino-ε-caprolactam was alkylated with benzyl bromide via the benzylidene Schiff base intermediate and hydrolyzed to give a racemic quaternary α-amino-lactam•HCl salt in multigram quantities. Resolution of the intermediate via

formation and separation of suitable diastereomeric pairs was investigated. Coupling of this sterically encumbered amine with α-N-protected amino acids by conventional protocols proceeded slowly and in poor yields. However, application of the EDC/HOAt system[13] generally delivered good yields of products. After preparing a range of diastereomer derivatives, we found the Cbz-(*S*)-Ile-(*R,S*)-lactam diastereomer pairs to be readily separable by both flash chromatography and HPLC. The separated diastereomer pairs were then each processed as shown



Scheme 3. *Reagents and conditions:* (a) PhCHO, benzene, reflux, -H_2O, quant; (b) $LiN(TMS)_2$, THF, rt, 2 h; BnBr, 0 °C to rt, 22 h, 61-70% recryst'd; (c) 1 N HCl, rt, 5 h, ~quant; (d) Cbz-Ile, EDC, HOAt, DIEA, rt, flash column diastereomer separation, ~1:1 ratio, 65%; (e) H_2, Pd/C, EtOH 35 psi, 95%-quant; (f) PhNCS, THF, rt to reflux, 2 h, ~quant; (g) TFA, CH_2Cl_2, reflux, 2 h, 83-100%; (h) Cbz-OSu, $NaHCO_3$, THF, H_2O, 0 °C to rt, 79-85%; (i) LiHMDS, THF, rt, 30 min, $BrCH_2CO_2tBu$, 0 °C to rt, NH_4Cl, 59-67%; (j) TFA, CH_2Cl_2, 0 °C to rt, ~quant; (k) HCl•Arg(NO_2)-H Et aminal, EDC, HOBt, DIPEA, CH_3CN, rt, 35-55% (*R*-isomer), 68% (*S*-isomer); 55% (*R,S*)-isomer; (l) H_2, Pd/C, EtOH, HOAc, H_2O, 40-55 psi, ~quant (*R*-isomer); ion-xchg chrom., 69% (*S*-isomer); ~quant (*R,S*)-isomer; (m) 3 N HCl, rt, 3 hr; (n) RP HPLC purification, **2e**: 36%; **2f**: 58%; **2g**: 42%; (o) MeOCOCl, Et_3N, CH_3CN, 0 °C to rt, 66%.

in Scheme 3. Hydrogenolysis afforded the optically pure intermediates **13**, which upon conversion to the phenyl thiourea **14** underwent efficient acid-catalyzed Edman degradation.[14] Amino group reprotection, alkylation and acid-catalyzed *t*-butyl ester cleavage delivered the optically pure N-Cbz-lactam acetic acid intermediate **15**. Coupling with the P_1-precursor, hydrogenolysis, hydrolysis, and HPLC purification afforded the chiral quaternary 7-membered lactam dipeptide mimics **2e** (α-*R*-lactam)and **2f** (α-*S*-lactam). The assignment of chirality followed from the considerations discussed above. Starting with the racemic N-α-protected lactam intermediate **17**, a five step protocol delivered the advanced intermediate possessing an α-benzyl-N-α-methyl carbamate residue. Hydrolysis and HPLC purification then afforded the methyl carbamate analog **2g** (α-(*R,S*)-lactam).

Biological Activity

The biological activity of the targets **2a–g** along with three P_4-benzyl-sulfonamide standards **1a–c** is shown in Table 1. The in vitro assays were carried out using human serine protease enzymes including the procoagulants thrombin (FIIa), factor Xa (FXa) and the digestive enzyme trypsin.[15] The targets were selective against FXa while demonstrating potent to moderate levels of activity on thrombin.

