3D-modeling of thrombin-fibrinogen interaction*

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Abbreviations used: FpA, fibrinopeptide A; FpB, fibrinopeptide B; PPACK, H-D-Phe-Pro-Arg-CH₂Cl.
Abstract: 3D-models of thrombin complexed with large fragments of the fibrinogen Aα and Bβ chains are presented. The models are consistent with the results of recent mutagenesis studies of thrombin and with the available information on naturally occurring fibrinogen mutants. Thrombin recognizes fibrinogen with an extended binding surface, key elements of which are Y76 in exosite I, located about 20 Å away from the active site, and the aryl binding site located in close proximity to the catalytic triad. A highly conserved aromatic-Pro-aromatic triplet motif is identified in the primed site region of fibrinogen and other natural substrates of thrombin. The role of this triplet, based on the 3D-models, is to correctly orient the substrate for optimal bridge-binding to exosite I and the active site. The 3D-models suggest a possible pattern of recognition by thrombin that applies generally to other natural substrates.
Thrombin plays multiple functional roles in the blood by interacting with a variety of proteins. The procoagulant role of thrombin unfolds upon interaction with fibrinogen and culminates in the formation of fibrin intermediates that polymerize into a blood clot. The kinetic steps defining this interaction and the mechanism of fibrin polymerization have been characterized in great detail (1). The determinants of fibrinogen recognition by thrombin have also been elucidated by site-directed mutagenesis (2,3) and provide an important database of information that complements clinical findings on naturally occurring fibrinogen variants that are associated with bleeding phenotypes.

The thrombin-fibrinogen interaction has enjoyed renewed interest in recent years after the landmark solution of the crystal structure of fibrinogen derivatives (4-7). These structures have offered clues on the molecular events underlying the end-to-end assembly of fibrin monomers generated after the thrombin induced release of FpA from the Aα chain, the subsequent formation of fibrin protofibrils and the thrombin induced release of FpB from the Bβ chain (4). Information on the structural epitopes of thrombin recognizing fibrinogen has also been obtained. Fragments of FpA covalently bound to the active site S195 of thrombin have been reported by X-ray crystallography (8,9) and NMR spectroscopy (10). These studies have delineated the interactions made by FpA with the active site moiety of thrombin.

It has long been known, however, that regions of thrombin away from the active site are involved in fibrinogen recognition (11). Specifically, exosite I located about 20 Å away from the active site contains residues that are critical for fibrinogen binding. Macromolecular bridge-binding of fibrinogen to exosite I and the active site confers high specificity to the interaction and serves as a binding mode exploited by other natural substrates, like the G-protein coupled thrombin receptors (3). Recent Ala scanning mutagenesis studies of thrombin have identified a hot spot in exosite I, centered around Y76, that stores much of the energy responsible for the interaction with fibrinogen (2,3). Unfortunately, the available crystal structure of the thrombin-fibrinogen complex does not provide information on the contacts made by the natural substrate with exosite I. In the case of the interaction of thrombin with the Bβ chain of fibrinogen, responsible for the release of FpB and protofibril polymerization, no structural information is currently available.

This study fills an important structure-function gap in our understanding of the thrombin-fibrinogen interaction. Here we report 3D-models of thrombin complexed with large fragments of the Aα
and Bβ chains of fibrinogen, following a strategy recently used in the case of thrombin interaction with the G-protein coupled receptors PAR1, PAR3 and PAR4 (3). The models are highly consistent with available data on site-directed and naturally occurring mutants of thrombin and fibrinogen.

**Materials and Methods**

The N-terminal fragments of the fibrinogen Aα(20-62) and Bβ(31-72) chains were built, capped and completed for missing hydrogens (pH 7.0) with Biopolymer and InsightII (Accelrys, San Diego CA) using the human sequences P02671, P02675 and P02679 from the Swissprot sequence database (12). First, 500 models were produced with Modeller4 (13) by comparative modeling of every substrate on the surface of thrombin using several available crystal structures of peptide-thrombin complexes as templates. Substrate conformation was then optimized from the best model by simulated annealing during molecular dynamic processes with Discover (Accelrys, San Diego, CA).

