Electronic Supplementary Material (ESI) for RSC Advances.

Two statins and cromolyn as possible drugs against the cytotoxicity of Aβ(31-35) and Aβ(25-35) peptides: a comparative study by advanced computer simulations methods

Supporting Information

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Content

1 Drug models: partial atomic charges

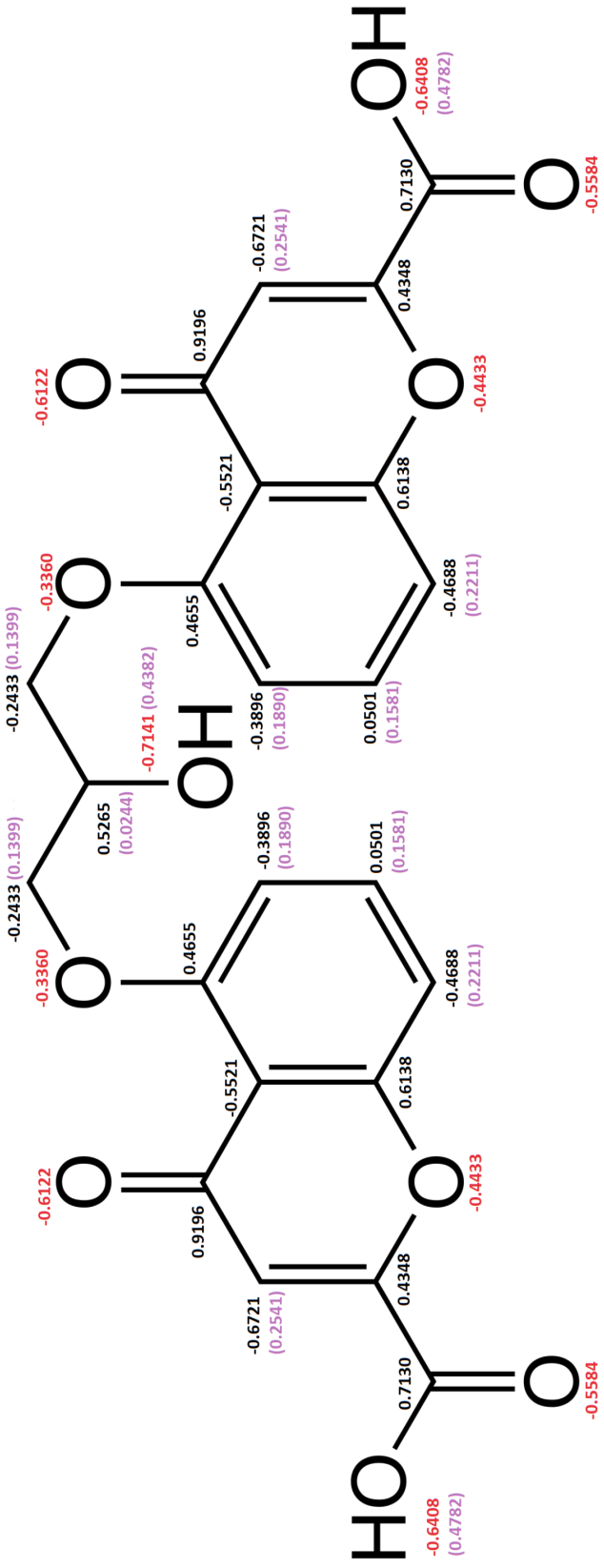

Figure S1: Partial atomic charges for cromolyn. Charges for hydrogen atoms are in parenthesis. Charge colors have the following meaning: red is for oxygen, black is for carbon, light violet is for hydrogen.

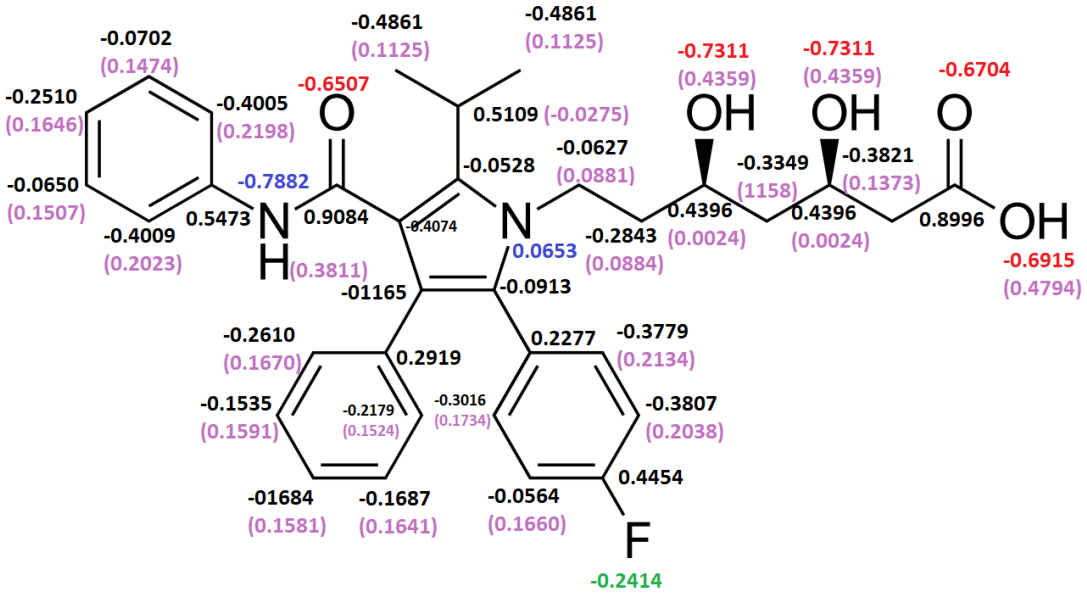

Figure S2: Partial atomic charges for atorvastatin. Charges for hydrogen atoms are in parenthesis. Charge colors have the following meaning: red is for oxygen, black is for carbon, light violet is for hydrogen, blue is for nitrogen, green is for fluor.

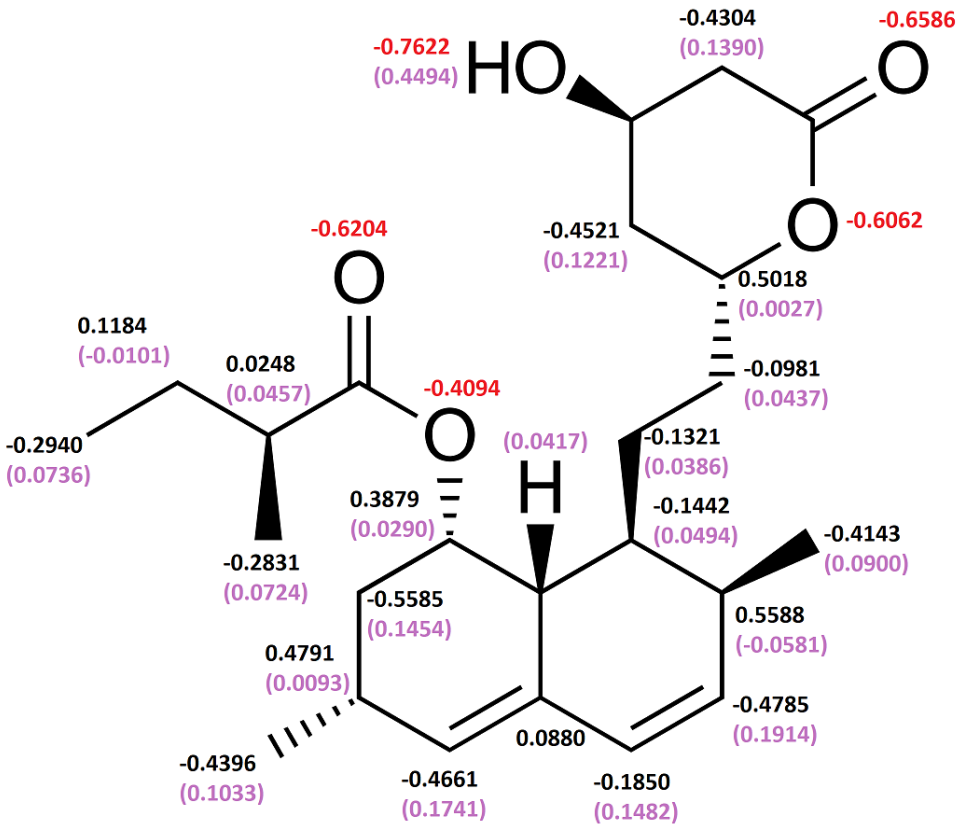

Figure S3: Partial atomic charges for lovastatin. Charges for hydrogen atoms are in parenthesis. Charge colors have the following meaning: red is for oxygen, black is for carbon, light violet is for hydrogen.

2 Classical MD: Final dimensions of simulation boxes and proofs of equilibration

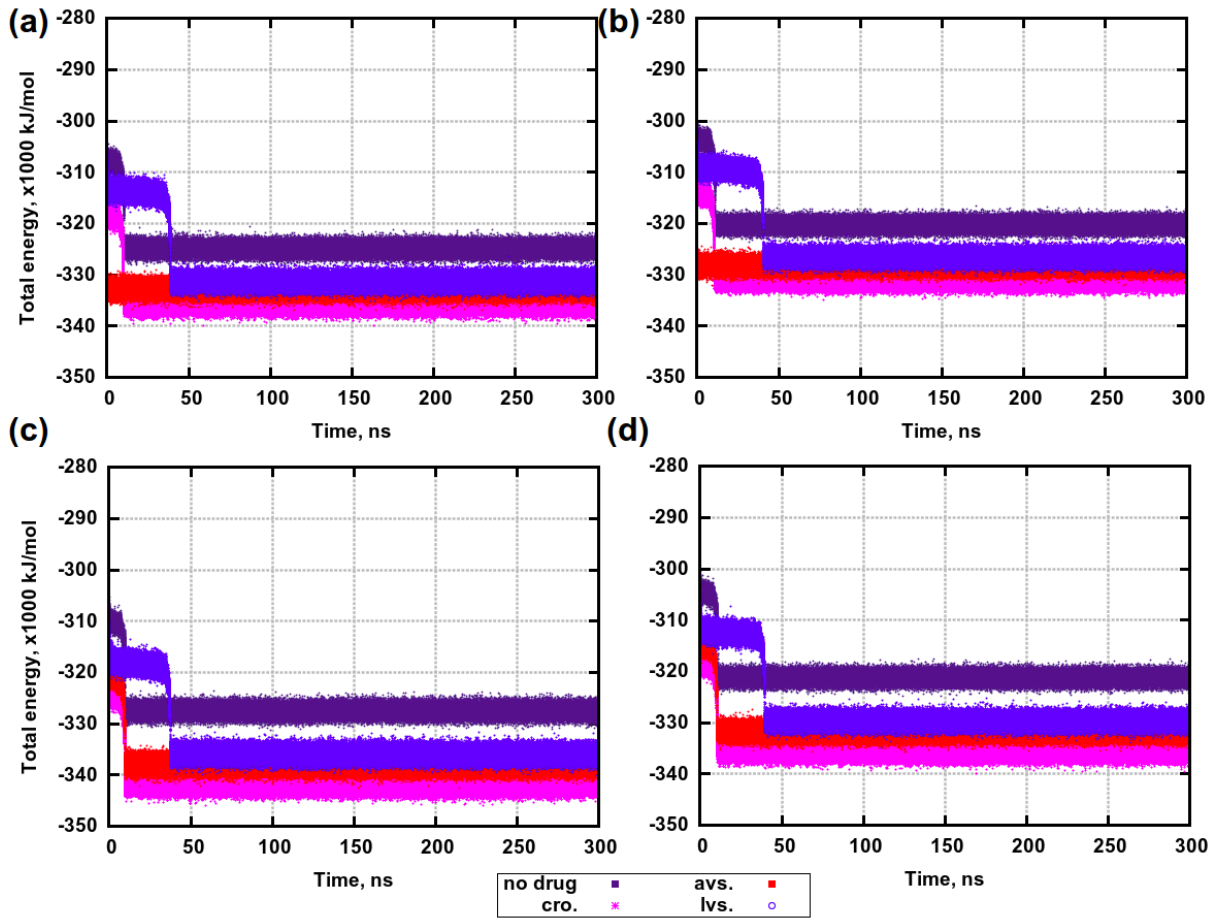

Figure S4: Convergence of total energy profiles for some simulated systems. (a) Systems containing 6 A$\beta(25-35)$ (b) Systems containing 6 A$\beta(31-35)$ (c) Systems containing 8 A$\beta(25-35)$ (d) Systems containing 8 A$\beta(31-35)$. Abbreviations mean the following: "no drug" - systems with no drugs, "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