Table 1. In vitro IC_{50} values (nM) of quaternary lactam argininals **2a–g** and reference standards **1a–c** against a range of important serine proteases.[a,b]

Cmpd	P_4	n	P_3 Chirality	FIIa	FXa	Hu Tryp	FXa/FIIa	Tryp/FIIa
2a	H	0	(*R*)-	1375	2500	1375	1.8	1.0
2b	H	1	(*R*)-	2.07	Inact.	139	high	67.1
2c	H	1	(*S*)-	137.5	Inact.	2500	high	18.2
2d	CH_3SO_2	1	(*R,S*)-	31.9	>2500	52.2	>78.4	1.6
2e	H	2	(*R*)-	14.9	>2500	969	>168	65.0
2f	H	2	(*S*)-	193	Inact.	2500	high	13.0
2g	CH_3O_2C	2	(*R,S*)-	466	2500	2500	5.4	5.4
1a	$BnSO_2$	0	(*S*)-	125	>2500	538	>20	4.3
1b	$BnSO_2$	1	(*S*)-	6.2	>2500	1271	>403	205.0
1c	$BnSO_2$	2	(*S*)-	0.71	22.8	151.8	32.1	213.8

[a]Concentration of **1a–c** and **2a–g** necessary to inhibit thrombin (FIIa), FXa, and human trypsin cleavage of the chromogenic substrates described in ref. 4a by 50%. Reported value for each compound is from a single IC_{50} determination which confirmed initial range values. [b]All target compounds were characterized by ^{1}H-NMR, RPHPLC, low/high resolution mass spectroscopy.

Quaternary lactams of the (*R*)-absolute configuration expressed optimal activity. Thrombin inhibitory potency decreased (IC_{50} values) as a function of P_3-lactam ring size in the following order: 6 (**2b**) > 7 (**2e**) > 5 (**2a**). These results contrast those found in the P_4-benzylsulfonamide series,[4] where thrombin inhibitory potency decreased as a function of P_3-lactam ring size in the following order: 7 (**1c**) > 6 (**1b**) > 5 (**1a**). Lactams of the (*S*)-absolute configuration showed inferior activity. N-Substitution on the α-aminolactam moiety with small carbamate or sulfonamide groups afforded less active, less selective inhibitors.

Modeling of the **2b**-thrombin complex based upon the **1b**-thrombin active site X-ray structure[4a] suggested that important interactions commonly found in small molecule thrombin inhibitors are present at the active, S_1, S_2, and S_3 subsites.[16] Our model of the inhibitor **2b** indicated a nearly substrate-like binding mode. The lactam carbonyl and α-amino group provide essential hydrogen bond acceptor and donor elements necessary for high affinity antiparallel β-hydrogen bonding with the Gly216 residue in the thrombin active site. Since the quaternary center confers further rigidifying characteristics, the entire benzyl-lactam-acetyl array appears to occupy the S_2–S_3 subsites with slight conformational differences relative to **1b**. The phenyl group is efficiently tethered into the hydrophobic S_3 subsite, therefore mimicking the role of the endogenous P_3-phenylalanine sidechain. Both the lactam ring and the appended N-methylene moieties occupy S_2, being mostly buried and slightly shifted relative to other substrate-like inhibitors, by Tyr60A and Trp60D of thrombin's unique 60 specificity loop.[16a,c] The argininal sidechain in S_1 participates in a close electrostatic contact with Asp189. Thus, numerous active site interactions coupled with the rigidity and geometry of the quaternary benzylic lactam may be of paramount importance for conferring good thrombin inhibitory potency and trypsin selectivity onto this class.

Conclusion

Our rational design considerations employing the reference P_3–P_4 lactam sulfonamide **1b** and related inhibitors afforded a series of novel P_1-argininals which incorporate peptidomimetic P_3–P_4 quaternary lactam moieties as active-site directed transition state analog inhibitors of thrombin. In vitro evaluation against serine proteases involved in the blood coagulation cascade and trypsin revealed targets with high to moderate levels of thrombin (FIIa) inhibitory potency and useful selectivity. The six-membered derivative **2b** was the most interesting and trypsin-selective candidate prepared. P_3-Lactams possessing the α-(*R*)-configuration showed the

greatest biological activity. Related scaffolds are currently under active study in our laboratories and the results from these investigations will be reported in due course.

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