Supplementary Information:

General procedures

1. NMR EXPERIMENTS:

NMR experiments were performed at 15°C using 3 mm match tubes on a Bruker Avance II+ 600 MHz NMR-spectrometer. Samples were prepared in phosphate buffer pH 7.4 with 150mM sodium chloride and 150µM TSP-d_4 in D_2O. Fragments were screened as mixtures containing 3-5 compounds per sample and were preclassified based on properties such as electrophilic/nucleophilic nature of their substituents, acidic/basic or neutral properties. Component mixtures included fragments from the same class to avoid inter-compound reactions.The reference ^{1}H NMR spectra of the pure substances were taken into account when performing the compound pooling to avoid excessive overlap in the spectra of the mixtures and to have at least two isolated signals per compound to perform the STD analysis. ^{1}H NMR spectra of the proposed mixtures were recorded to ensure that indeed no reactions/interactions occurred between fragments.

For all STD experiments the protein to ligand ratio was kept to 1:25, with the protein concentration at 20µM. The spectra were referenced using TSP-d_4. For STD experiments, a pseudo 2D sequence was used with water suppression using a 3-9-19 pulse sequence with gradients and measured with a sweep width of 18.0221ppm and 32K data points. A train of Gaussian pulses with a length of 50 ms each and 49 dB of attenuation interleaved by a 1ms delay was used for selective saturation. The duration of saturation was set to 3 s in all experiments. A total of 198 scans was acquired. The on resonance irradiation was set to -1 ppm, and the off resonance irradiation to 100 ppm.

2. PHARMACOPHORE BASED SELECTION OF ANALOGUES:

All molecular modeling (chemo informatics, flexible alignment, consensus pharmacophore modeling and pharmacophore screening) was performed using MOE2011.10 with default parameters. Molecular docking simulations were performed using GOLD5 in precision mode on the RIKEN integrated cluster of clusters (RICC).The collection of active fragment molecules, as identified by STD NMR, was analyzed using the Molecular Operating Environment (MOE, The chemical computing group, Montreal, Canada) in order to select the most promising molecules. All active fragment molecules were clustered based on their graph based 3-point pharmacophore fingerprint (with a Tanimoto similarity cut-off of 0.55) using the Jarvis-Patrick algorithm implement in MOE. Consequently two similar fragments (occupying one cluster) were identified that possess sufficient pharmacophore features for the rational selection of fragment derivatives and are selective for the A1 domain. These fragments corresponded to the ones selective for the VWF-A1 domain. The 2 fragments were flexibly aligned in 3D and a consensus pharmacophore query was created (Figure S1). A virtual screening for novel compounds was performed with this pharmacophore query using a library constructed from the "in stock only" compounds from Maybridge and Enamine that passed the Rule of 5, resulting in a total of around 500,000 compounds Additional molecules originating from graph based 3 point pharmacophore fingerprint similarity searches were also included to ensure diversity in the linker and aromatic groups for exploratory reasons. This resulted in 20 and 10 molecules according to the respective method. (see Table S2 below) 8 compounds were insoluble, of the remaining 22 all except 2 exhibited affinity for the VWF-A1 domain.

3. INFLUENCE OF FRAGMENTS ON THE VWF/GPIbα INTERACTION -- BIO-ASSAY

To determine the influence of the fragments on the VWF/GPIbα interaction, a bio-assay known as the ristocetin co-factor ELISA (VWF:RiCof-ELISA) was performed, essentially as described by Vanhoorelbeke *et al.*, 2000.[1] Briefly, a recombinant GPIbα fragment[2] is first captured on a microtiter plate using a monoclonal antibody 2D4. Next, a VWF containing anticoagulated human plasma pool pre-incubated for 30 min at 37°C with 400µM of the reported fragment is added in combination with 760µg/mL ristocetin (Ristocetin A SO4, abp, New York, NY). The ristocetin will induces conformational changes that allow binding of VWF to GPIbα under static conditions. Finally, the amount of interaction between both protein partners is quantified using a rabbit anti-humanVWF antibody labeled with horse radish peroxidase (anti-vWF-Ig-HRP, Dako, Glostrup, Denmark) and measurement of the absorbance at 490nm after o-phenylene diamine/ H_2O_2 staining. Data are expressed normalized to the control plasma sample containing 1% DMSO and presented as means of three independent repeats with their corresponding standard error of the mean (SEM). Statistical analysis was performed with GraphPad Prism5 (San Diego, CA) using a one way ANOVA and a Dunnett's multiple comparison test. Data are considered significant when $p<0.05$.