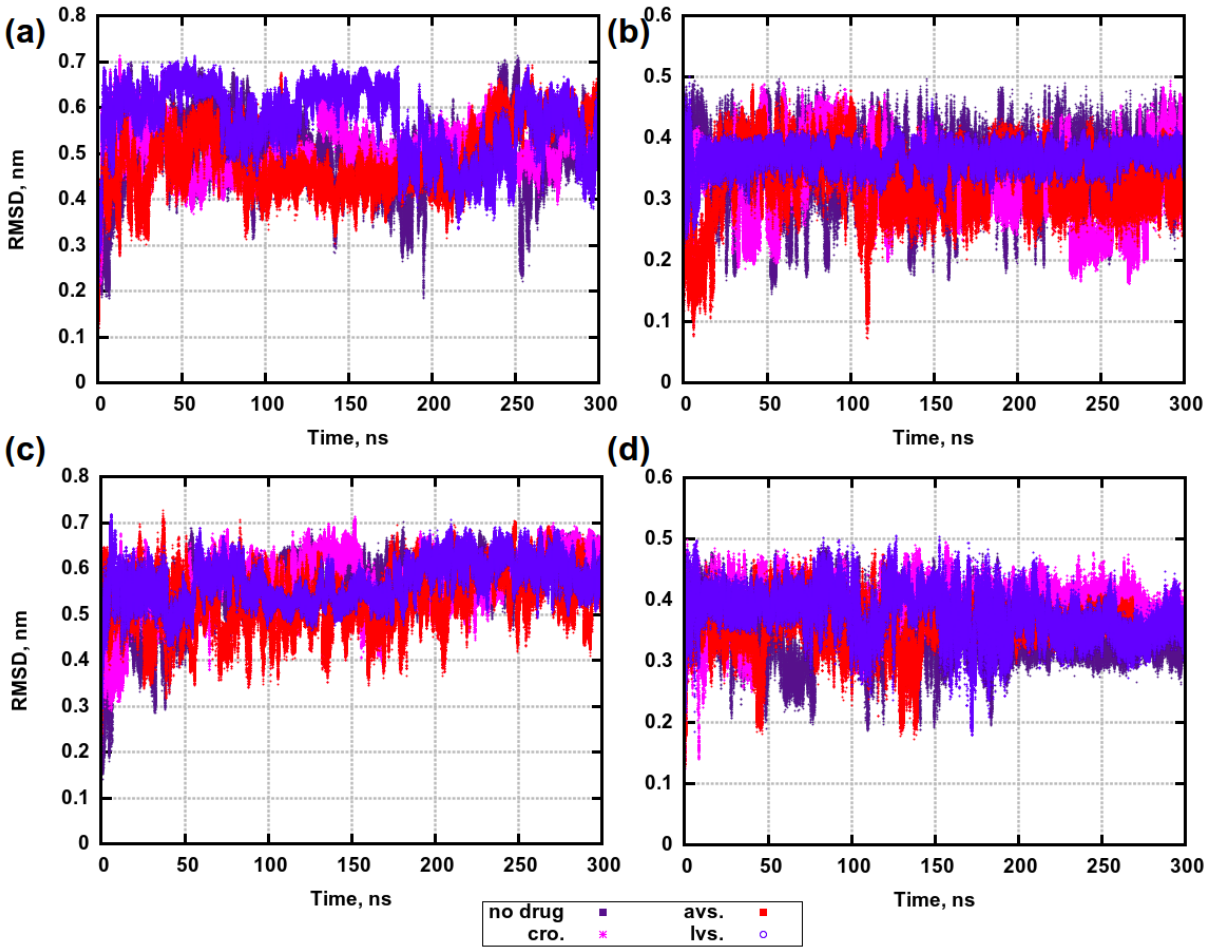

Figure S5: Root mean square deviation (RMSD) for selected single peptides in some simulated systems. (a) Systems containing 6 A$\beta(25-35)$ (b) Systems containing 6 A$\beta(31-35)$ (c) Systems containing 8 A$\beta(25-35)$ (d) Systems containing 8 A$\beta(31-35)$. Abbreviations mean the following: "no drug" - systems with no drugs, "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

Table S1: Dimensions of simulation boxes (in nm) after the equilibration (classical MD).

System	Cromolyn x=y=z	Atorvastatin x=y=z	Lovastatin x=y=z
6 Drug	6.77	6.78	6.77
8 Drug	6.77	6.79	6.78
6 A$\beta(25-35)$+ 6 Drug	6.82	6.83	6.82
8 A$\beta(25-35)$+ 8 Drug	6.84	6.86	6.85
6 A$\beta(31-35)$+ 6 Drug	6.80	6.81	6.80
8 A$\beta(31-35)$+ 8 Drug	6.82	6.83	6.82

For calculations of molar concentrations the following equation was applied:

$$c = \frac{N}{N_A V} \tag{S1}$$

In this formula: N is the number of molecules of a component, $N_A = 6.02214076 \cdot 10^{23}\ mol^{-1}$ is the Avogadro's number, V is the volume of the simulation box after the equilibration.

Table S2: Concentrations (c) of components (in mol/m^3) for systems with Cromolyn. "counter" represents Cl counter ions.

System	c(Aβ)	c(Drug)	c(counter)
6 Drug	none	32.11	none
8 Drug	none	42.81	none
6 A$\beta(25-35)$+6 Drug	31.41	31.41	31.41
8 A$\beta(25-35)$+8 Drug	41.51	41.51	41.51
6 A$\beta(31-35)$+6 Drug	31.69	31.69	none
8 A$\beta(31-35)$+8 Drug	41.88	41.88	none

Table S3: Concentrations (c) of components (in mol/m^3) for systems with Atorvastatin. "counter" represents Cl counter ions.

System	c(Aβ)	c(Drug)	c(counter)
6 Drug	none	31.97	none
8 Drug	none	42.44	none
6 A$\beta(25-35)$+6 Drug	31.27	31.27	31.27
8 A$\beta(25-35)$+8 Drug	41.15	41.15	41.15
6 A$\beta(31-35)$+6 Drug	31.55	31.55	none
8 A$\beta(31-35)$+8 Drug	41.69	41.69	none

Table S4: Concentrations (c) of components (in mol/m^3) for systems with Lovastatin. "counter" represents Cl counter ions.

System	c(Aβ)	c(Drug)	c(counter)
6 Drug	none	32.11	none
8 Drug	none	42.62	none
6 A$\beta(25-35)$+6 Drug	31.41	31.41	31.41
8 A$\beta(25-35)$+8 Drug	41.33	41.33	41.33
6 A$\beta(31-35)$+6 Drug	31.69	31.69	none
8 A$\beta(31-35)$+8 Drug	41.88	41.88	none

3 Classical MD: RDFs, radius of gyration and contact maps

Table S5: Radius of gyration in nm (systems with 6 molecules).

System	Peptide	Drug
pure cro.	–	1.59
pure avs.	–	2.05
pure lvs.	–	2.17
A$\beta(25-35)$ & cro.	3.06	2.16
A$\beta(25-35)$ & avs.	2.82	1.62
A$\beta(25-35)$ & lvs.	3.15	2.14
A$\beta(25-35)$ (pure)	2.94	–
A$\beta(31-35)$ & cro.	2.82	1.99
A$\beta(31-35)$ & avs.	2.61	1.83
A$\beta(31-35)$ & lvs.	2.29	1.93
A$\beta(31-35)$ (pure)	3.00	–

Table S6: Radius of gyration in nm (systems with 8 molecules).

System	Peptide	Drug
pure cro.	–	1.94
pure avs.	–	2.17
pure lvs.	–	1.94
A$\beta(25-35)$ & cro.	2.92	2.17
A$\beta(25-35)$ & avs.	3.06	2.08
A$\beta(25-35)$ & lvs.	3.30	2.75
A$\beta(25-35)$ (pure)	3.01	–
A$\beta(31-35)$ & cro.	2.42	1.94
A$\beta(31-35)$ & avs.	2.84	2.52
A$\beta(31-35)$ & lvs.	2.61	2.20
A$\beta(31-35)$ (pure)	2.73	–

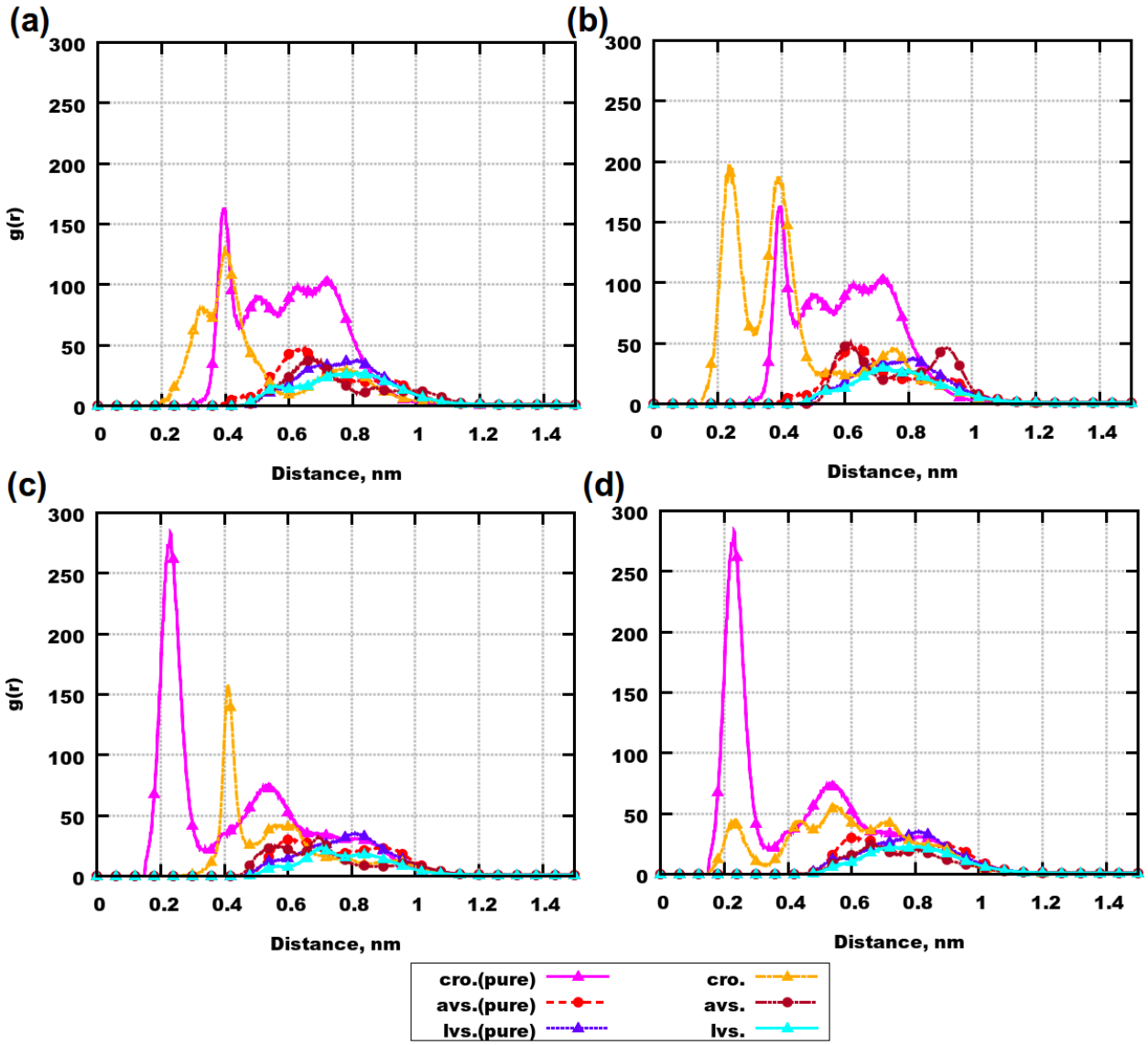

Figure S6: Radial distribution functions between molecular centers of mass of drugs. (a) Systems without (pure) and with 6 A$\beta(25-35)$. (b) Systems without (pure) and with 6 A$\beta(31-35)$. (c) Systems without (pure) and with 8 A$\beta(25-35)$. (d) Systems without (pure) and with 8 A$\beta(31-35)$. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin. Here curves for systems without peptides were plotted for a comparison.

