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Design of selective phenylglycine amide tissue factor/factor VIIa inhibitors

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Abstract—Proof of concept experiments have shown that tissue factor/factor VIIa inhibitors have antithrombotic activity without enhancing bleeding propensity. Starting from lead compounds generated by a biased combinatorial approach, phenylglycine amide tissue factor/factor VIIa inhibitors with low nanomolar affinity and good selectivity against other serine proteases of the coagulation cascade were designed, using the guidance of X-ray structural analysis and molecular modelling.

1. Introduction

Thromboembolic disorders belong to the leading causes for morbidity and mortality in the industrialized world. Thrombosis of either the venous or the arterial vascular system may cause pulmonary embolism, myocardial infarction or ischaemic stroke.[1] The development of new anticoagulant therapies represents therefore an important medical need.

The tissue factor/factor VIIa (TF/F.VIIa) complex is the main trigger of thrombotic events.[2] This complex is part of the extrinsic pathway of coagulation and effects the activation of factor X and factor IX, ultimately resulting in the generation of thrombin. The thrombin-mediated conversion of fibrinogen to fibrin is crucial for venous thrombosis, whereas activation of platelets via thrombin-mediated cleavage of the platelet thrombin receptor is important for arterial thrombosis.

Tissue factor is an integral membrane protein, which is located in the adventitia of the vessel wall, functioning as a hemostatic envelope around blood vessels.[3] Furthermore, it has been described that tissue factor is highly enriched in atherosclerotic plaques.[4] Upon vessel damage or plaque rupture, tissue factor is exposed to factor VII circulating in the blood, leading to the initialization of thrombotic processes.

Because TF is buried in the endothelium and not exposed to blood circulating in a healthy vessel, normal haemostasis should not be affected by blockade of F.VIIa. Indeed, proof of concept experiments from our laboratories[5] as well as other research groups[6] demonstrate that specific inhibition of the TF/F.VIIa complex results in antithrombotic effects without enhancing bleeding propensity. These results suggested that F.VIIa is a very promising target for a novel anticoagulant and stimulated substantial efforts in the pharmaceutical industry to discover a low molecular weight TF/F.VIIa inhibitor.[7]

2. Results and discussion

Screening of the Roche compound depository did not provide a drug-like hit. Therefore lead compounds **1**–**4** (Table 1) were generated by a biased combinatorial approach[8] using a novel Ugi-type three-component condensation (Scheme 1). The aminobenzamidine component in these condensation reactions was chosen for its potential to form a salt bridge with the Asp189 carboxylate at the bottom of the S1 pocket. The resulting phenylglycine amide compounds **1**–**4** are submicromolar inhibitors of F.VIIa, but have also quite substantial inhibitory activity against thrombin.

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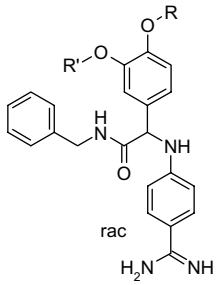
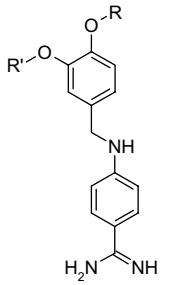
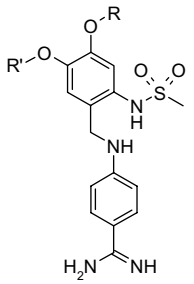
Table 1. Inhibition of TF/F.VIIa and related serine proteases by lead compounds **1**–**4** and benzylamines **5**–**7**



1: R = R' = Me
2: R = R' = Et
3: R = Bn, R' = Me
4: R = Bn, R' = Et



5: R = R' = Et,
6: R = Bn, R' = Me



7: R = Bn, R' = Me

Compd	K_i (μM)				Thrombin / F.VIIa
	F.VIIa	Thrombin	F.Xa	Trypsin	
1	0.35	0.46	30	1.7	1.3
2	0.04	0.57	19	2.0	14
3	0.22	0.043	5.3	0.21	0.2
4	0.13	0.048	4.5	1.1	0.4
5	4.2	4.5	39	2.0	1.1
6	1.0	0.27	1.20	0.58	0.3
7	0.38	1.4	26.0	0.40	3.7