Plasma from two VWD type I patients showed only 68.1 ±3.2% and 44.1 ±3.4% of the normal VWF binding in the VWF:RiCof-ELISA, however upon addition of 400µM F6 the binding efficiencies could be increased to respectively 82.4 ±3.5% and 62.9 ±2.6% (with $n=3$ and $p<0.05$).

Table S1: STD NMR data from initial screening of Maybridge Fragments with VWF-A1 and VWF-A3.

Proteins screened	Number of Hits ($A_{STD} \geq 1$) (out of 80)	Percentage (%)
VWF-A1	24	30
VWF-A3	43	53.75
VWF-A1 and not VWF-A3	2	2.5

Table S2: Summary of NMR Screening results with SMILES structure of compounds tested; B=Line Broadening, NB=No Line Broadening, NS=Not soluble

No.	Comp. ID	VWF-A1	GPIb	SMILES	Selection method
119		B	B	Cc1ccc(C)cc1SCc2cc(ccc2)C(O)=O	pharmacophore query
121		B	B	Clc1ccc(Cl)cc1SCc2cc(ccc2)C(O)=O	pharmacophore query
120		B	B	Clc1cc(Cl)ccc1SCc2cc(ccc2)C(O)=O	pharmacophore query
128	EN300-09323	B	B	Clc1ccc(Cl)cc1SCc2cc(ccc2)C(O)=O	pharmacophore query
130	EN300-70825	B	B	Clc1ccc(Cl)cc1SC(C(O)=O)c2ccccc2	fingerprint search
131	T6640650	B	B	S(Cc1cc(ccc1)C(O)=O)c3cc2OCCOc2cc3	pharmacophore query
132	T6876933	B	B	Clc1ccc(Cl)cc1SCc2cc(ccc2)C(O)=O	pharmacophore query
133	T6457898	NS	NS	Clc1ccc(Cl)cc1SCc3cc(S(=O)(=O)N2CCOCC2)ccc3	pharmacophore query
134	T5525334	NS	NS	Clc1ccc(Cl)cc1SCc2cc(ccc2)C(=O)N3CCN(CC3)c4nccn4	fingerprint search
135	T6264233	NS	NS	Clc1ccc(Cl)cc1SCc2cc(ccc2)C(=O)NC3(CCS(=O)(=O)C3)C	fingerprint search
136	EN300-30770	NB	NB	O(Cc1ncccc1)c2cc(ccc2OC)C(O)=O	pharmacophore query
137	EN300-30780	NB	NB	O(Cc1cccnc1)c2cc(ccc2OC)C(O)=O	pharmacophore query
138	T6624771	B	B	S(Cc1ccc([N+](=O)[O-])cc1[N+](=O)[O-])c1nc(nc(c1)C)C	fingerprint search
139	T5572839	B	B	Clc1cc(NC(=O)c2sc(Cl)cc2)c(cc1)C(O)=O	fingerprint search
140	T0508-7642	NS	NS	Clc1ccc(Cl)cc1NC(=O)c2sc(Cl)cc2	fingerprint search
141	EN300-04661	B	NB	S(Oc1ccc(cc1)C(O)=O)(=O)(=O)c2cc(ccc2C)C	fingerprint search
142	T5427689	NS	NS	Clc1cc([N+](=O)[O-])c(SCc2cc([N+](=O)[O-])ccc2)cc1	pharmacophore query
143	T5440925	NS	NS	Clc1cc([N+](=O)[O-])c(SCc2cc(ccc2)C(OC)=O)cc1	fingerprint search
144	EN300-30982	B	B	S(Cc1cc(ccc1)C(O)=O)c1cc(F)ccc1F	pharmacophore query
145		B	B	Clc1cc(SCc2cc(ccc2)C(O)=O)cc(Cl)c1	pharmacophore query
146		NS	NS	Clc1cccc(Cl)c1SCc1cc(ccc1)C(O)=O	pharmacophore query
147		B	B	Clc1ccc(Cl)cc1N1C(=O)c2c(ccc(c2)C(O)=O)C1=O	pharmacophore query
148		B	B	S(Cc1cc(ccc1)C(O)=O)c1cc(C)ccc1C	fingerprint search
108	Maybridge: KM08293	NS	NS	O(C(=O)c1cc(cnc1)C#Cc2ccccc2)CC	pharmacophore query
109	Maybridge: KM08328	B	B	OC(=O)c1cc(cnc1)C#Cc2ccccc2	pharmacophore query
110	Maybridge: KM08907	B	B	OC(=O)c1cc(cnc1)C#CCC2CCCCC2	pharmacophore query
117	T6405228	B	NB	S(=O)(=O)(Cc1cc(ccc1)C(O)=O)c2ccccc2	fingerprint search
119	T5289781	B	B	Cc1ccc(C)cc1SCc2cc(ccc2)C(O)=O	pharmacophore query
120	T5380649	B	B	Clc1cc(Cl)ccc1SCc1cc(ccc1)C(O)=O	pharmacophore query
121	T5302614	B	B	Clc1ccc(Cl)cc1SCc1cc(ccc1)C(O)=O	pharmacophore query