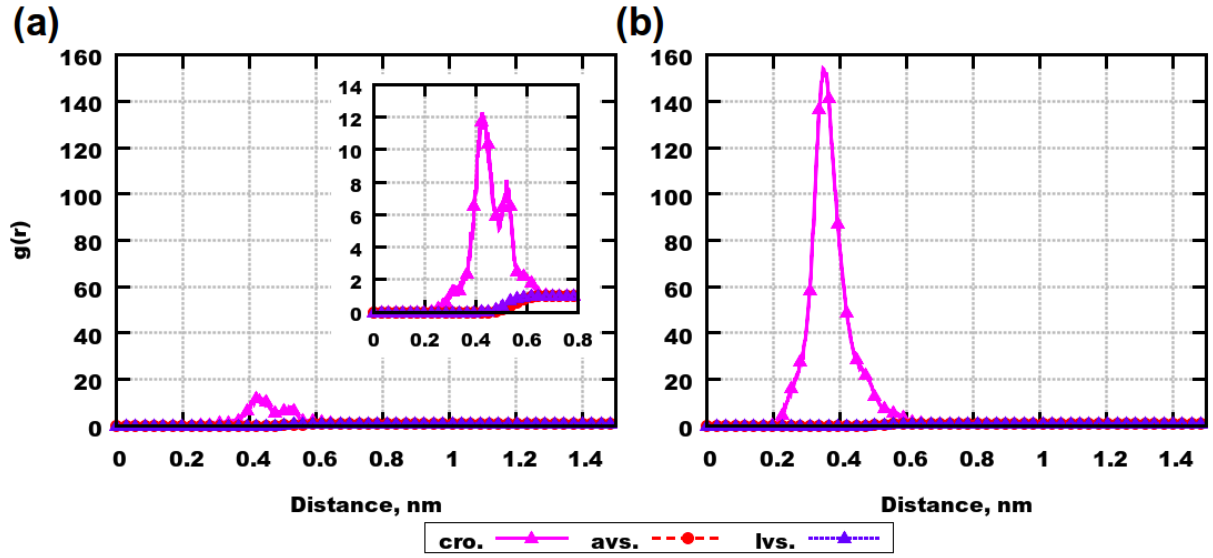

Figure S7: Radial distribution functions between molecular centers of mass of glycine (GLY_{25}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 8 A$\beta(25-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

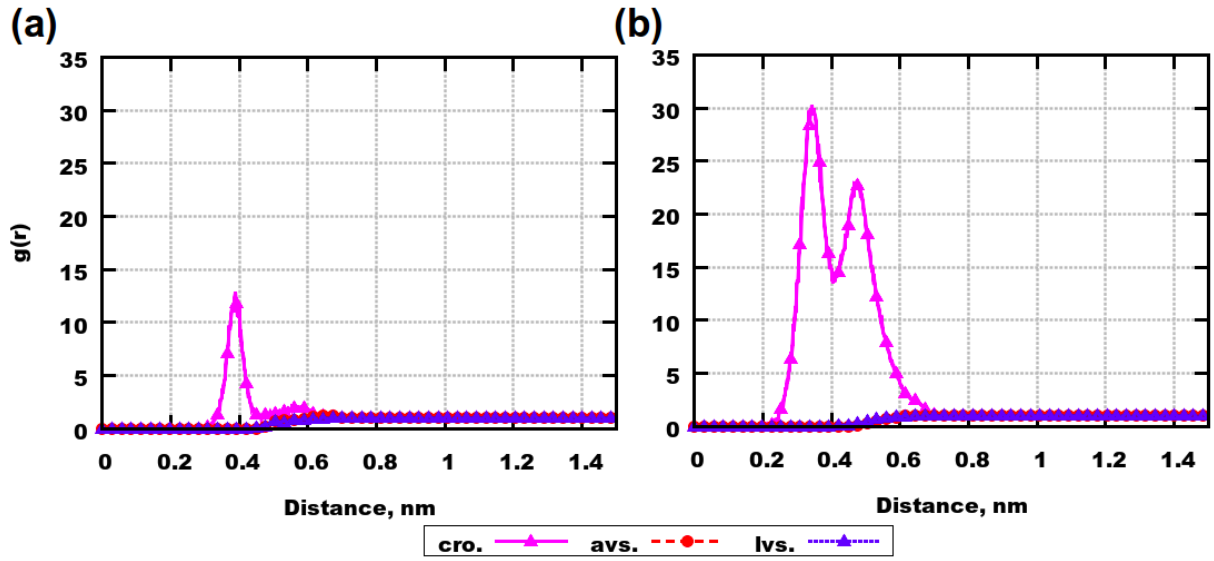

Figure S8: Radial distribution functions between molecular centers of mass of serine (SER_{26}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 8 A$\beta(25-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

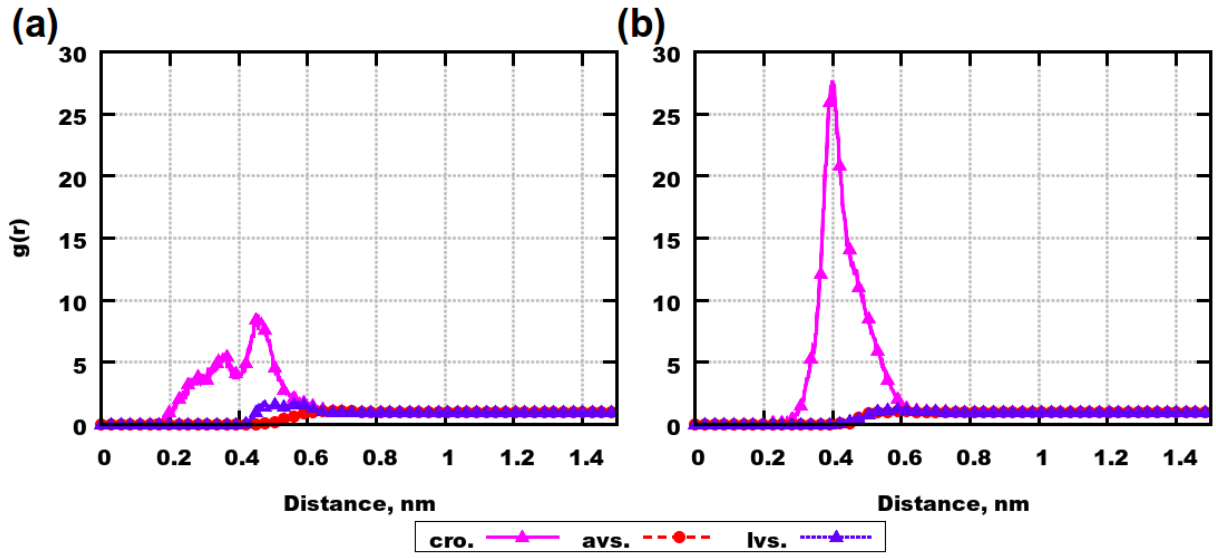

Figure S9: Radial distribution functions between molecular centers of mass of asparagine (ASN_{27}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 8 A$\beta(25-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

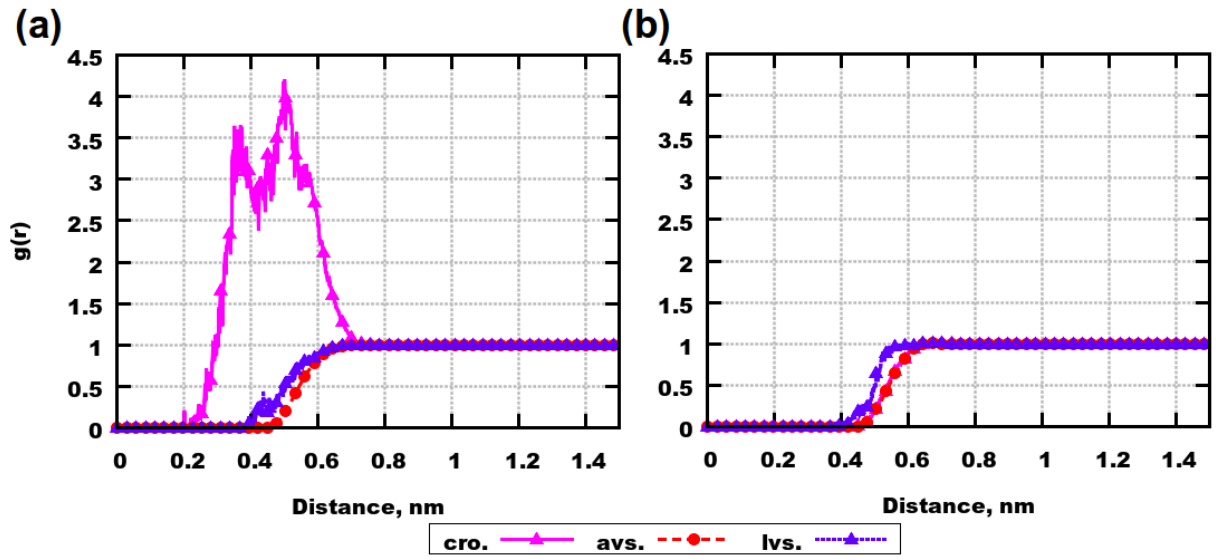

Figure S10: Radial distribution functions between molecular centers of mass of lysine (LYS_{28}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 8 A$\beta(25-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

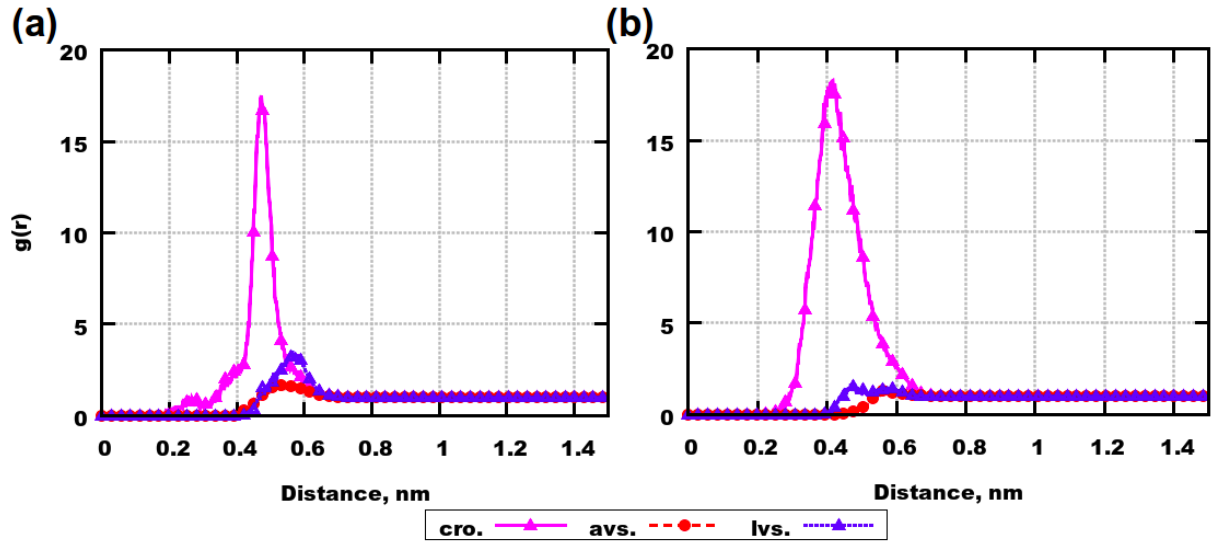

Figure S11: Radial distribution functions between molecular centers of mass of glycine (GLY_{29}) and drugs. (a) Systems containing 6 Aβ(25−35) with and without drugs. (b) Systems containing 8 Aβ(25−35) with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

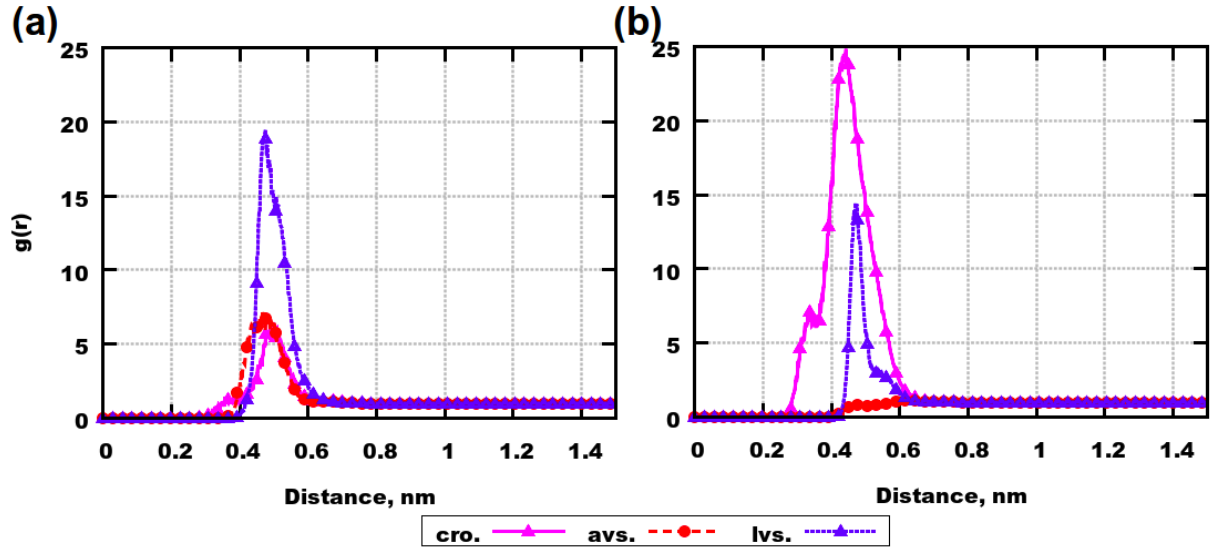

Figure S12: Radial distribution functions between molecular centers of mass of alanine (ALA_{30}) and drugs. (a) Systems containing 6 Aβ(25−35) with and without drugs. (b) Systems containing 8 Aβ(25−35) with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

