Species Specificity of the Complement Inhibitor Compstatin by All-atom Molecular Dynamics Simulations

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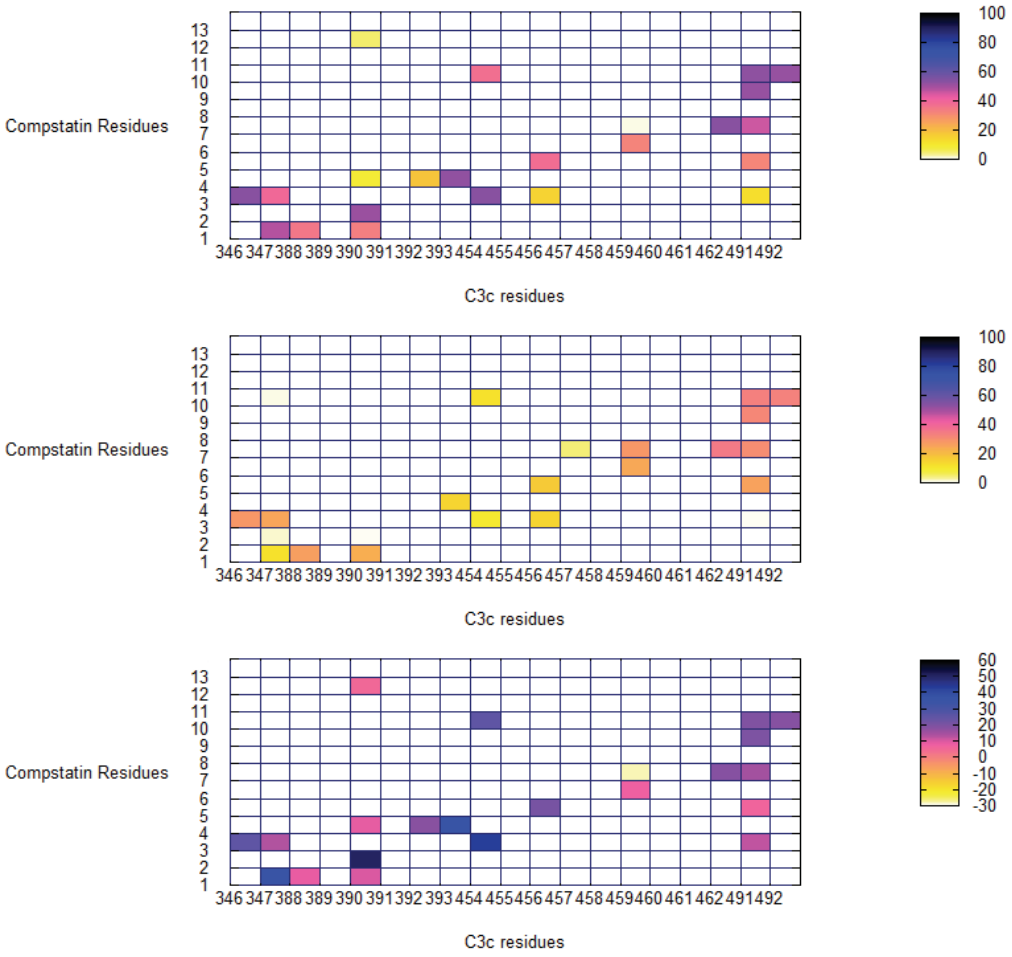
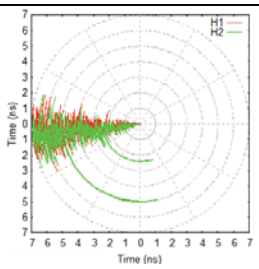
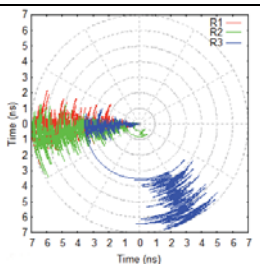
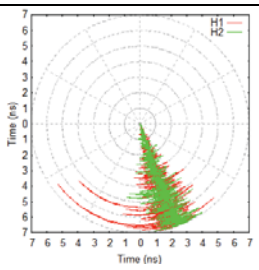
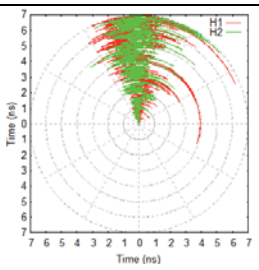
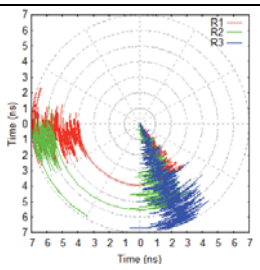
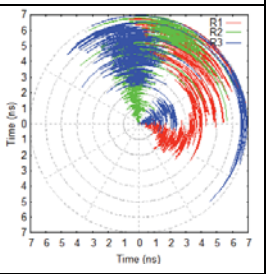
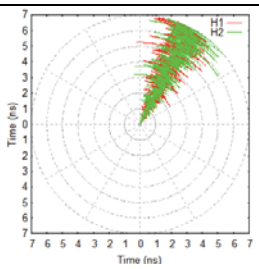