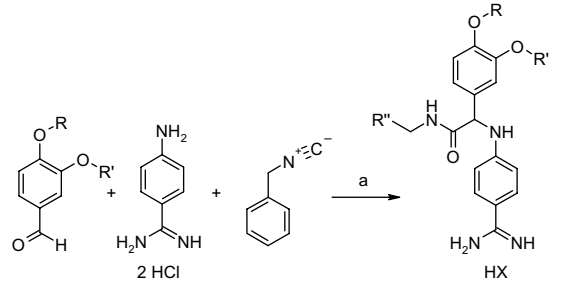
In a first attempt to define the minimal structural requirements for F.VIIa binding, a series of analogues lacking the benzylamide moiety was prepared. This led to an approximately 5–10-fold reduction of F.VIIa affinity as exemplified by compounds **5** and **6**. Affinity was restored in compound **7** by introduction of a sulfonamide substituent *ortho* to the benzylic methylene group as may be seen from comparison of compounds **3** and **7**, which are almost equipotent. Furthermore, the sulfonamide derivative **7** has a substantially improved selectivity against thrombin.

The X-ray crystal structure of compound **1** bound to the active site of TF/F.VIIa is shown in Figure 1A. The amidine forms the expected salt bridge with the carboxylate of Asp 189 at the bottom of the S1 pocket. Additionally, a hydrogen bond is formed between the aniline NH and the hydroxyl group of the active site serine (Ser 195).

A comparable binding mode is observed for compound **7** (Fig. 1B). Analogous to compound **1**, the methoxy group *meta* to the benzylic methylene group of compound **7** is accommodated in the small S2 pocket of F.VIIa. The S3 pocket, which is shallow and exposed to solvent, is filled by the benzyloxy group *para* to the benzylic methylene group. The sulfonamide substituent, which is negatively charged at physiological pH is directed towards solvent. It is possibly involved in an indirect hydrogen bond with the NH of Gly 219 via a water molecule.

From the X-ray structures of compounds **1** and **7** it becomes apparent that there is room to combine both the benzylamide moiety and the sulfonamide substituent in the same molecule. This was confirmed by preparing compound **8** (Table 2), which has a slightly better affinity for F.VIIa than compounds **3** and **7**. As observed before for the benzylamine derivatives **6** and **7**, the introduction of a sulfonamide substituent *ortho* to C_α of the phenylglycine moiety led to an increase in selectivity against thrombin as can be seen by comparison of compounds **3** and **8**.

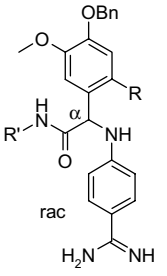
Systematic variation of the benzylamide moiety led to the first single digit nanomolar TF/F.VIIa inhibitor of the phenylglycine amide class. Compound **9** has a K_i of 4 nM, but is a good thrombin inhibitor as well. Selectivity could again be improved by introduction of a substituent *ortho* to C_α of the central phenylglycine moiety. Both compounds **10** and **11** are characterized by low



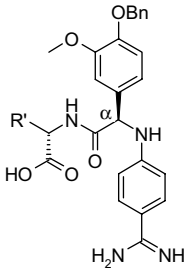
1: R = R' = Me, R'' = Ph
2: R = R' = Et, R'' = Ph
3: R = Bn, R' = Me, R'' = Ph
4: R = Bn, R' = Et, R'' = Ph

Scheme 1. Preparation of lead compounds **1**–**4** by an Ugi-type three-component condensation. Reagents: (a) THF/H_2O 9:1.