The fibrinogen fragment Aα(26-35) was threaded over the Ac-DFLAEGGGVR peptide from X-ray crystal structures 1BBR and 1UCY (9,14). Residue R35 of the Aα chain was linked through its carbonyl O to thrombin S195 Oγ to form a reaction intermediate analogous to the Arg of PPACK in 1PPB (15). The conformation of fragment Aα(35-49) was templated on the protein fragments KILDKVVERIKERMKDSNVKL from 1A0E and AFWRELVECFQKISKDSDCRA from 1DCI. These fragments were selected from our database of 48 million conformers constructed by dissecting the entire Protein Data Bank into peptides from 3 to 18 residues in length. The conformers were screened for optimal shape, length and fit to the thrombin surface. The conformation of fragment Aα(46-57) was loosely threaded over the NGDFEEIPEEYL hirugen peptide from the structures 1HAH (16) and 1NRS (17). The fibrinogen fragment Bβ(41-44) was threaded over the peptide LDPR from the structure 1NRS (17). Residue R44 of the Aα chain was linked through its carbonyl O to thrombin Ser195 Oγ as described above. The conformation of fragment Bβ(49-61) was loosely threaded over the NGDFEEIPEEYL hirugen peptide from structures 1HAH and 1NRS and also over the proline-rich peptide APTMPPPLPP from the structure 1ABO of a tyrosine kinase Src homology domain 3 (18).

Peptides were docked over thrombin using 1PPB and 1HAH as templates and yielded 500 models that were ranked in terms of stereochemistry quality and lowest potential binding energies. Models
containing a ligand with a r.m.s. deviation within 2 Å from a better ranked one were eliminated. We
selected the best ten models, extracted the ligand and docked it over thrombin in 1PPB as a starting
point. Water molecules and Na\(^+\) as defined in 1HAH and 1PPB were pooled and filtered for overlaps with
thrombin or ligand atoms and added to the starting model. The backbone of thrombin secondary
structures templated on 1PPB was kept frozen during simulated annealing applied by molecular dynamics
in cartesian space (fast annealing from 50 to 600 K in 3 ps, slow cooling from 600 to 50 K during 10 to
30 ps with progressive constraint to bring back thrombin backbone to the 1PPB reference). Models were
sampled every 1 ps. About 300 models (10 starts and 30 samples per trajectory) were minimized (200
steepest descent then 1500 conjugate gradient cycles). All processes were performed with the force field
CFF91 and Discover. Constraints were used to hold the Na\(^+\) coordination shell in place. The dielectric
constant was set at 1xr, cut offs were used to threshold non covalent bonds at 14 Å during Monte-Carlo
processes and dynamics, and set to infinite during minimizations.

Models of thrombin-substrate complexes with an r.m.s. deviation <1.5 Å for the thrombin
backbone and peptide residues <10 Å from the enzyme were considered acceptable. The stereochemistry
of final conformations was systematically checked with Procheck 3.0 (19) to satisfy a quality expected for
a 2.4 Å resolution model (the lowest resolution of the structures that we used as template). The solvent
accessible surface of thrombin was calculated according to the Connolly algorithm and rendered as a solid
surface with InsightII using a 1.4 Å radius probe.

Thrombin mutations were modeled with Biopolymer. Dihedral angles were explored with the
Monte-Carlo/Metropolis method for the main chains of the wild-type residue, its flanking residues, and
the side chains of residues within 6Å from the site of mutation. Minimizations were run in two steps with
Discover using the force field CFF91 and keeping the constraints on the Na\(^+\) and its coordination shell. A
steepest descent algorithm was applied during 300 cycles, followed by a conjugate gradient algorithm up
to 1500 cycles.

Thrombin sequences were selected from the non-redundant sequence database (NCBI, Bethesda
MY) with the BLAST program (20) and aligned with Clustal X (21). Sequences of thrombin natural
substrates were aligned according to the best model threaded and docked on the thrombin surface as
described above, using one substrate fragment per orthologous group of sequences. Other orthologous sequences were aligned over the multi-aligned sequence core with Clustal X.