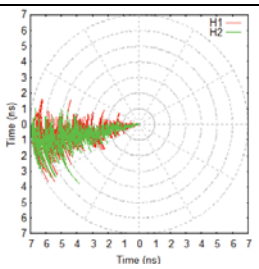
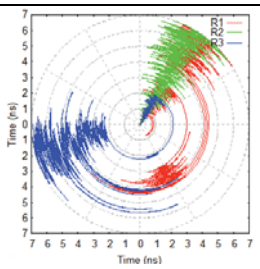
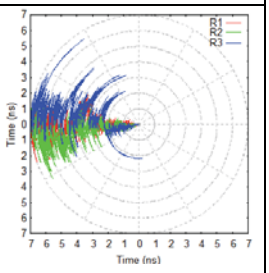
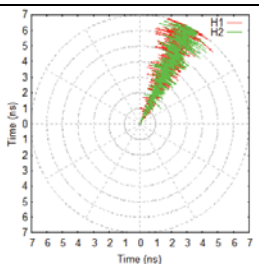
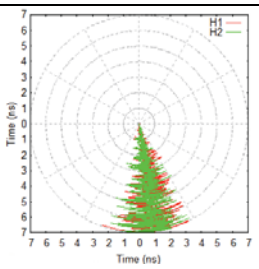
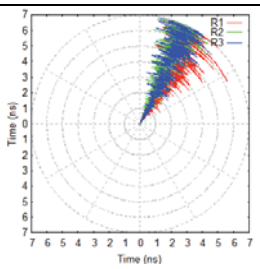
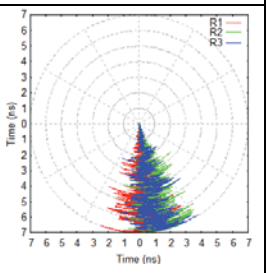
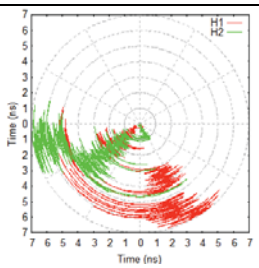
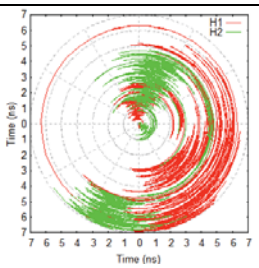
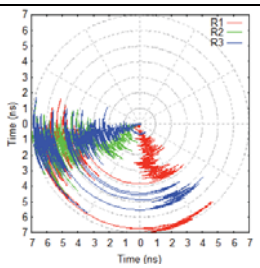
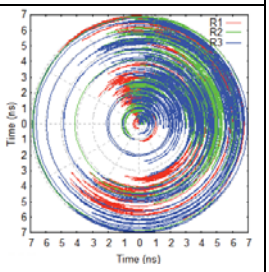
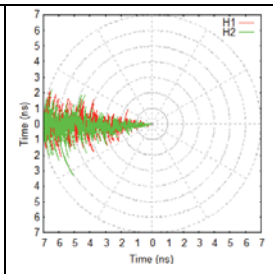