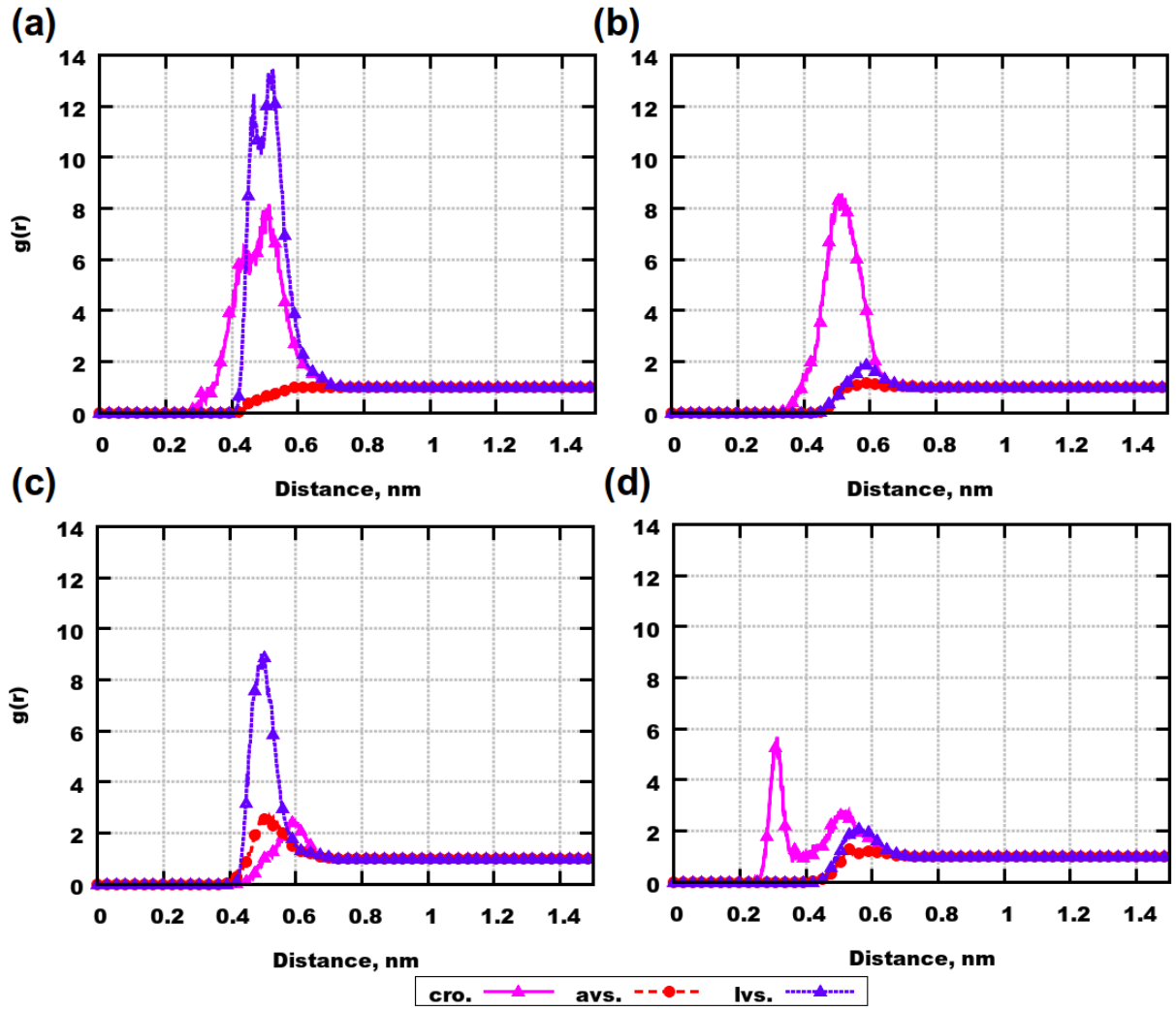

Figure S13: Radial distribution functions between molecular centers of mass of isoleucine (ILE_{31}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 6 A$\beta(31-35)$ with and without drugs. (c) Systems containing 8 A$\beta(25-35)$ with and without drugs. (d) Systems containing 8 A$\beta(31-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

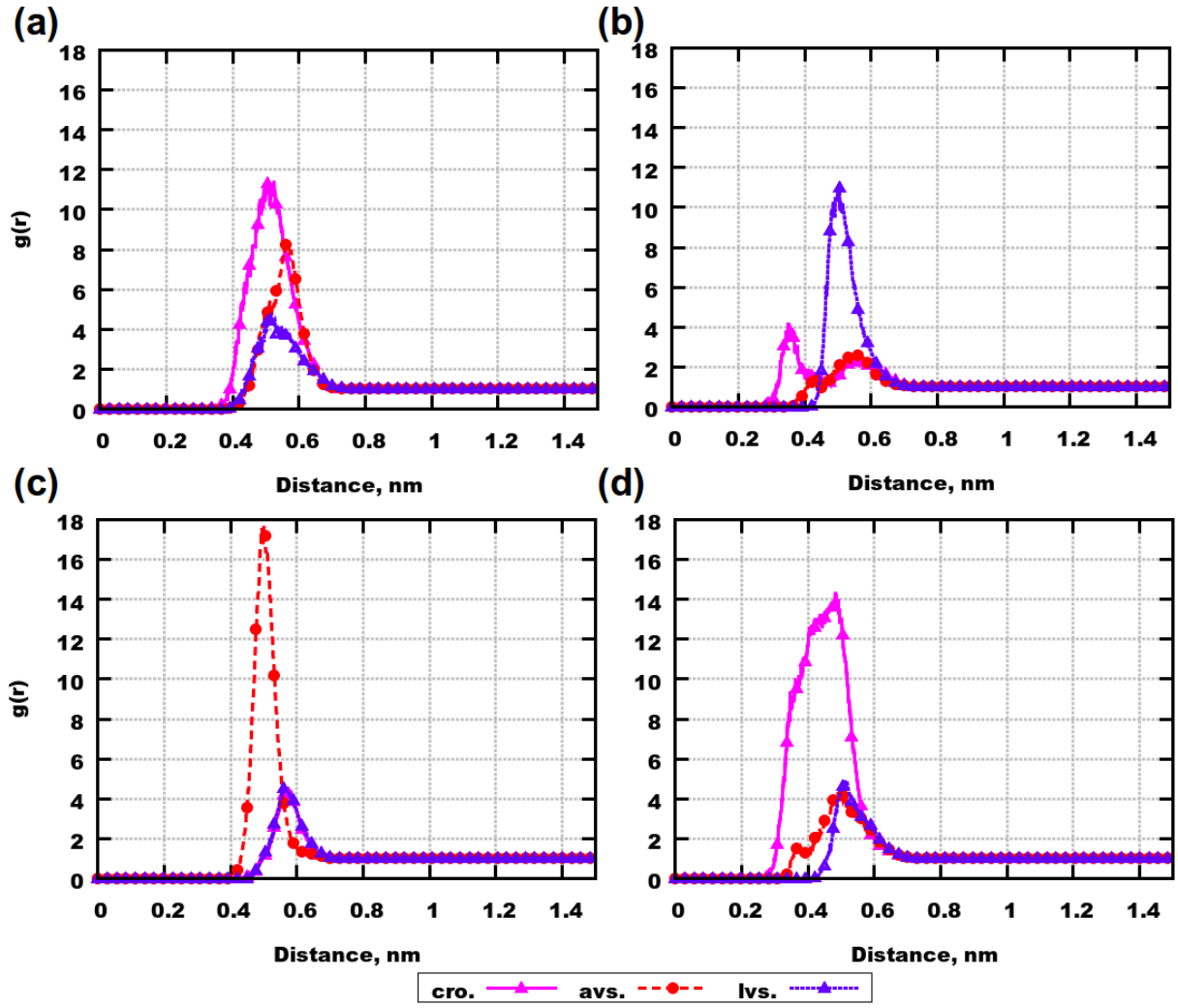

Figure S14: Radial distribution functions between molecular centers of mass of isoleucine (ILE_{32}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 6 A$\beta(31-35)$ with and without drugs. (c) Systems containing 8 A$\beta(25-35)$ with and without drugs. (d) Systems containing 8 A$\beta(31-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

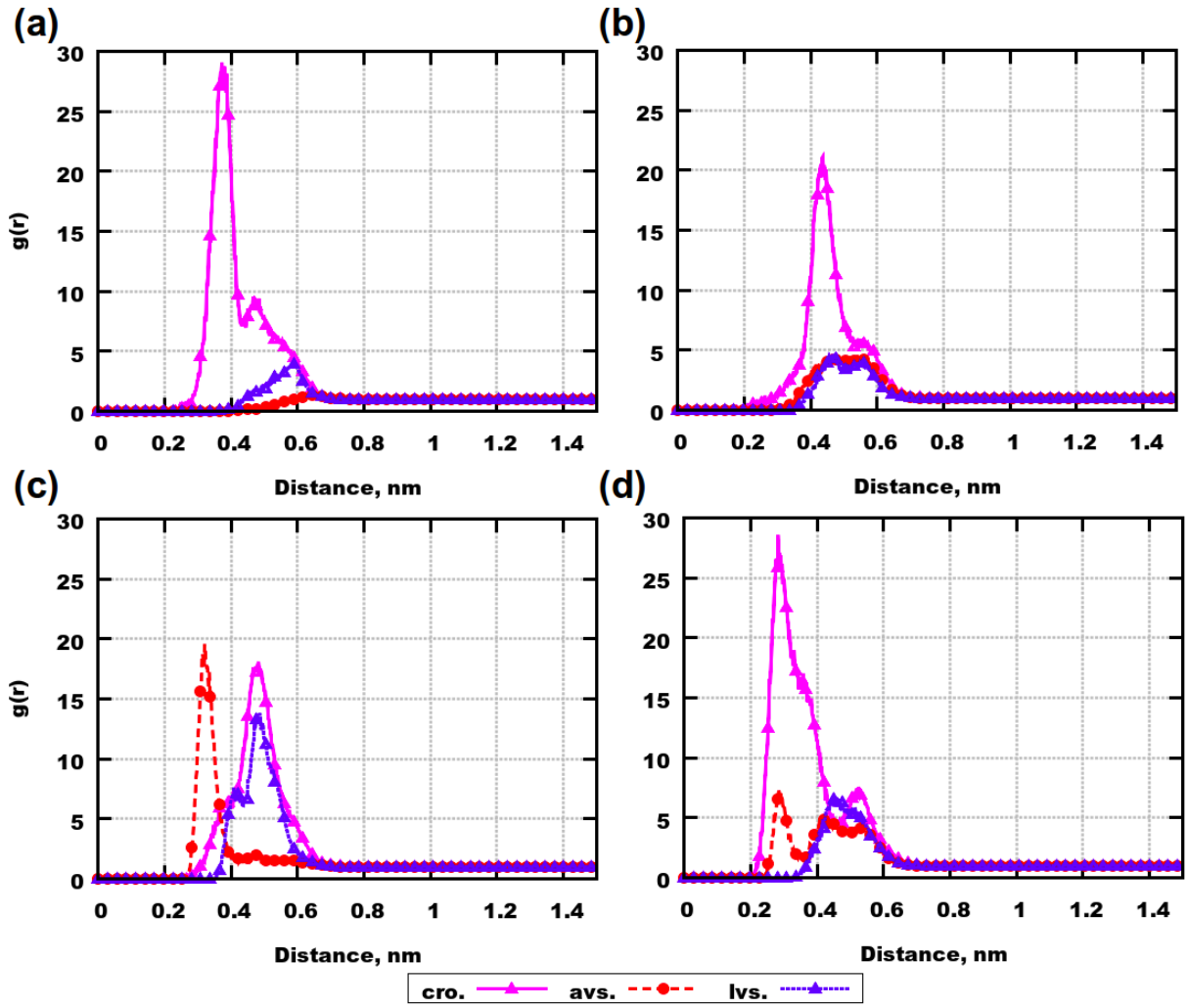

Figure S15: Radial distribution functions between molecular centers of mass of glycine (GLY_{33}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 6 A$\beta(31-35)$ with and without drugs. (c) Systems containing 8 A$\beta(25-35)$ with and without drugs. (d) Systems containing 8 A$\beta(31-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