**Results**

**Interaction with the Aα chain.** The biggest fragment from fibrinogen crystallized with thrombin is the FpA(11-19) from bovine equivalent to human FpA(27-35) (9). Aα(26-39) is the longest fragment from human fibrinogen bound to thrombin studied by NMR (10). Hirugen peptides inhibit fibrinogen cleavage by binding to exosite I (16). We used these peptides as templates to model Aα(43-54). The three structures 1BBR, 1UCY and 1HAH helped build the core F27LAEGGGVRPRVERHQSAKDSWPF54 of the human Aα(20-62) fragment. Equivalent positions of the human Aα(20-62) residues are not visible in the crystal structure of the bovine fibrinogen Aα chain (5,8). The first documented motif is a helix starting at position 63 in the corresponding human chain numbering. The helix end is accessible to solvent and we therefore assumed that the N-terminal fragment 1-62 folds in a way accessible to thrombin. The fragment is probably responsible for most of the interactions between fibrinogen and thrombin, because Aα(20-70) produced by the cyanogen bromide hydrolysis of fibrinogen is a thrombin substrate as good as the entire fibrinogen (22,23). We extended the templated peptide core to Aα(20-62) and docked it on thrombin. The peptide is mainly in extended conformation with two short loops 28-33 (loop 1) and 39-48 (loop 2).

The Aα chain fragment explores different portions of the thrombin surface (Figure 1). Residues 20-25 interact with exosite II, residues 26-38 fit into the active site, residues 39-51 bind to the groove connecting the active site with exosite I, and residues 52-62 dock onto exosite I. The change in exposed surface area upon formation of the complex between thrombin and Aα(20-62) is 3501 Å² (25% of the thrombin surface), comparable to 3304 Å² in the thrombin-hirudin interface (24). Half of the contact area maps outside the region from the aryl binding site to the S3’ site framing the portion of substrate interacting with the active site. The relevant contacts of the Aα(20-62)-thrombin complex are reported in Figure 2 and compared to those of the templates.

There is a site of phosphorylation in the human fibrinogen Aα chain at AαS22 that results in an intermediate showing higher specificity for thrombin (25). NMR analysis of the 31P 1D spectra changes
due to binding to thrombin of the synthetic phosphorylated peptide $\alpha(20-41)$ suggests contribution of this group to binding (26). Transferred nuclear Overhauser effect experiments locate the contact of this group in the vicinity of R175 of thrombin, in exosite II. The phosphate seems to stabilize the otherwise disordered residues $\alpha(22-26)$ in their interaction with thrombin (26). The backbone structure of residues $\alpha(22-35)$ of our model of the $\alpha(20-62)$-thrombin complex is superimposable to the bundle of NMR conformers proposed by Maurer and colleagues (26). Our 3D-model suggests the interaction of the phosphate group within the pocket formed by the basic side chains of R165, K169 and R175. $\alphaD21$ interacts with K169, and $\alphaD26$ with R97 to form ion-pairs. The naturally occurring mutant fibrinogen Lille I (27) carries the substitution $\alphaD26N$ and shows reduced clotting activity. The mutation should lead to breakage of this ion-pair.

$\alphaF27$ is framed by W215, I174 and L99 forming the aryl binding site (15) and accounts for a major fraction of the binding specificity of fibrinogen toward thrombin. The $\alphaF27Y$ mutant abrogates cleavage by thrombin in model peptides (28). A 3D-model of thrombin complexed with the $\alpha$ chain carrying the F27Y mutation shows that the hydroxyl group of $\alphaY27$ H-bonds to the N atom of $\alphaV34$, fixing the aromatic ring of $\alphaY27$ into a distorted position that pulls thrombin W215 1.4 Å higher and out of the aryl binding site (Figure 3). This perturbation increases the solvent exposure of the hydrophobic surface of the entire aryl binding site. Similar perturbations of W215 have been shown to produce drastic (up to 500-fold) reduction in clotting activity (29). Furthermore, the steric hindrance introduced in the thrombin mutant L99Y skews the $\alphaF27$ side chain away from the W215 ring, explaining the 260-fold decrease in specificity for FpA release (3).

$\alphaV34$ is in close contact with thrombin Y60a and W60d in the S2/S3 sites. $\alphaE30$ is ion-paired with R173, and the naturally occurring fibrinogen Mitaka II (30) shows reduced clotting activity presumably because of the loss of this ion-pair.

$\alphaR35$ is the P1 residue of fibrinogen and is engaged in the expected ion-pair with D189 in the S1 pocket via its side chain and a H-bond interaction with the carbonyl O of S214 through its N atom (8,9). Mutation of this Arg to His as in fibrinogen Petoskey I (31), or Cys as in fibrinogen Metz I (32), results in drastic or complete loss of clotting activity.
Residues G31GG33 are important for positioning AαF27 and AαR35 in their respective pockets. The mutation AαG31V in fibrinogen Rouen (33) causes reduced clotting activity. The intervening Gly in this sequence makes a contact with the side chain of E217 through its carbonyl O atom. Removal of this contact in the E217A mutant causes a significant loss of fibrinogen clotting (34). Removal of both this contact and the strong coupling with W215 in the aryl binding site in the double mutant W215A/E217A generates a thrombin mutant that has lost fibrinogen clotting, but retains activity toward the anticoagulant protein C (35). The N atom of AαG33 H-bonds to the carbonyl O of G216.