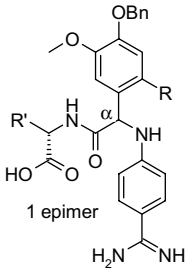
Table 2. Inhibiton of TF/F.VIIa and related serine proteases by optimized compounds **8**–**11**



8: R = -SO_2-Ph, R' = Bn



9: R' = Ph



10: R = -SO_2-Ph, R' = Ph
11: R = -CO-CH_2-Ph, R' = Ph

Compd	K_i (μM)				Thromb. / F.VIIa	$2 \times PT$[a] (μM)
	F.VIIa	Thrombin	F.Xa	Trypsin		
8	0.16	1.7	>74	0.42	10.7	85
9	0.004	0.035	8.0	0.04	8.8	4
10	0.002	0.54	12.4	0.05	270	12
11	0.007	6.4	19.0	0.08	913	44

[a] Human citrated plasma is spiked with at least six concentrations of inhibitor. Clotting is initiated by addition of exogenous tissue factor (Innovin). Clotting time is determined by a turbidity measurement. The concentration of inhibitor necessary to double control clotting time is determined by fitting the data to an exponential regression.[11]

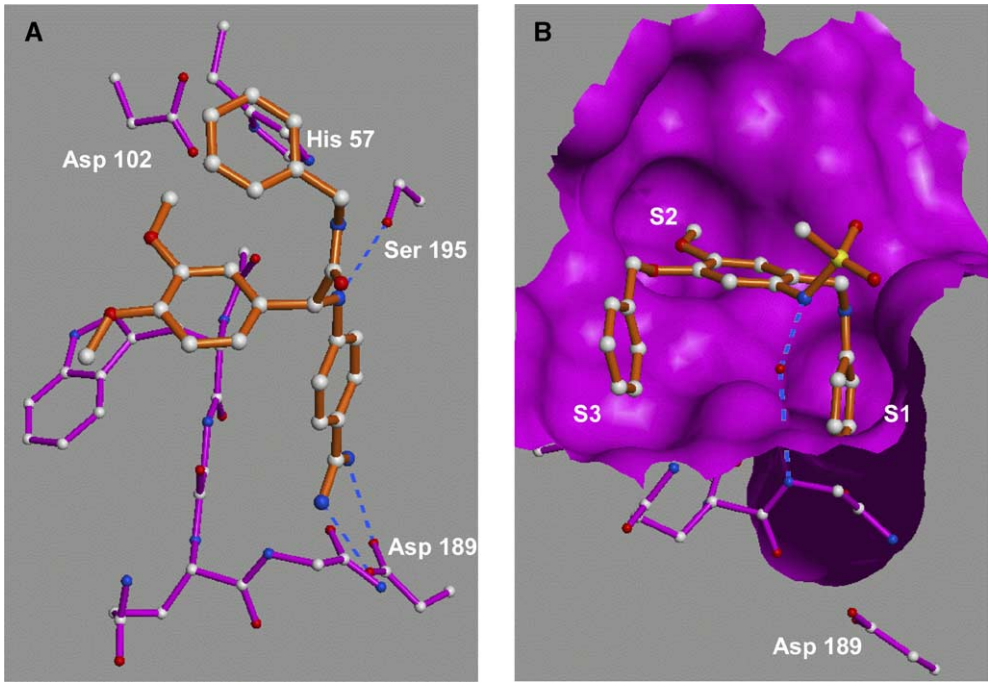


Figure 1. (A) Crystals of human soluble tissue factor/factor VIIa were prepared as described[9] except that proteolysis of tissue factor was not used. Crystals of the complex with **1** were frozen and data measured in house to 3.0 Å resolution. The unit cell is *P*212121, with $a = 71.87$ Å, $b = 82.64$ Å, $c = 123.72$ Å. This is close to the unit cell of 1dan.pdb[10] (room temperature), which was used as start model. The structure was refined to final overall crystallographic *R*-factors of 19.7% (working) and 25.7% (free), with values in the outer shell of 27.0% and 34.3%, respectively. The inhibitor density is clear. The coordinates have been deposited in the Protein Data Bank as 1w2k.pdb. (B) Crystals of the complex with **7** were frozen and data measured at the SNBL beamline at the ESRF synchrotron to 2.5 Å resolution. The unit cell is *P*212121, with $a = 71.34$Å, $b = 82.38$ Å, $c = 123.96$ Å. The structure was refined to final overall crystallographic *R*-factors of 19.9% (working) and 25.8% (free), with values in the outer shell of 23.8% and 27.9%, respectively. The inhibitor density is clear. The coordinates have been deposited in the Protein Data Bank as 1w0y.pd.