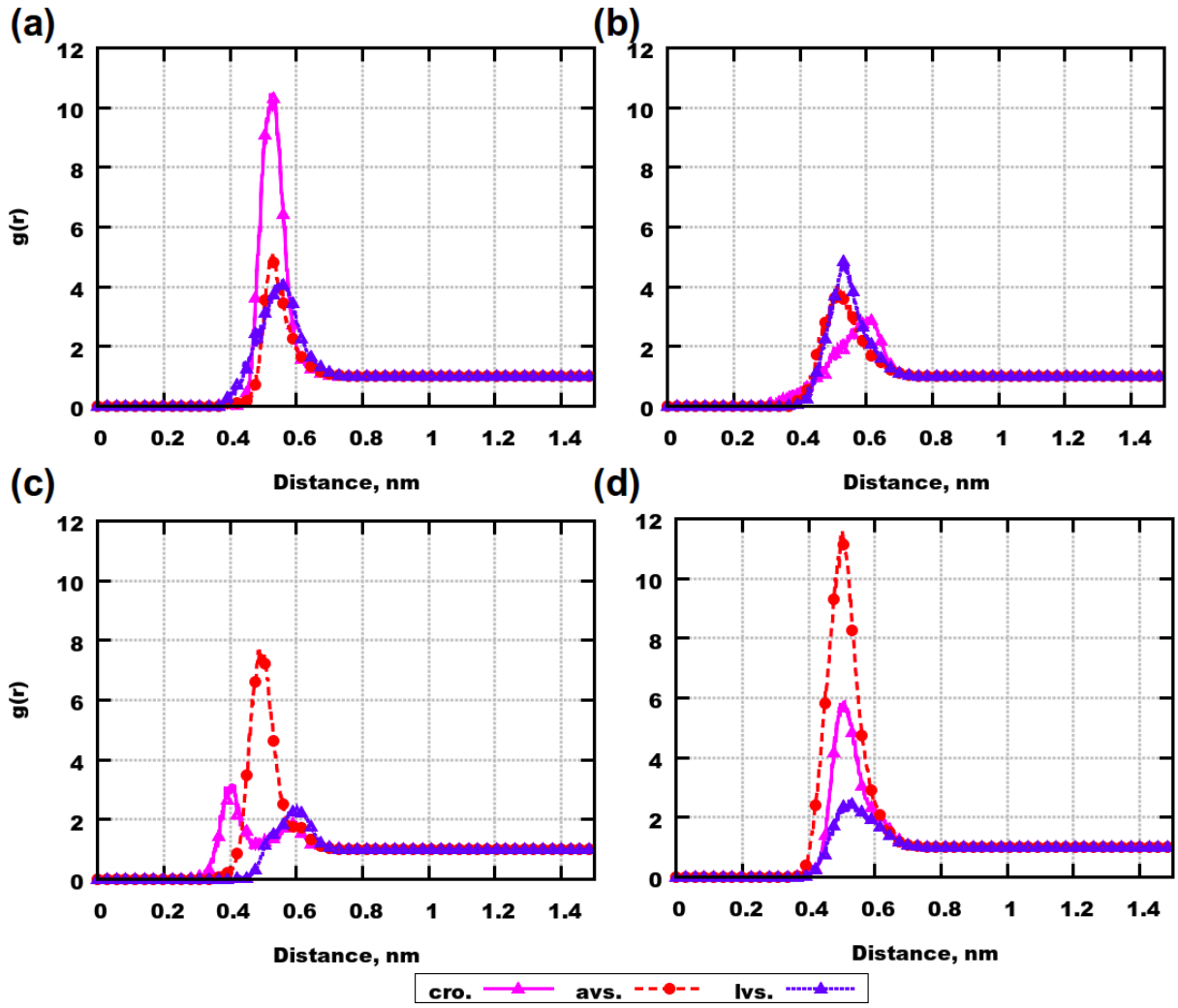

Figure S16: Radial distribution functions between molecular centers of mass of leucine (LEU_{34}) and drugs. (a) Systems containing 6 A$\beta(25-35)$ with and without drugs. (b) Systems containing 6 A$\beta(31-35)$ with and without drugs. (c) Systems containing 8 A$\beta(25-35)$ with and without drugs. (d) Systems containing 8 A$\beta(31-35)$ with and without drugs. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.

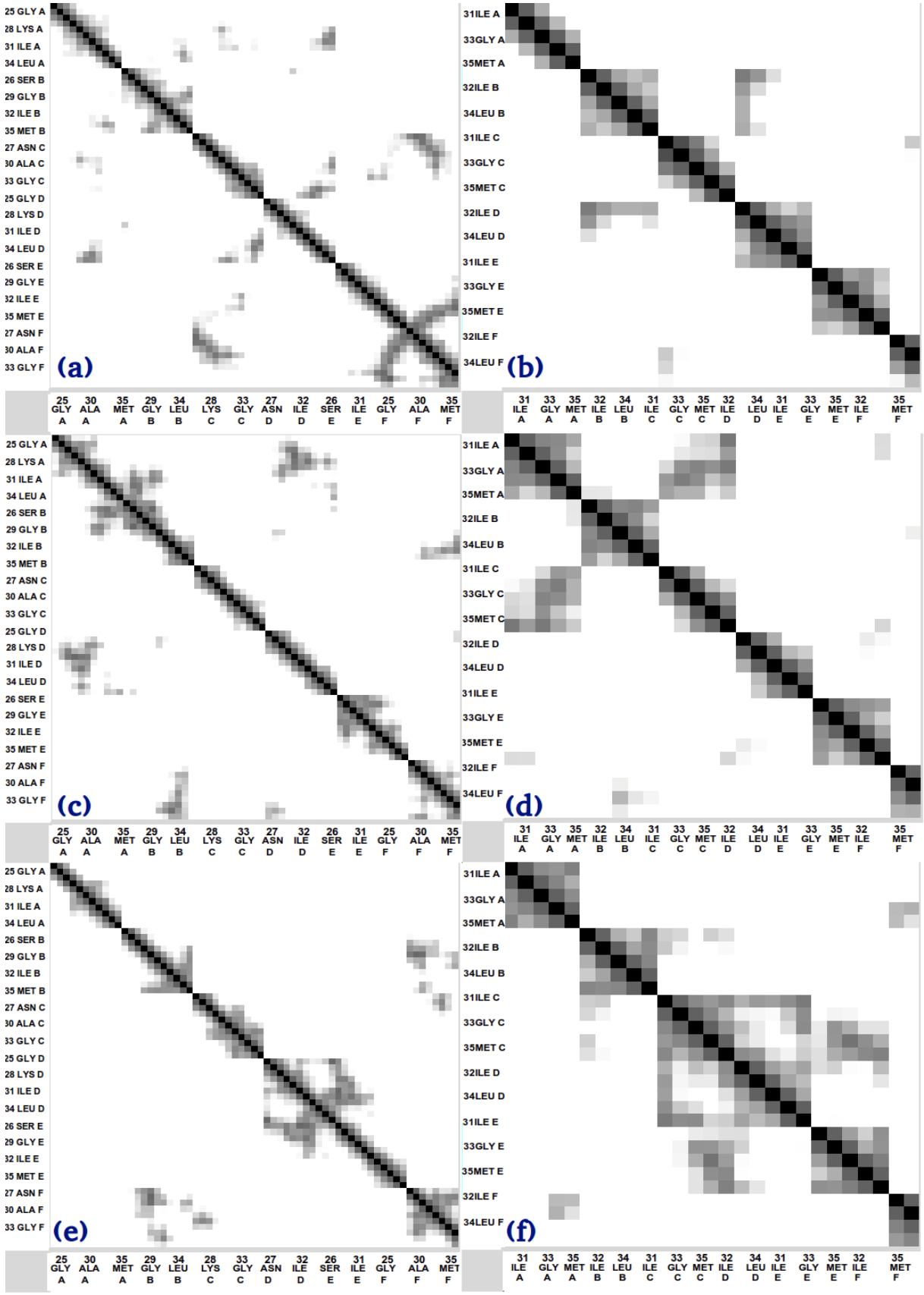

Figure S17: Contact maps for systems with 6 molecules, computed during the last 50 ns. (a) A$\beta(25-35)$ and cromolyn. (b) A$\beta(31-35)$ and cromolyn. (c) A$\beta(25-35)$ and atorvastatin. (d) A$\beta(31-35)$ and atorvastatin. (e) A$\beta(25-35)$ and lovastatin. (f) A$\beta(31-35)$ and lovastatin.

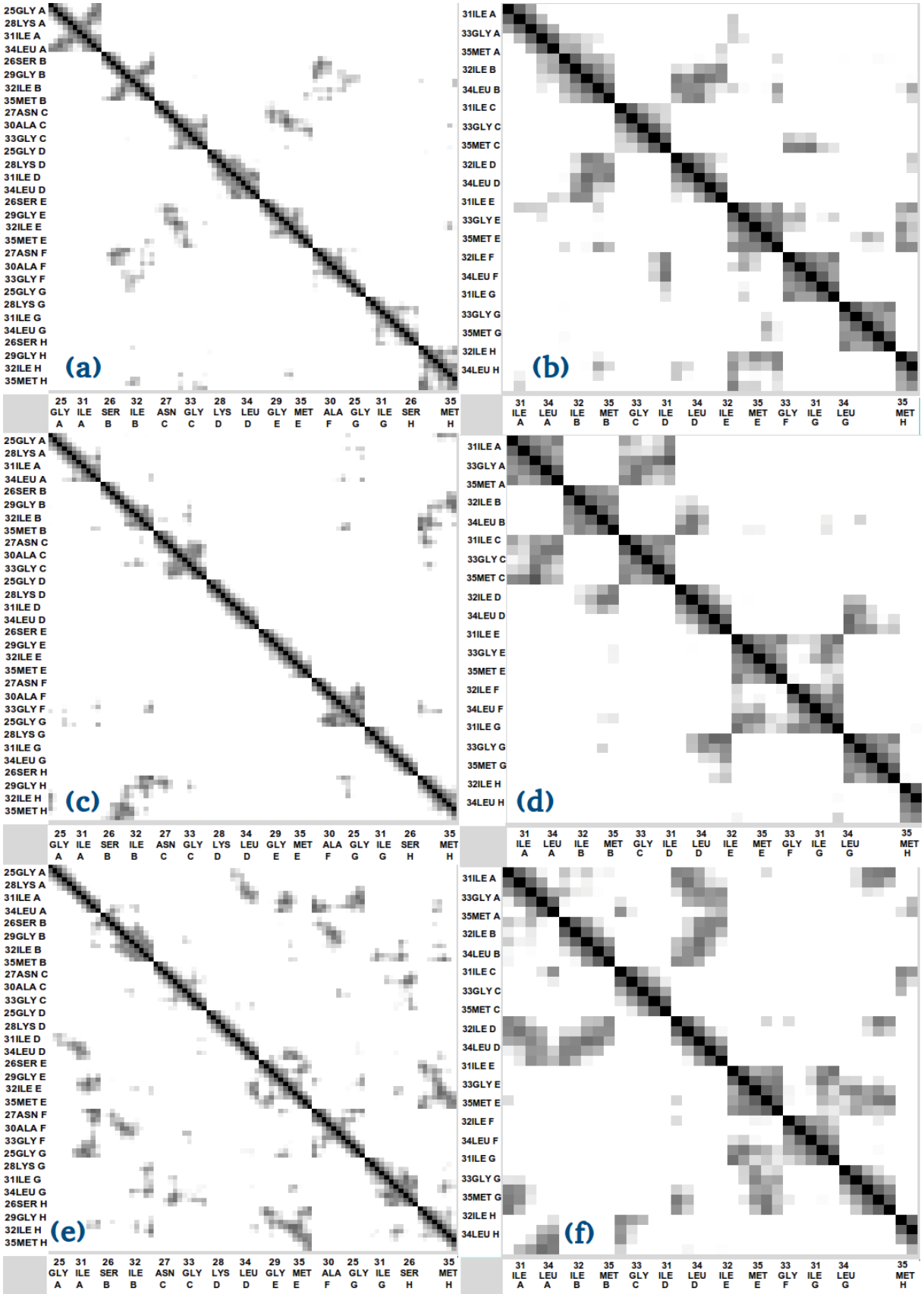

Figure S18: Contact maps for systems with 8 molecules, computed during the last 50 ns. (a) A$\beta(25-35)$ and cromolyn. (b) A$\beta(31-35)$ and cromolyn. (c) A$\beta(25-35)$ and atorvastatin. (d) A$\beta(31-35)$ and atorvastatin. (e) A$\beta(25-35)$ and lovastatin. (f) A$\beta(31-35)$ and lovastatin.