Residues AαL28 and AαP37 frame W60d. The AαP37L substitution in fibrinogen Kyoto II (36) has no effect on clotting. The model suggests that the Leu substitution can be accommodated well in the hydrophobic environment between L41 and W60d of thrombin. On the other hand, the W60dS mutant of thrombin shows significant perturbation of fibrinogen clotting (3,37), consistent with a drastic disruption of the favorable hydrophobic interactions with AαL28 and AαP37 caused by the replacement of W60d with a polar side chain.

Residue AαR38 makes a solvent accessible ion-pair with E39. The energetic contribution of this ion-pair is modest because the E39A mutant of thrombin has clotting activity comparable to wild-type (3), and the fibrinogen mutants AαR38S Detroit (38), AαR38G Aarhus (39) and AαR38N Munich (40) have normal or slightly reduced clotting activity.

The Aα and Bβ chains have a loop segment between the anchor positioned into the S1 pocket and the region binding to exosite I. Within this loop, AαC47 is exposed to solvent in the Aα(20-62)-thrombin complex and is available for a disulfide bridge with AαC47 from the second Aα chain of the fibrinogen dimer.

AαD51 is ion-paired with R67 in exosite I. The mutation R67A affects equally FpA and FpB release (3), although there is no residue in the Bβ chain available for an ion-pair with R67. That suggests that the loss of thrombin activity toward the Aα and Bβ chains is due to perturbation of the buried ion-pair quartet involving R67, K70, E77 and E80 which holds the 70-loop and the all important residue Y76 in their correct conformation (15). Indeed the mutants R67A, K70A, E77A and E80A alter the kinetics of FpA and FpB release drastically and to the same extent (3), even though K70 and E80 do not contact the Aα or Bβ chains. Furthermore, the effect of these mutations is practically identical to that caused by the
Y76A mutation (3), suggesting that the role of the buried quartet is to orient Y76 on the surface of the 70-loop for optimal interaction with fibrinogen.

The sequence W52PF54 of the Aα chain frames residue Y76 making a hydrophobic cluster with L65 and I82. AαP53 kinks the Aα chain into exosite I and enables optimal clipping of Y76 by the flanking aromatic residues.

Other contacts made by residues of the Aα chain in this region are energetically dispensable. The sequence D57ED59 of the Aα chain, also present in PAR1 as D58EE60 (3), makes ion-pairs with K81 and K110 through AαD57, and with R77a through AαE58. However, the K81A, K110A and R77aA mutations have little effect on the release of fibrinopeptides (3). Finally, the side chains of AαC55 and AαC65 are accessible to solvent and available for disulfide bridging.

**Interaction with the Bβ chain.** The peptide Bβ(31-148) produced by cyanogen bromide hydrolysis is not as good a substrate as the entire Bβ chain (41). We templated the conformation of F11SAR44 of the Bβ chain by homology with the peptide LDPR complexed with thrombin in 1NRS (17). The Bβ chain also shows a highly conserved proline-rich region in the range of contact with thrombin. The structures of LDPR-hirugen-thrombin 1NRS (17), hirugen-thrombin 1HAH (16) and APTMPPPLPP bound to the SH3 domain 1ABO (18) were used to build the core F11SARGHRPLDDKREEAPSLRPAPP65 of the human Bβ chain fragment. We extended the peptide over its two ends to make a 3D-model of the fragment Bβ(31-72) bound to thrombin. This portion of the Bβ chain is not visible in the available crystal structures (5,7). The first motif visible is a helix starting at position 77 in the corresponding human chain numbering.