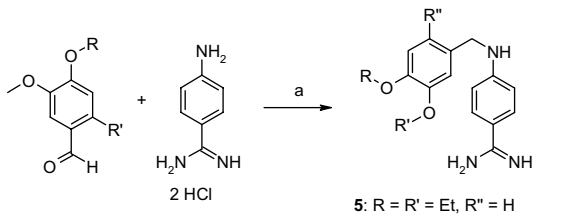
nanomolar inhibitory activity for TF/F.VIIa and a selectivity against thrombin in the range of 2–3 orders of magnitude. Unfortunately, the excellent activity of these two compounds is not reflected by a corresponding plasma activity in in vitro clotting assays. Twofold PT (prothrombin time)[11] prolongation, which serves as a measure for inhibition of the coagulation cascade via the extrinsic pathway, is only reached at concentrations of 12 μM and 44 μM, respectively.

According to the 'Rules of Five'[12] the high molecular weight and the structural features of these two inhibitors suggest poor oral bioavailability. Not surprisingly their permeation through an artificial membrane is low. Additionally, their unfavourable pharmacokinetic profiles (high clearance, short half life) do not allow a sufficient plasma concentration to be achieved. Therefore the phenylglycine amide TF/F.VIIa inhibitors were not considered for further development. Nevertheless, the insights gained from X-ray structure analysis led to the discovery of a related class of TF/F.VIIa inhibitors with potential for oral activity. Results of these investigations will be reported in due course.

3. Chemistry

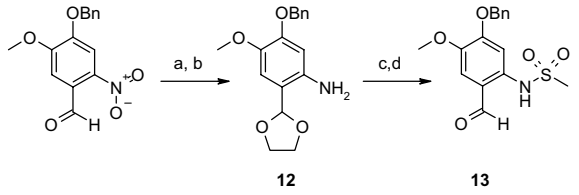
The library of compounds, which led to the identification of lead structures **1**–**4** was synthesized by a three-component variation of the Ugi reaction,[13] mixing equal amounts of an isonitrile, a benzaldehyde and an amine in methanol. Amines were chosen to have potential for binding to the S1 pocket of the active site of F.VIIa. Hits resulted eventually from a condensation between benzylisonitrile, a substituted benzaldehyde and 4-aminobenzamidine, which was carried out in THF/H_2O (Scheme 1).

The benzylamine derivatives **5**–**7** were prepared by an optimized reductive amination procedure between 4-aminobenzamidine and the appropriate benzaldehydes (Scheme 2). The sulfonamide-substituted aldehyde necessary for the preparation of compound **7** was prepared starting from 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde (Scheme 3). Protection of the aldehyde and reduction of the nitro group gave aniline **12**, which



5: R = R' = Et, R" = H
6: R = Bn, R' = Me, R" = H
7: R = Bn, R' = Me, R" = Me-SO_2-NH

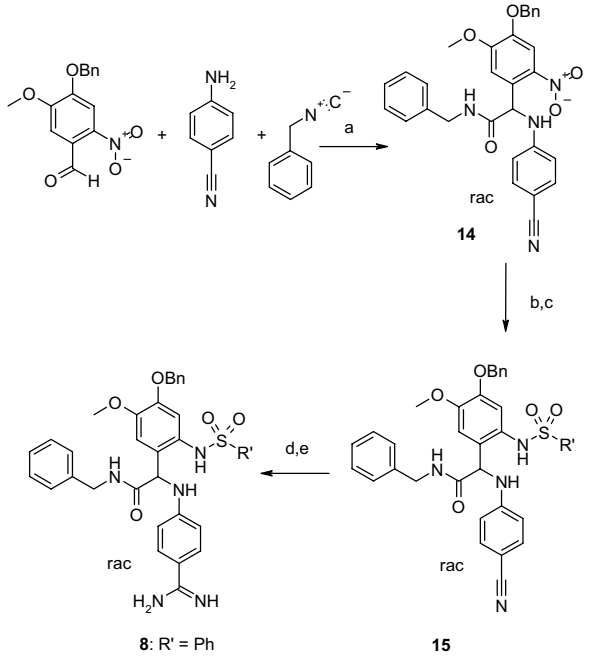
Scheme 2. Reductive amination of 4-aminobenzamidine dihydrochloride with benzaldehydes. Reagents and conditions: (a) 1 equiv NaOMe, $MgSO_4$, MeOH; then H_2, Pt/C (5%), MeOH.