4 Classical MD: secondary structures of peptides

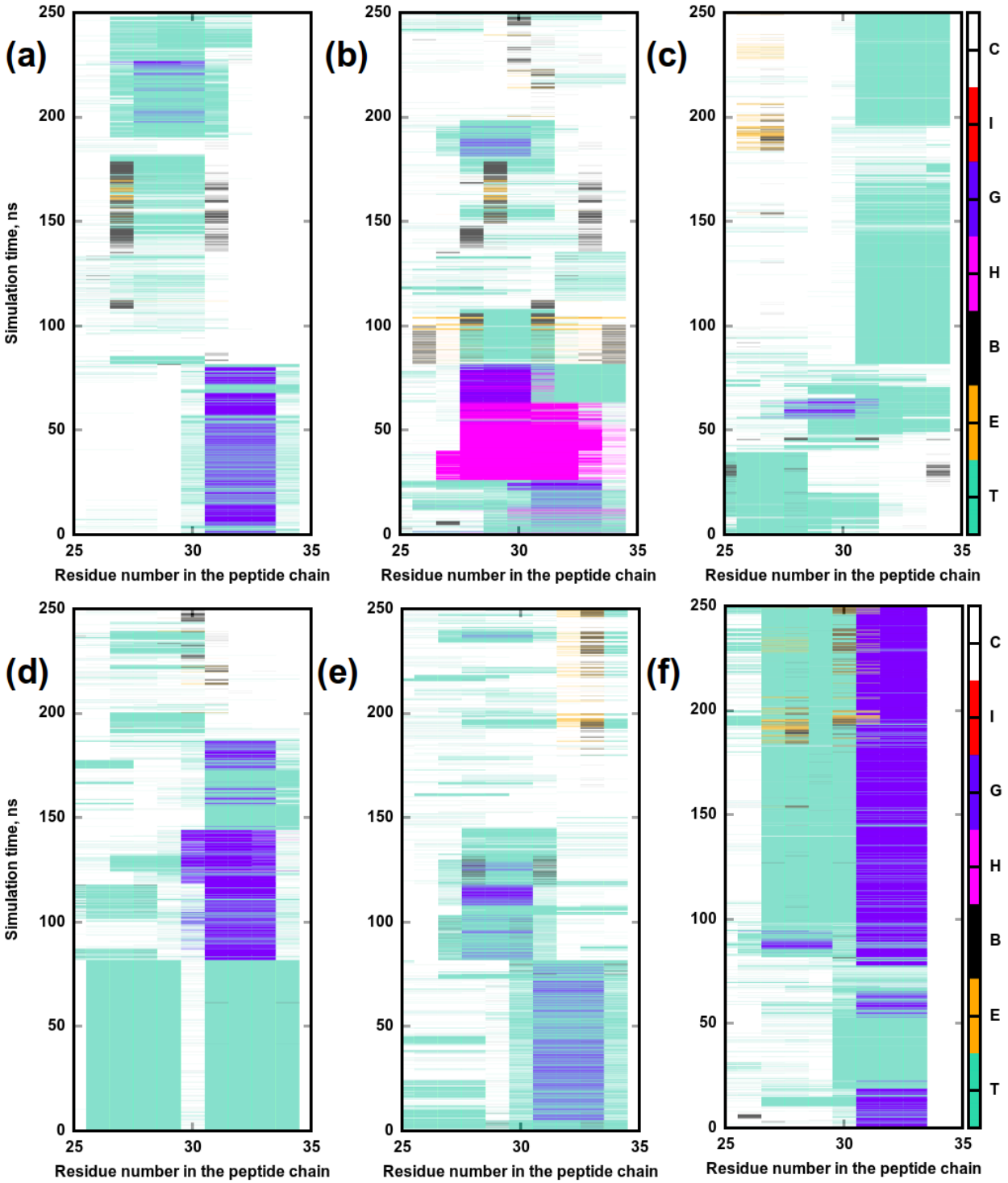

Figure S19: Secondary structures of A$\beta(25-35)$ for the system containing 6 peptides and 6 molecules of cromolyn. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(f) are denoting separate peptides.

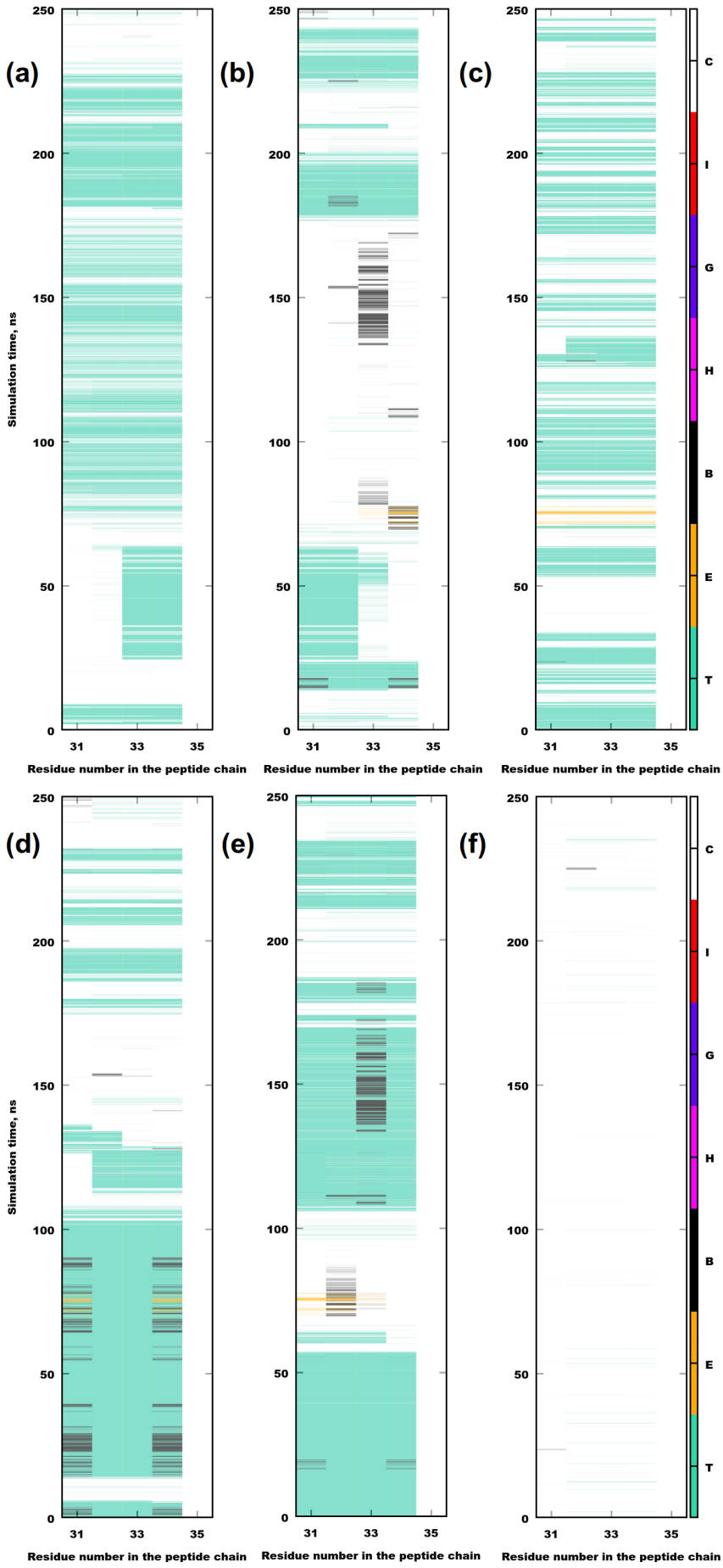

Figure S20: Secondary structures of A$\beta(31-35)$ for the system containing 6 peptides and 6 molecules of cromolyn. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(f) are denoting separate peptides.

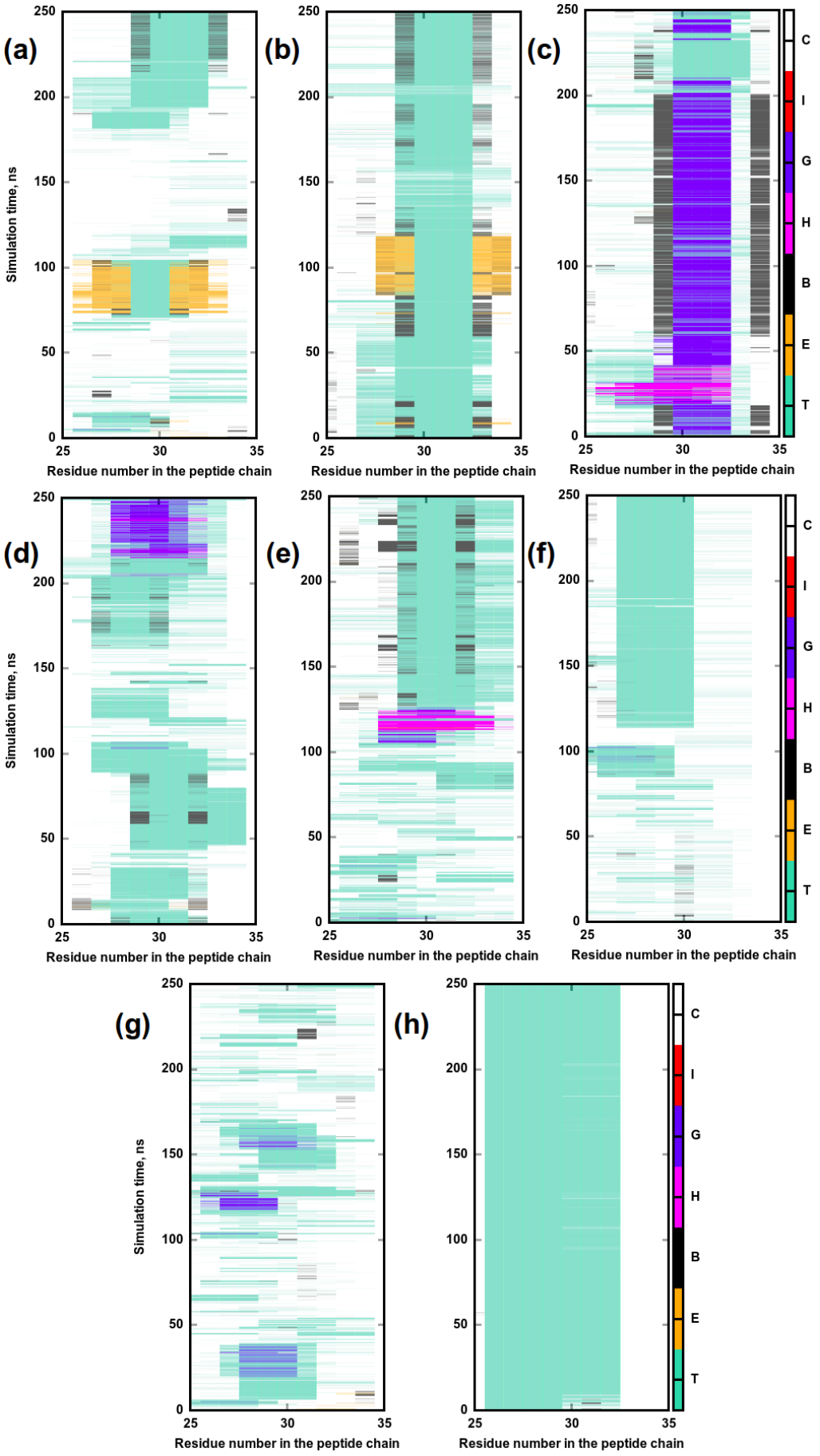

Figure S21: Secondary structures of A$\beta(25-35)$ for the system containing 8 peptides and 8 molecules of cromolyn. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(h) are denoting separate peptides.