As for the Aα chain, the Bβ chain makes contact with an extended surface of thrombin (Figure 1). Residues 31-39 contact exosite II, residues 40-47 bind to the active site, residues 47-55 dock into the groove connecting the active site to exosite I, and residues 56-72 interact with exosite I. The change in exposed surface area when fragment Bβ(31-72) binds to thrombin is 3901 Å² (28% of the thrombin surface), a value that exceeds that of the Aα(20-62)-thrombin complex by 11%. Up to 60% of the contact surface is located outside of the subsites from the aryl binding site to S3'. The relevant contacts for the Bβ(31-72)-thrombin complex are reported in Figure 2 and compared to those of the templates.
The terminal amine and BjG32 amide hydrogen interact with the carboxyl O atoms of D178. The carbonyl O atoms of BjQ31 interact with the guanidinium group of R175. BjD35 interacts with K169, BjE37 superimposes with AαE30 and makes a water-accessible ion-pair with R173, whereas BjE38 forms a solvent accessible ion-pair with R97. As for the Aα chain, these interactions involve solvent exposed residues and are expected to be energetically dispensable.

In the active site region, BjF41 superimposes well with AαF27 and fits in the aryl binding site formed by W215, I174 and L99. Mutations of W215 or L99 have a drastic impact on the release of FpB (3), underscoring the importance of this favorable hydrophobic interaction.

The side chain of BjF40 superimposes with AαL28 and is in close contact with Y60a and W60d in the hydrophobic cluster acting as a lid over the S1 pocket. Mutation of W60d greatly affects the release of FpB (3,37).

BjR44 is embedded into the S1 pocket, with its side chain ion-paired with D189 and its N atom H-bonding to the carbonyl O atom of S214. Mutation of this Arg to Cys as in fibrinogen Ijmuiden (42) abrogates FpB release, as expected.

The Gly residue in P1’ is conserved in all Aα and Bj chains and comes into contact with G193. The P1’ Gly is replaced by Cys in fibrinogen Ise (36), leading to a reduction in clotting activity. The BjH46 heterocycle at P2’ is staked against W60d, as are residues F43 in PAR1, F40 in PAR3 and Y49 in PAR4 (3). Residue BjR47 at the P3’ position makes a solvent exposed ion-pair with E39, whose energetic contribution to recognition is dispensable in view of the properties of the E39A mutant (3).

Unlike the Aα chain, the Bj chain does not possess an exposed Cys available for disulfide bridging in the sequence upstream to the fragment that makes contact with exosite I. The carbonyl O atom of BjP60 interacts weakly with the N atom of R67 in exosite I. As for the Aα chain, the loss of the buried quartet involving R67, K70, E77 and E80 is responsible for the loss of specificity toward the Bj chain in the R67A, K70A or E80A mutations (3). The Bj chain lacks aromatic groups around BjP63, unlike the Aα chain. BjP58 and BjP61 frame F34 and BjP63, BjP64 and BjP65 cage Y76, in a face-to-face or face-to-edge orientation.
BβL59 points into the hydrophobic cluster formed by L65, Y76 and I82. The crucial involvement of Y76 in all these interactions explains why the mutation Y76A has a drastic effect on the release of FpB, as seen for the release of FpA (3).

Residues of the Bβ chain further downstream do not make relevant contacts with the thrombin surface, except for the carbonyl O atom of BβI66 and the hydroxyl of BβS67 that H-bond to the charged amine of K81. The sequence I66SGGG70 is absolutely conserved in all Bβ chains among different species. Of these residues, BβY71 clusters with F114 and BβR72 ion-pairs with D116.

Discussion

The 3D-models of thrombin bound to fragments of the human fibrinogen Aα and Bβ chains are consistent with available data on site-directed mutagenesis of thrombin, and with the phenotype observed with several naturally occurring mutants of fibrinogen. These models also make it possible to align the sequences of fibrinogens from other species and other thrombin natural substrates around their cleavage site. The alignment (Figure 4) suggests a pattern of recognition by thrombin that applies generally to other natural substrates. The two loops 1 and 2 fix the docking into the active site and groove region. In the case of the fibrinogen Aα chain, loop 2 also provides room for the disulfide bridge with the homologous Aα chain via AαC47. Acidic residues are frequently found in the region of the unprimed sites that binds to exosite II. A hydrophobic/aromatic residue fills systematically the aryl binding site, as documented in the crystal structures of thrombin bound to FpA (8,9) or PAR1 (17). A hydrophobic side chain often precedes the residue bound to the aryl binding site (see for example the Aα and Bβ chains of fibrinogen). The added hydrophobicity from this side chain provides optimal packing against the aromatic moiety of W60d. In the primed sites, the P2’ position is often occupied by F, Y, H or P (noted ϕ in Figure 3) to frame the ring of W60d in sandwich with a Pro often found in the P2 position. Furthermore, a Pro residue is often located downstream to the site of cleavage in a position to contact exosite I and appears to be highly conserved among all thrombin substrates, with the exception of factor V, factor XIII and TAFI. The role of this Pro (residue 53 in the case of the Aα chain) is to kink the substrate backbone into exosite I at the thrombin surface. Hydrophobic/aromatic residues often flank this Pro (e.g., Aα chain,
PAR3 and factor XI) and the Aα(20-60)-thrombin model indicates that the role of this aromatic-Pro-aromatic triplet is to cage Y76 for optimal bridge-binding of exosite I and the active site.