Scheme 3. Preparation of sulfonamide-substituted benzaldehyde **13** for the synthesis of compound **7**. Reagents and conditions: (a) 2,2-dimethyl-propanediol, *p*-TsOH, toluene, reflux; (b) H_2, Pt/C (5%), EtOH/dioxane 2:1; (c) $MeSO_2$–Cl, DIPEA, DMF, CH_2Cl_2; (d) concd HCl (aq), acetone.

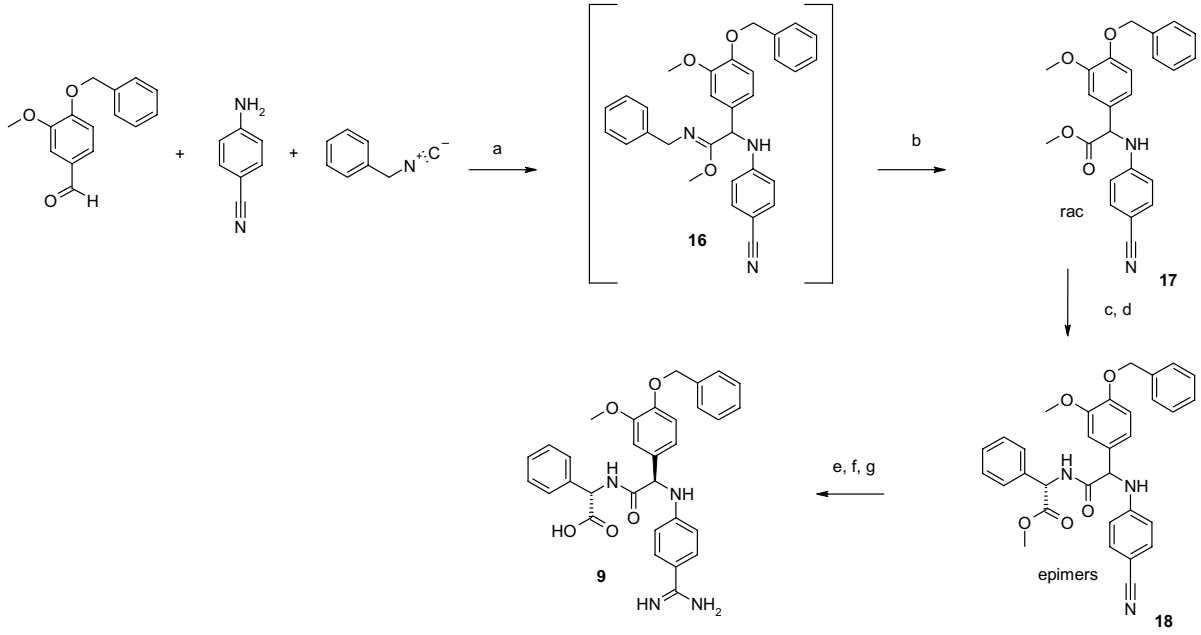
was allowed to react with methanesulfonyl chloride and subsequently deprotected to give the required aldehyde **13**.

Compound **8** was prepared by starting with Lewis acid-catalyzed condensation of 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde, benzylisonitrile and 4-aminobenzonitrile to give phenylglycine amide **14** (Scheme 4). Reduction of the nitro group and subsequent reaction of the aniline with benzenesulfonyl chloride led to intermediate **15**. Finally the nitrile was converted to the amidine **8** via the corresponding amidoxime.