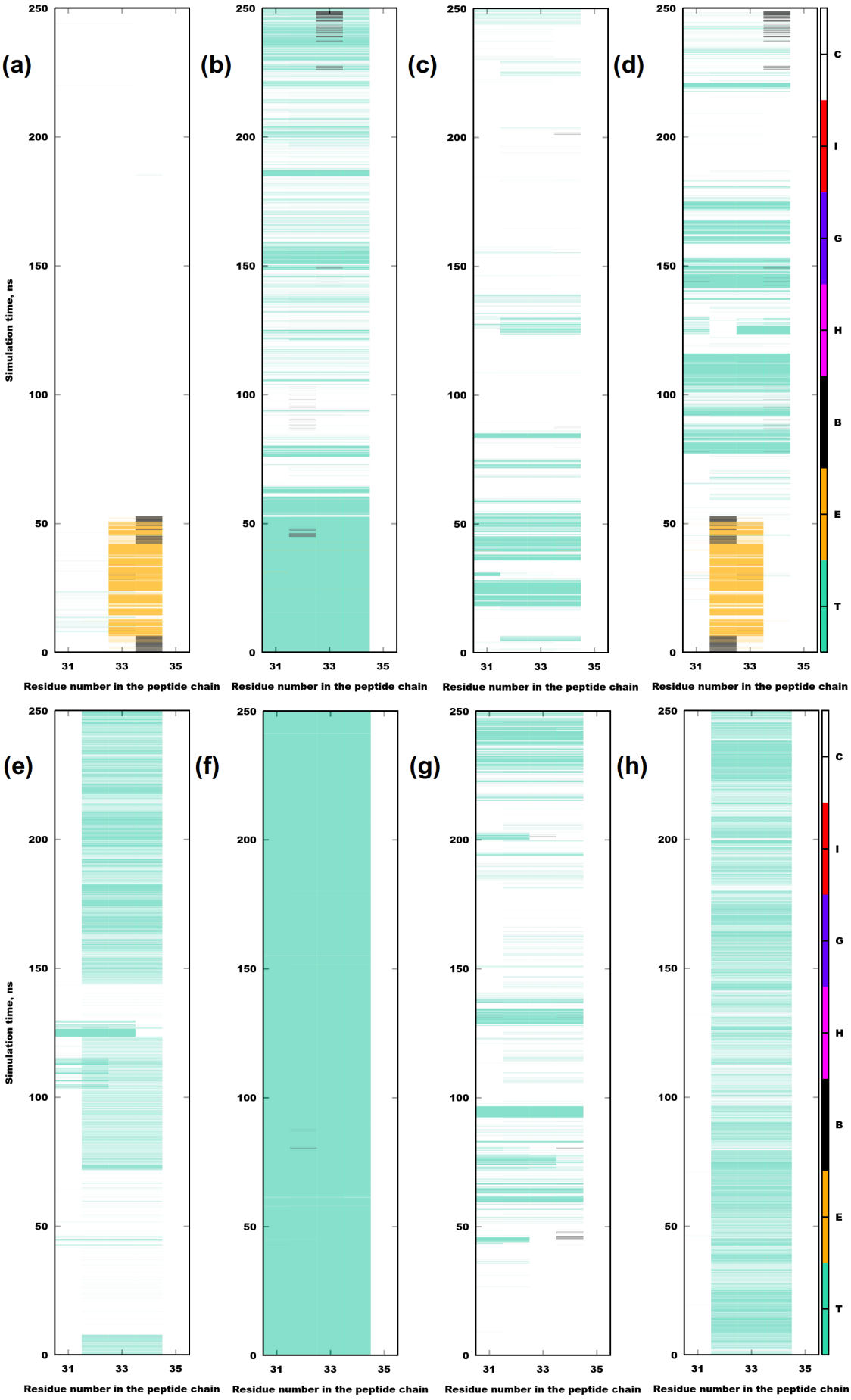

Figure S22: Secondary structures of A$\beta(31-35)$ for the system containing 8 peptides and 8 molecules of cromolyn. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(h) are denoting separate peptides.

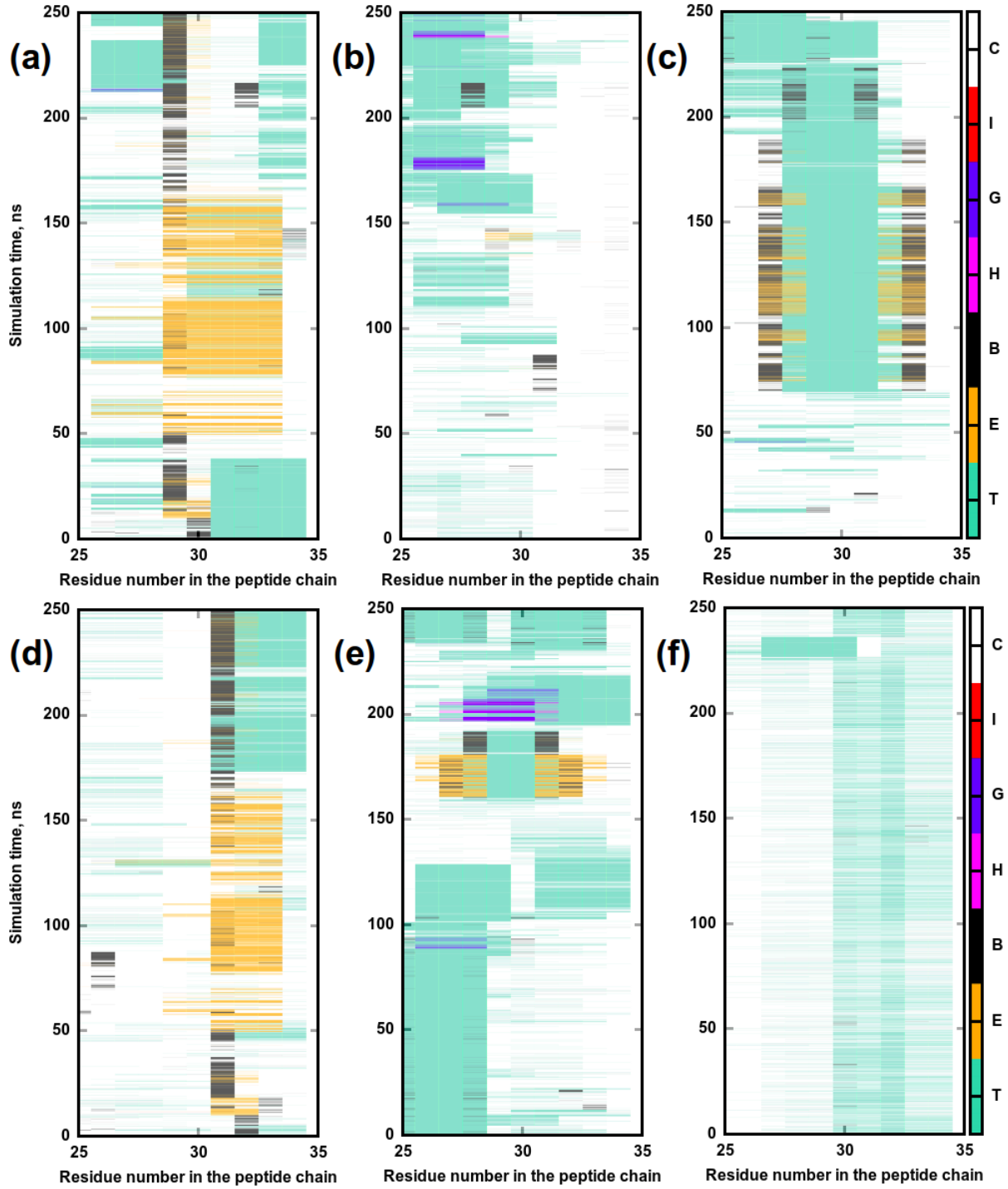

Figure S23: Secondary structures of A$\beta(25-35)$ for the system containing 6 peptides and 6 molecules of atorvastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(f) are denoting separate peptides.

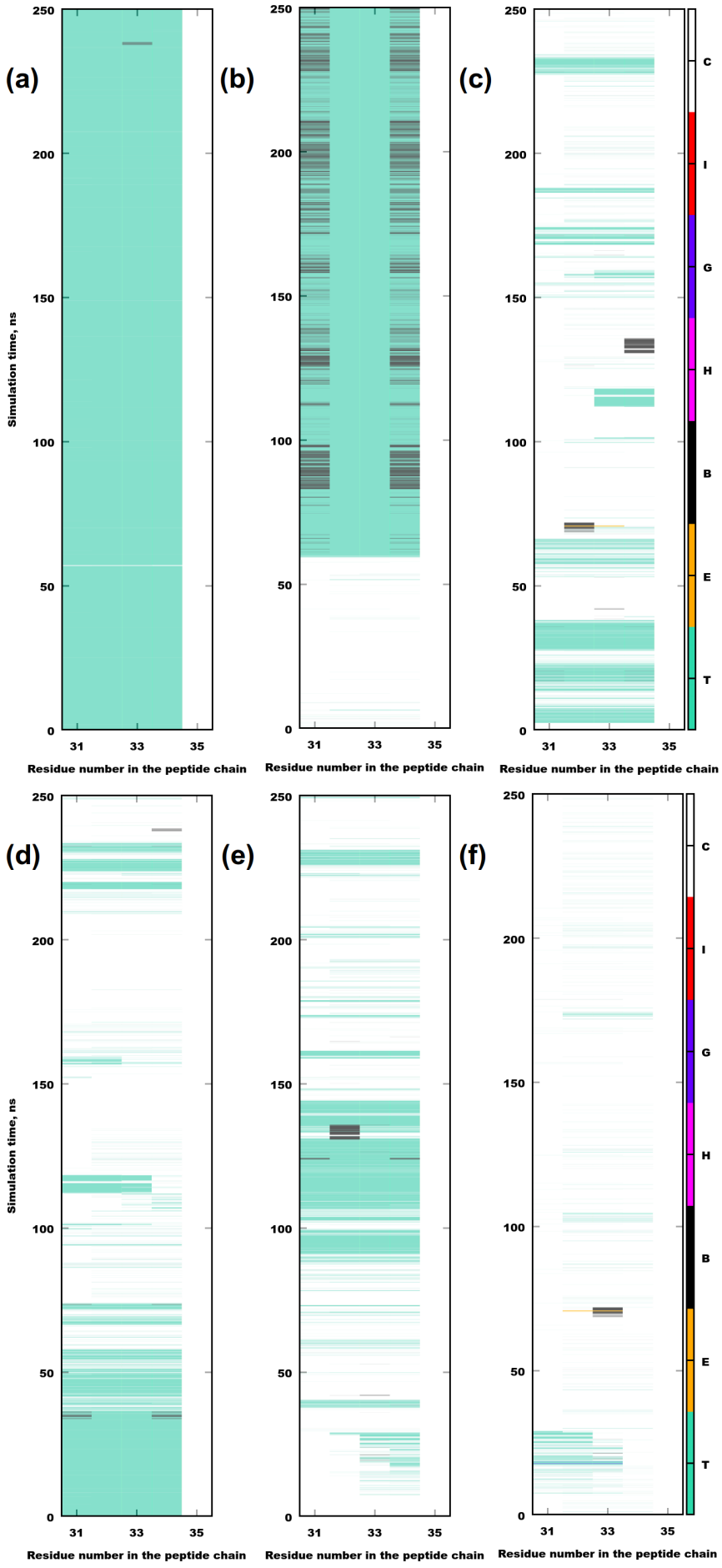

Figure S24: Secondary structures of A$\beta(31-35)$ for the system containing 6 peptides and 6 molecules of atorvastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(f) are denoting separate peptides.

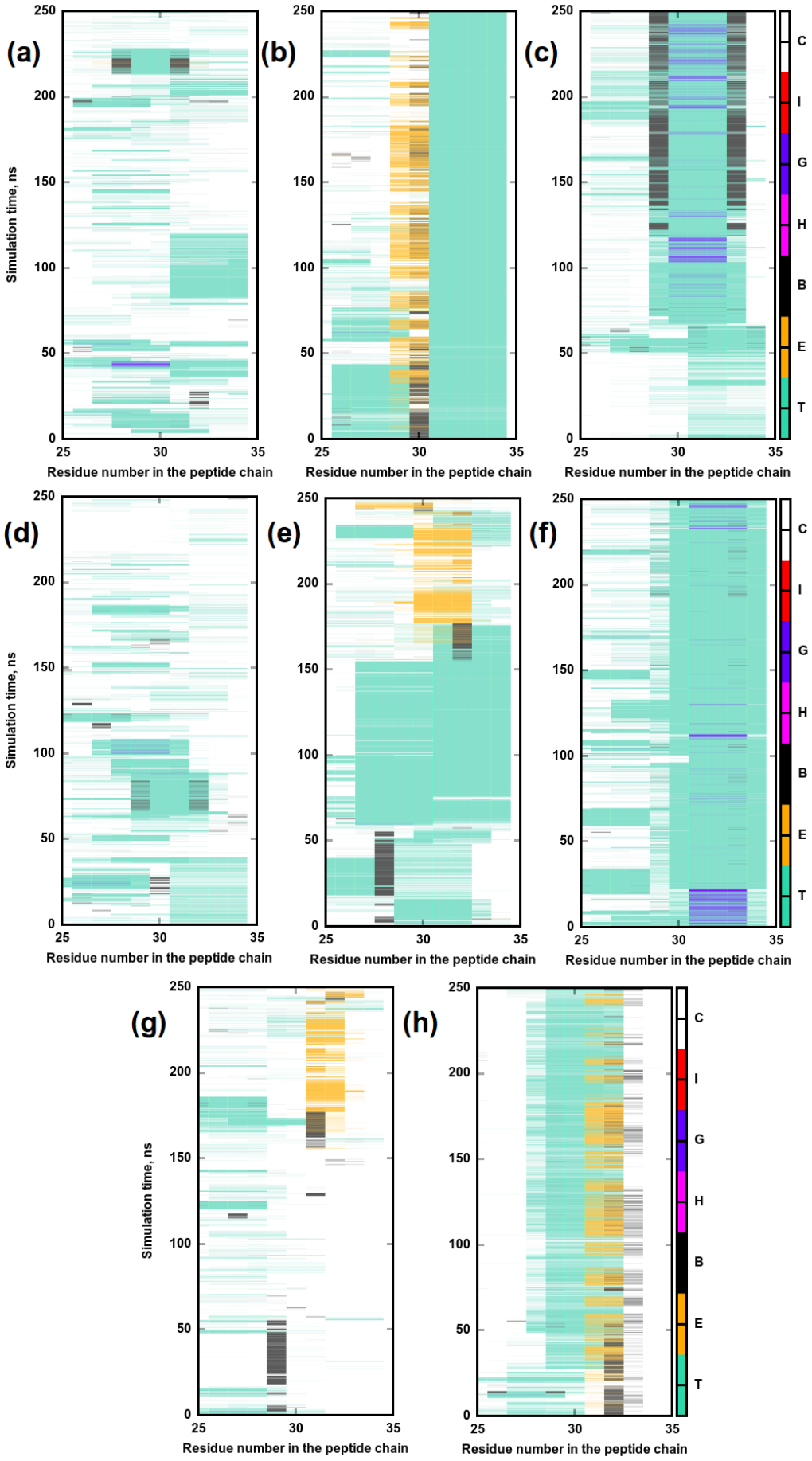

Figure S25: Secondary structures of A$\beta(25-35)$ for the system containing 8 peptides and 8 molecules of atorvastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(h) are denoting separate peptides.