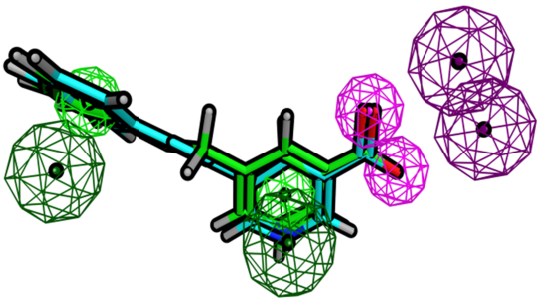

Figure S1. Superposition of **F1** (green carbons) and **F2** (cyan carbon atoms), two fragments that clustered together, was used to create a consensus pharmacophore query that described the 3 key pharmacophore features: two aromatic groups (represented by green and dark green (normal vector of the aromatic plane) spheres, as well as the acid functionality, represented by a pink and purple (direction of the free electron pairs) spheres.

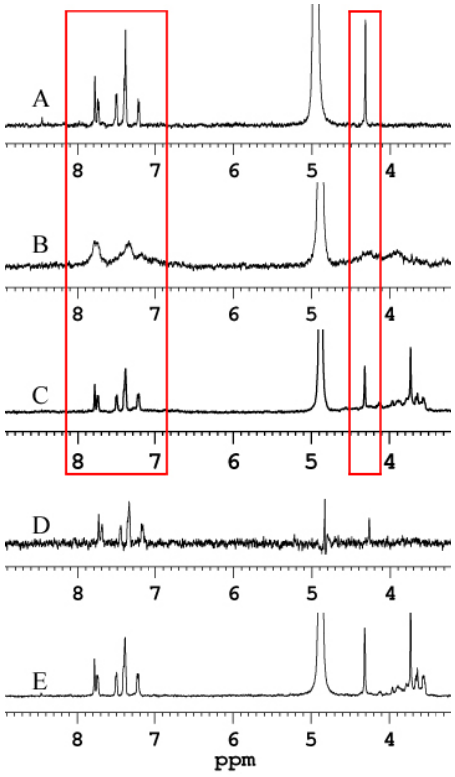

Figure S2. (A) ^{1}H NMR spectrum of **F6**. (B) and (C) ^{1}H NMR spectrum of **F6** in presence of VWF-A1 and GPIbα respectively. The STD off resonance (reference) spectrum of **F6** in the presence of GPIbα is depicted in (E) and binding of **F6** to GPIbα is confirmed in the STD NMR spectrum in (D).

References

1 Vanhoorelbeke, K. *et al.* A reliable and reproducible ELISA method to measure ristocetin cofactor activity of von Willebrand factor. *Thromb Haemost* **83**, 107-113 (2000).

2 Schumpp-Vonach, B., Kresbach, G., Schlaeger, E. J. & Steiner, B. Stable expression in Chinese hamster ovary cells of a homogeneous recombinant active fragment of human platelet glycoprotein Ib alpha. *Cytotechnology* **17**, 133-141 (1995).