There are 838 examples of aromatic-Pro-aromatic triplets in the Protein Database, of which 20% show the aromatic residues pointing in the same direction and caging another aromatic side chain in 5% of the cases. Interestingly, a screening of all sequences in the S1 family of serine proteases shows the presence of a Pro residue located 13 residues downstream to the activation cleavage site in 83% of the cases (the Pro is at position 27 in the standard chymotrypsin numbering). The origin of this conservation is unclear, although the analogy with thrombin substrates discussed above should draw attention to a possible “universal” role of this residue in optimizing the alignment of unprimed residues of substrate for cleavage by the target protease. Site-directed mutagenesis of this conserved Pro in different systems will be necessary to test this hypothesis.
References


**Figure legends**

**Figure 1.** 3D-models of thrombin bound to fragments of the fibrinogen $A\alpha$ (A,B) and $B\beta$ (C,D) chains. Thrombin is displayed as its solvent-accessible surface based on the coordinates 1PPB (15). The fibrinogen fragments $A\alpha$(20-62) and $B\beta$(31-72) are rendered as solid sticks in purple. The orientation is with the thrombin active site at the center (A,C), or exosite I at the center (B,D). The thrombin surface is color-coded to reflect the extent of perturbation induced by the mutation of specific residues (labeled in the top panel) on the value of the specificity constant $k_{cat}/K_m$ for the release of $FpA$ or $FpB$ (3). The scale is: red ($-3.5\div-2.5$ log units), orange ($-2.5\div-1.5$ log units), green ($-1.5\div-0.5$ log units), cyan ($-0.5\div0.5$ log units), blue (0.5$\div$1.5 log units). Residue K70 is buried under Y76 in exosite I and is not visible.

**Figure 2.** Bound fragments $A\alpha$(20-57) (blue in A and B) and $B\beta$(31-68) (magenta in C and D) displayed over the thrombin surface of the active site (A and C) and exosite I (B and D) and superimposed to the peptides used as templates: DFLAEKGGR from 1BBR (green in A), hirugen NGDFEELPEEYL from 1HAH (green in B and D), LDPR from 1NRS (green in C). The r.m.s. deviations between the backbones of fragments $A\alpha$ and $B\beta$ relative to hirugen are 1.44 Å and 0.41 Å, respectively. Contacts with thrombin residues <6 Å are listed in E for $A\alpha$(20-57), $B\beta$(31-68), and the templates LDPR and hirugen. Sequences in E are aligned according to the 3D-models of complexes. The position of phosphate groups and disulfide bridges are indicated.

**Figure 3.** 3D-models of the fibrinogen fragments (with residues numbered in blue) $A\alpha$(20-57) for wild-type (blue) and the F27Y mutant (green), displayed over the thrombin surface of the active site (with residues numbered in black). The F27Y mutation introduces a H-bond between the hydroxyl group of Y27 and the N atom of V34, which fixes the aromatic ring of Y27 into a distorted position that pulls thrombin W215 1.4 Å higher and out of the aryl binding site. This perturbation results in a non-favorable increase in the solvent exposure of the hydrophobic surface of the entire aryl binding site around W215.
Figure 4. Thrombin substrate sequences docked over thrombin and aligned from their 3D-superposition. Sequences refer to human unless otherwise specified. Orthologous Aα and Bβ chains of fibrinogen were aligned below human sequences with Clustal X. The position of the first residue is indicated in the second column. Sequence and structure files in the last column are specified from SwissProt, Genbank and Protein Data Bank.
Figure 1  Rose & Di Cera, 2002
Figure 2  Rose & Di Cera, 2002
Figure 3  Rose & Di Cera, 2002
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3D-modeling of thrombin-fibrinogen interaction
Thierry Rose and Enrico Di Cera

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