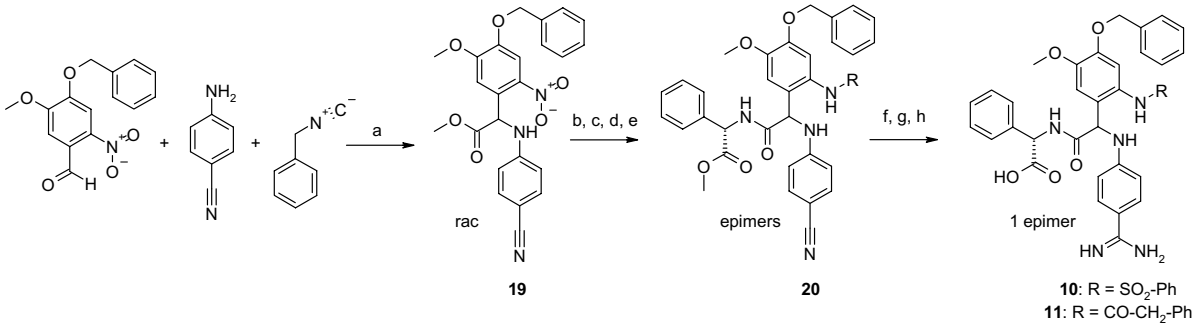


Scheme 4. Preparation of sulfonamide-substituted phenylglycine amide **8**. Reagents and conditions: (a) 2 equiv BF_3–OEt_2, allyl alcohol, 1 h; (b) H_2, Pd/C (10%); (c) benzenesulfonyl chloride, DIPEA, THF, rt; (d) H_2N–OH, HCl, TEA, EtOH, reflux; (e) H_2, Raney nickel, EtOH/HOAc 8:1.

The phenylglycine ester starting material **17** for the synthesis of compound **9** was prepared by Lewis acid-catalyzed condensation between 4-benzyloxy-3-methoxy-benzyldehyde, 4-aminobenzonitrile and benzylisonitrile (Scheme 5). The intermediate iminoether **16** was hydrolyzed in situ to the corresponding phenylglycine ester **17** by the addition of an excess of water. The synthesis was completed by hydrolysis of the ester and coupling of phenylglycine ester to give **18**. Ester hydrolysis, chromatographic separation of diastereomers and conversion of the nitrile into the amidine via amidoxime finally led to the desired product **9**.



Scheme 5. Preparation of diphenylglycine derivative **9**. Reagents and conditions: (a) 3 equiv BF_3–OEt_2, MeOH, 1 h, 0 °C; (b) in situ addition of 20 equiv H_2O; (c) LiOH, THF/H_2O 3:1; (d) S–Phg–OMe, HCl, DIPEA, BOP, CH_2Cl_2; (e) LiOH, THF/H_2O 3:1, separation of diastereomers by chromatography on silica gel; (f) H_2N–OH, HCl, TEA, EtOH, reflux; (g) H_2, Raney nickel, EtOH/HOAc 8:1.



Scheme 6. Preparation of diphenylglycine derivatives **10** and **11**. Reagents and conditions: (a) 3 equiv BF_3–OEt_2, MeOH, 1 h, 0 °C; then in situ addition of 20 equiv H_2O; (b) H_2, Pt/C (5%), THF; (c) benzenesulfonylchloride or phenylacetyl chloride, DIPEA, DMF, CH_2Cl_2; (d) LiOH, THF/H_2O 2:1, 0 °C; (e) S–Phg–OMe, HCl, BOP, DIPEA, DMF; (f) LiOH, THF/H_2O 2:1; (g) H_2N–OH, HCl, TEA, EtOH, reflux; (h) H_2, Raney nickel, EtOH/HOAc 8:1, separation of diastereomers by chromatography on silica gel.

The nitro-substituted phenylglycine ester **19** (Scheme 6) was obtained using the three-component condensation procedure described in the preceding section. Reduction of the nitro group, derivatization of the aniline, hydrolysis of the ester and coupling with phenylglycine methylester led to intermediate **20**. Ester hydrolysis and conversion of the nitrile to the amidine via the corresponding amidoxime and subsequent chromatographic separation of diastereomers led to compounds **10** and **11**.

Acknowledgements

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