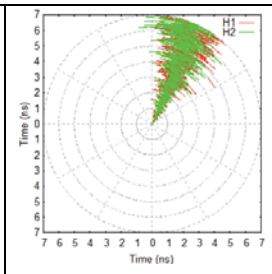
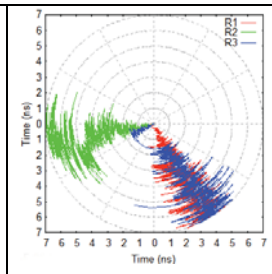
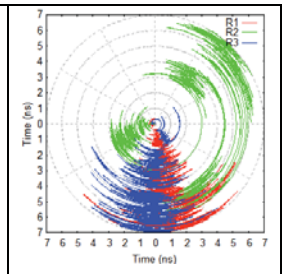
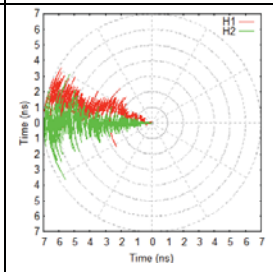
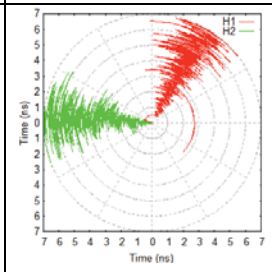
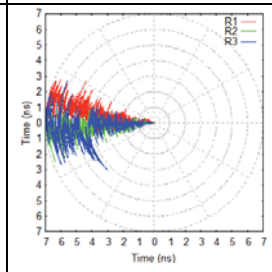
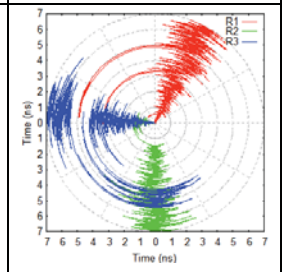
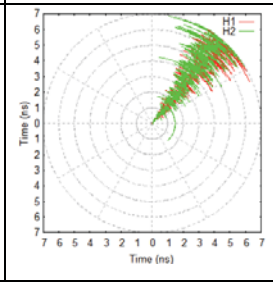
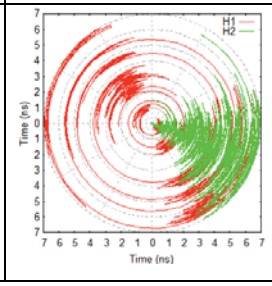
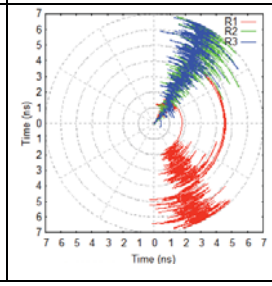
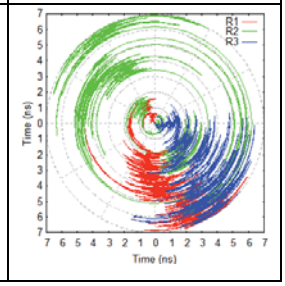
Supplementary Material

Supplementary Figure SF1. Probability density maps (%) of side-chain contacts for selected protein-ligand side-chain pairs. Two side-chains were considered in contact if the distance between their geometric centers was less than 6 Å. The plots from **top** to **bottom** display the human, rat and difference (human-rat) maps. The human and rat maps are averaged, respectively, over the human (H1-H2) and rat (R1-R3) complex simulations. The difference map shows that most protein-ligand side-chain contacts are less frequent in the rat complex.

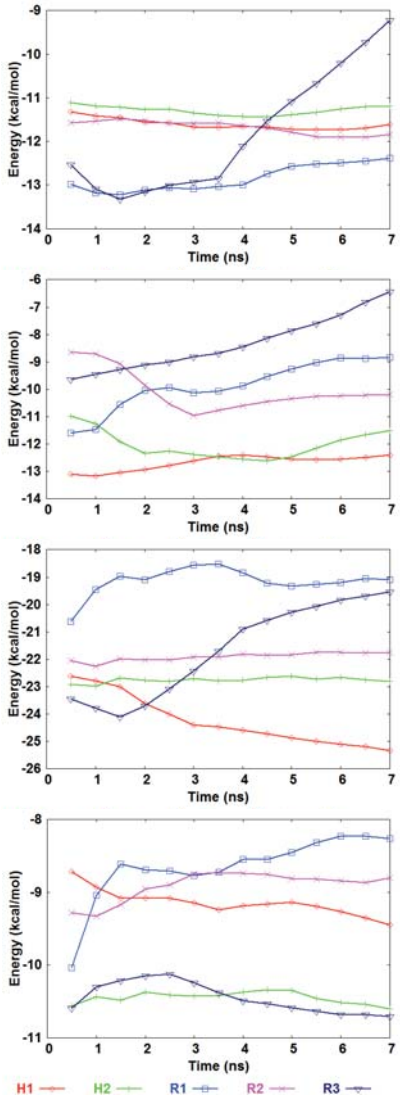


Supplementary Figure SF2. Dial plots of the time evolution of selected compstatin and C3c side-chain torsional angles, during the human and rat C3c:compstatin simulations.

Res.	Human Chi1	Human Chi2	Rat Chi1	Rat Chi2
Val3				
Trp4				
Gln5				
Trp7				
Asn 390				

Leu/ His 454				
Arg 456				
Asp 491				

Supplementary Figure SF3. Non-polar interaction energies between compstatin and proximal protein sectors in the human and rat complexes, plotted as a function of the simulation time. The plots from **top** to **bottom** correspond to sectors 344-349, 388-393, 454-462 and 488-492; residues in these sectors were located within 7 Å from compstatin.



Supplementary Figure SF3 contains plots of the non-polar interaction energy of W4A9 with the four C3c proximal sectors 344-349, 388-393, 454-462 and 488-492. The ligand-C3c interactions with sectors 388-393 and 454-462 are significantly stronger in the human simulations. In run R1, the ligand loses contacts with the last three sectors and optimizes its interaction with the segment 344-349. In run R3, the ligand loses contacts with the first three sectors and improves its interactions with the last sector.

Table ST1: Human Complex: Compstatin residue interaction energies of Fig. 3 in main text. Indicative errors (in parentheses) correspond to the standard deviation of mean values, computed over four successive trajectory segments of equal length (1.75 ns). All values are in kcal/mol.

Compstatin	Polar Energy (kcal/mol)	Non-polar Energy (kcal/mol)	Total Energy (kcal/mol)
Ile1	-3.13 (1.55)	-7.12 (0.89)	-10.24 (2.22)
Cys2	-3.10 (1.03)	-3.28 (0.31)	-6.38 (0.93)
Val3	-1.48 (0.08)	-8.63 (0.18)	-10.12 (0.20)
Trp4	-7.31 (2.38)	-9.63 (0.44)	-16.94 (2.50)
Gln5	-5.59 (0.87)	-6.06 (0.31)	-11.65 (1.09)
Asp6	-1.50 (0.62)	-1.83 (0.27)	-3.33 (0.80)
Trp7	-2.51 (0.34)	-16.79 (0.81)	-19.31 (1.07)
Gly8	-3.94 (0.18)	-1.96 (0.12)	-5.90 (0.13)
Ala9	-6.51 (1.37)	-0.67 (0.18)	-7.18 (1.21)
His10	-12.44 (2.81)	-3.05 (0.37)	-15.49 (2.56)
Arg11	-0.11 (0.42)	-0.63 (0.11)	-0.74 (0.33)
Cys12	0.24 (0.03)	-0.83 (0.08)	-0.59 (0.08)
Thr13	0.02 (0.02)	-0.03 (0.01)	-0.01 (0.02)

Table ST1 (continued): Human Complex: C3c residue interaction energies of Fig. 3 in main text. Indicative errors (in parentheses) correspond to the standard deviation of mean values, computed over four successive trajectory segments of equal length (1.75 ns). All values are in kcal/mol.

C3c	Polar Energy (kcal/mol)	Non-polar Energy (kcal/mol)	Total Energy (kcal/mol)
Pro344	-0.08 (0.04)	-0.29 (0.01)	-0.36 (0.05)
Gly345	-5.03 (0.32)	-2.68 (0.06)	-7.72 (0.27)
Met346	-0.53 (0.12)	-3.92 (0.11)	-4.45 (0.19)
Pro347	0.00 (0.18)	-4.22 (0.27)	-4.21 (0.38)
Phe348	0.03 (0.04)	-0.24 (0.05)	-0.21 (0.05)
Asp349	0.08 (0.13)	-0.13 (0.03)	-0.05 (0.12)
Ser388	-0.59 (0.72)	-1.25 (0.29)	-1.84 (0.85)
Ile389	0.27 (0.21)	-0.95 (0.32)	-0.68 (0.26)
Asn390	-5.62 (1.64)	-4.29 (0.57)	-9.92 (2.00)
Thr391	0.01 (0.04)	-1.15 (0.03)	-1.14 (0.05)
His392	-0.56 (0.14)	-1.91 (0.44)	-2.47 (0.46)
Pro393	-0.01 (0.03)	-2.48 (0.13)	-2.49 (0.14)
Leu454	-0.01 (0.03)	-2.86 (0.25)	-2.87 (0.24)
Leu455	-0.44 (0.29)	-2.90 (0.15)	-3.35 (0.23)
Arg456	-8.17 (0.65)	-5.73 (0.46)	-13.90 (0.34)
Met457	-3.47 (0.55)	-2.34 (0.10)	-5.82 (0.57)
Asp458	1.34 (0.25)	-2.03 (0.16)	-0.69 (0.24)
Arg459	-1.36 (0.73)	-4.76 (0.86)	-6.12 (1.49)
Ala460	0.11 (0.01)	-0.17 (0.02)	-0.07 (0.02)
His461	-0.46 (0.06)	-0.15 (0.02)	-0.61 (0.08)
Glu462	1.04 (0.10)	-3.30 (0.15)	-2.26 (0.09)
Pro488	-0.21 (0.01)	-0.19 (0.01)	-0.39 (0.01)
Gly489	-0.60 (0.06)	-1.84 (0.10)	-2.44 (0.15)
Gln490	0.19 (0.05)	-1.46 (0.02)	-1.27 (0.06)
Asp491	-23.33 (2.82)	-4.42 (0.69)	-27.75 (2.28)
Leu492	-0.02 (0.05)	-2.16 (0.33)	-2.18 (0.33)

Table ST2: Compstatin residue interaction energy differences (human – rat) of Fig. 3 in main text. Indicative errors (in parentheses) correspond to the standard deviation of mean values, computed over four successive trajectory segments of equal length (1.75 ns). All values are in kcal/mol.

Compstatin	Polar Energy (kcal/mol)	Non-polar Energy (kcal/mol)	Total Energy (kcal/mol)
Ile1	-1.54 (2.06)	-0.29 (1.64)	-1.83 (2.96)
Cys2	-2.15 (1.50)	-0.86 (0.75)	-3.01 (1.76)
Val3	-0.38 (0.70)	-1.23 (1.52)	-1.61 (2.06)
Trp4	0.42 (4.50)	-2.74 (3.04)	-2.32 (6.42)
Gln5	-1.96 (1.81)	-0.59 (1.41)	-2.55 (2.80)
Asp6	-1.05 (1.49)	-0.45 (0.54)	-1.49 (1.36)
Trp7	-0.84 (1.07)	-1.66 (1.43)	-2.50 (1.98)
Gly8	-0.34 (0.94)	-0.26 (0.37)	-0.60 (0.99)
Ala9	-0.24 (1.95)	-0.06 (0.34)	-0.31 (1.69)
His10	-3.79 (5.14)	0.21 (0.82)	-3.59 (5.10)
Arg11	0.50 (0.46)	-0.10 (0.19)	0.40 (0.44)
Cys12	0.13 (0.08)	-0.58 (0.18)	-0.45 (0.12)
Thr13	0.00 (0.03)	0.00 (0.06)	0.00 (0.06)

Table ST2 (continued): C3c residue interaction energy differences (human – rat) of Fig. 3 in main text. Indicative errors (in parentheses) correspond to the standard deviation of mean values, computed over four successive trajectory segments of equal length (1.75 ns). All values are in kcal/mol.

C3c	Polar Energy (kcal/mol)	Non-polar Energy (kcal/mol)	Total Energy (kcal/mol)
Pro344	-0.02 (0.09)	-0.07 (0.08)	-0.09 (0.13)
Gly345Ala	-1.66 (1.62)	0.33 (0.92)	-1.33 (2.46)
Met346	-0.50 (0.19)	-0.50 (0.85)	-1.00 (0.92)
Pro347	-0.08 (0.22)	0.04 (0.83)	-0.04 (0.92)
Phe348	0.01 (0.06)	0.01 (0.09)	0.02 (0.11)
Asp349	0.03 (0.14)	-0.05 (0.04)	-0.02 (0.13)
Ser388	-0.07 (1.18)	-0.01 (0.41)	-0.08 (1.19)
Ile389Val	0.27 (0.26)	0.08 (0.44)	0.35 (0.45)
Asn390	-3.80 (2.40)	-1.07 (1.17)	-4.88 (3.31)
Thr391	-0.12 (0.28)	-0.47 (0.32)	-0.58 (0.30)
His392Pro	-0.49 (0.20)	-1.49 (0.58)	-1.98 (0.66)
Pro393Asn	0.25 (0.25)	-0.52 (0.96)	-0.27 (1.14)
Leu454His	1.35 (1.42)	-0.88 (0.82)	0.47 (1.78)
Leu455	-0.32 (0.47)	-0.31 (0.35)	-0.64 (0.55)
Arg456	0.40 (3.12)	-0.77 (0.93)	-0.37 (3.57)
Met457Thr	-0.40 (1.37)	-0.29 (0.34)	-0.70 (1.55)
Asp458	-0.10 (0.51)	0.09 (0.55)	-0.02 (0.35)
Arg459Ala	-1.21 (0.73)	-1.87 (0.89)	-3.08 (1.51)
Ala460Gly	0.00 (0.03)	0.01 (0.03)	0.01 (0.03)
His461Gln	-0.02 (0.14)	0.04 (0.03)	0.01 (0.17)
Glu462	0.14 (0.42)	0.01 (0.38)	0.15 (0.41)
Pro488	-0.02 (0.05)	-0.01 (0.03)	-0.03 (0.07)
Gly489	-0.04 (0.16)	-0.17 (0.28)	-0.21 (0.44)
Gln490	0.02 (0.16)	-0.08 (0.17)	-0.06 (0.18)
Asp491	-4.86 (7.60)	0.09 (0.88)	-4.77 (7.15)
Leu492	0.04 (0.11)	-0.61 (0.88)	-0.57 (0.94)