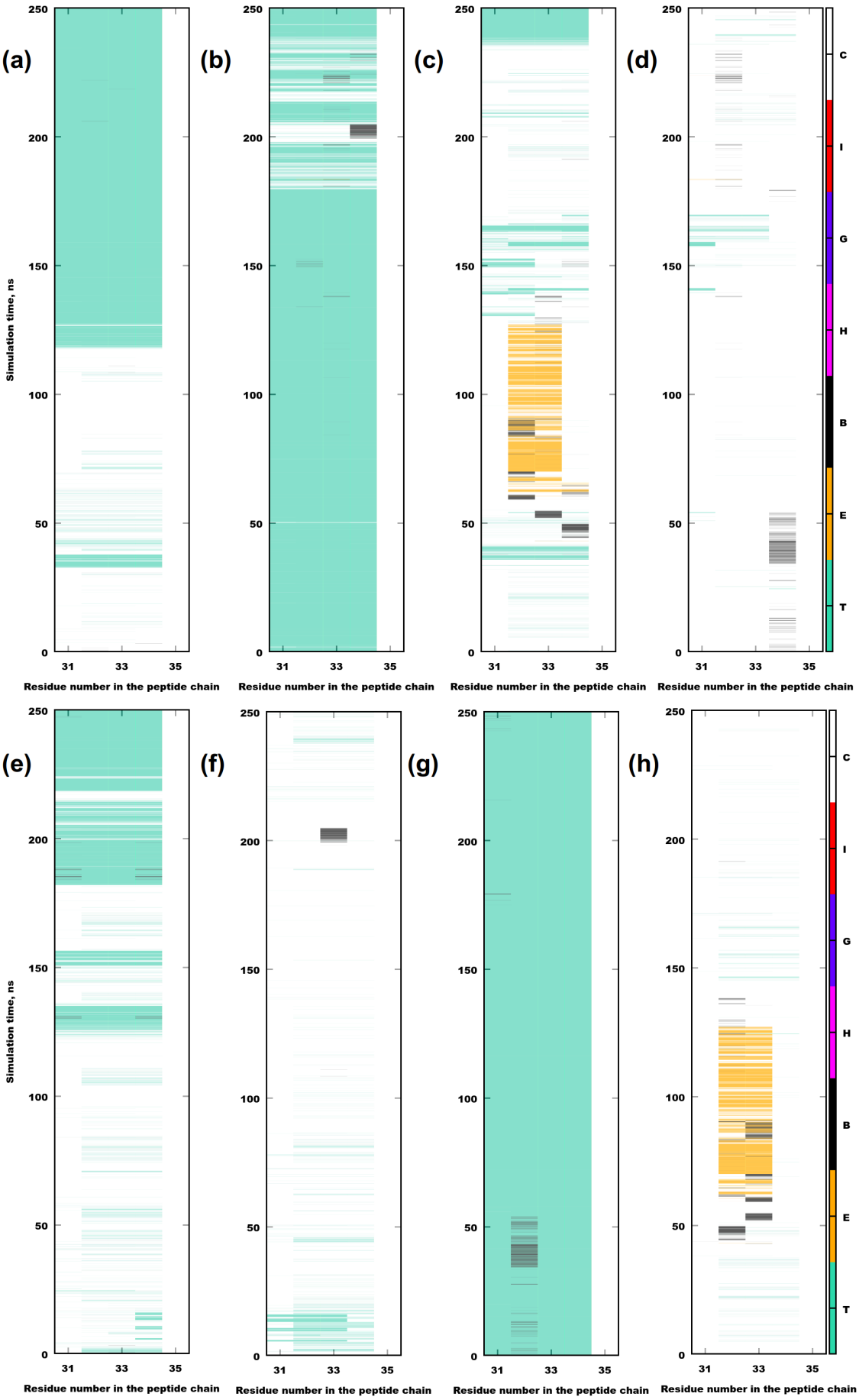

Figure S26: Secondary structures of A$\beta(31-35)$ for the system containing 8 peptides and 8 molecules of atorvastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(h) are denoting separate peptides.

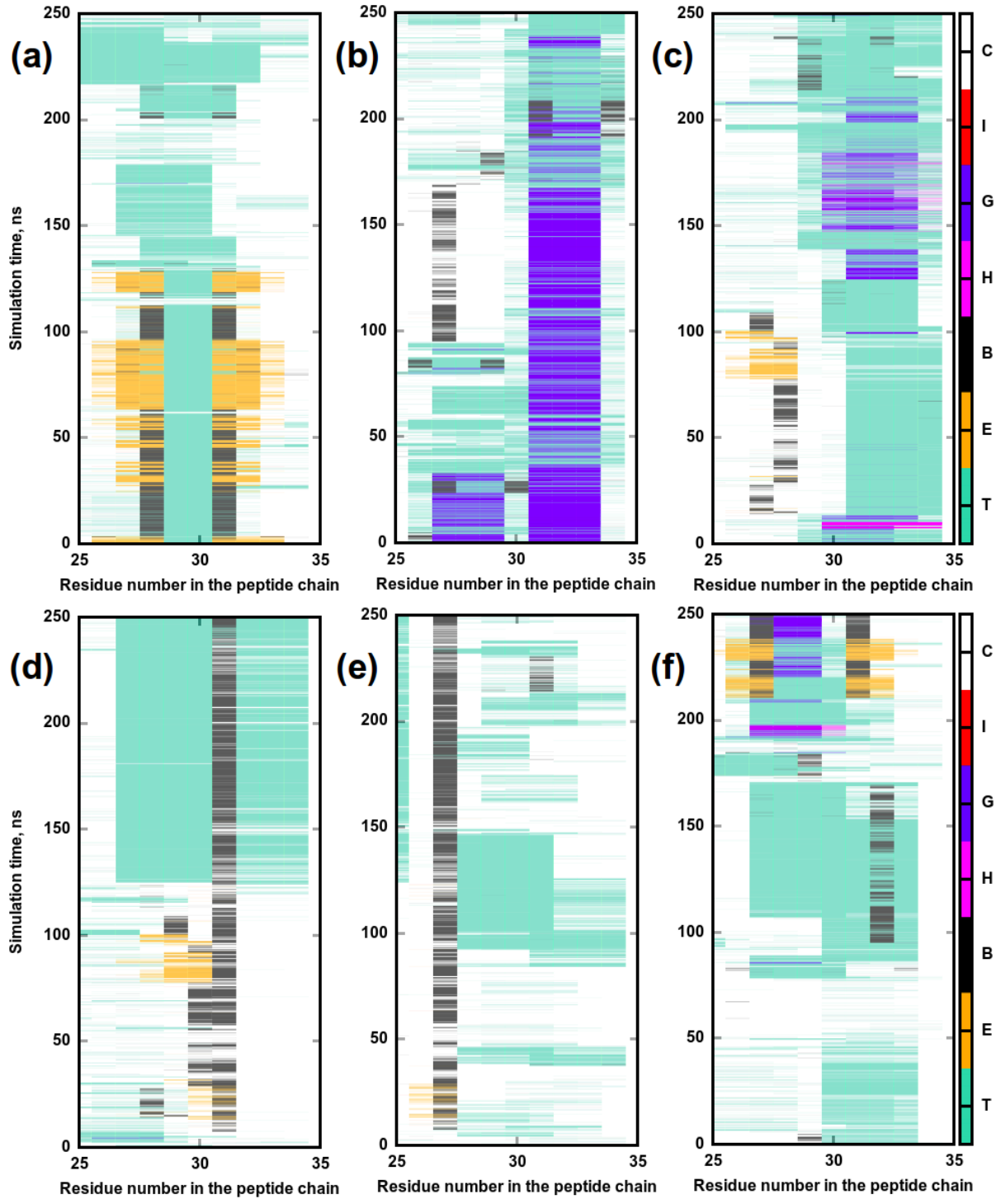

Figure S27: Secondary structures of A$\beta(25-35)$ for the system containing 6 peptides and 6 molecules of lovastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(f) are denoting separate peptides.

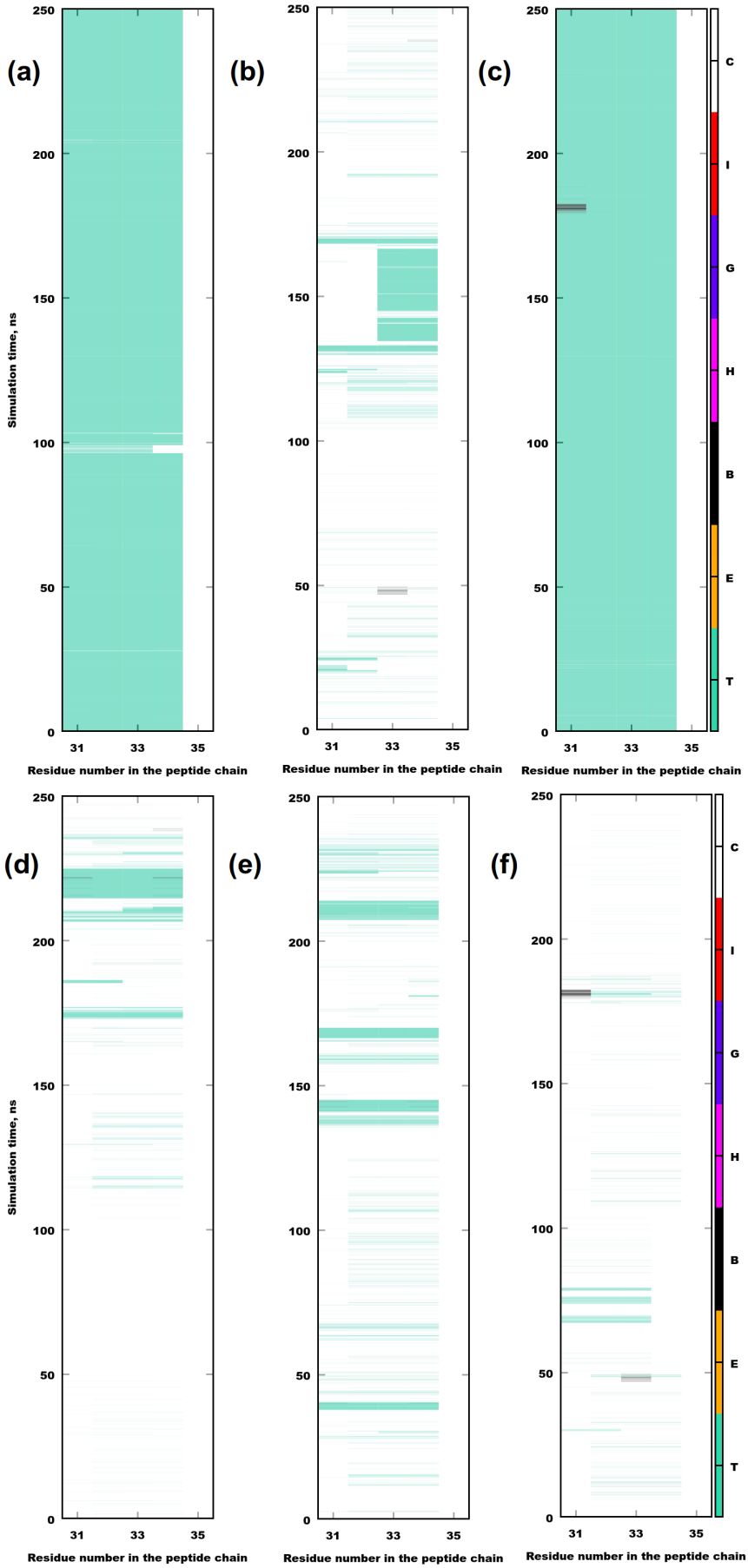

Figure S28: Secondary structures of A$\beta(31-35)$ for the system containing 6 peptides and 6 molecules of lovastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(f) are denoting separate peptides.

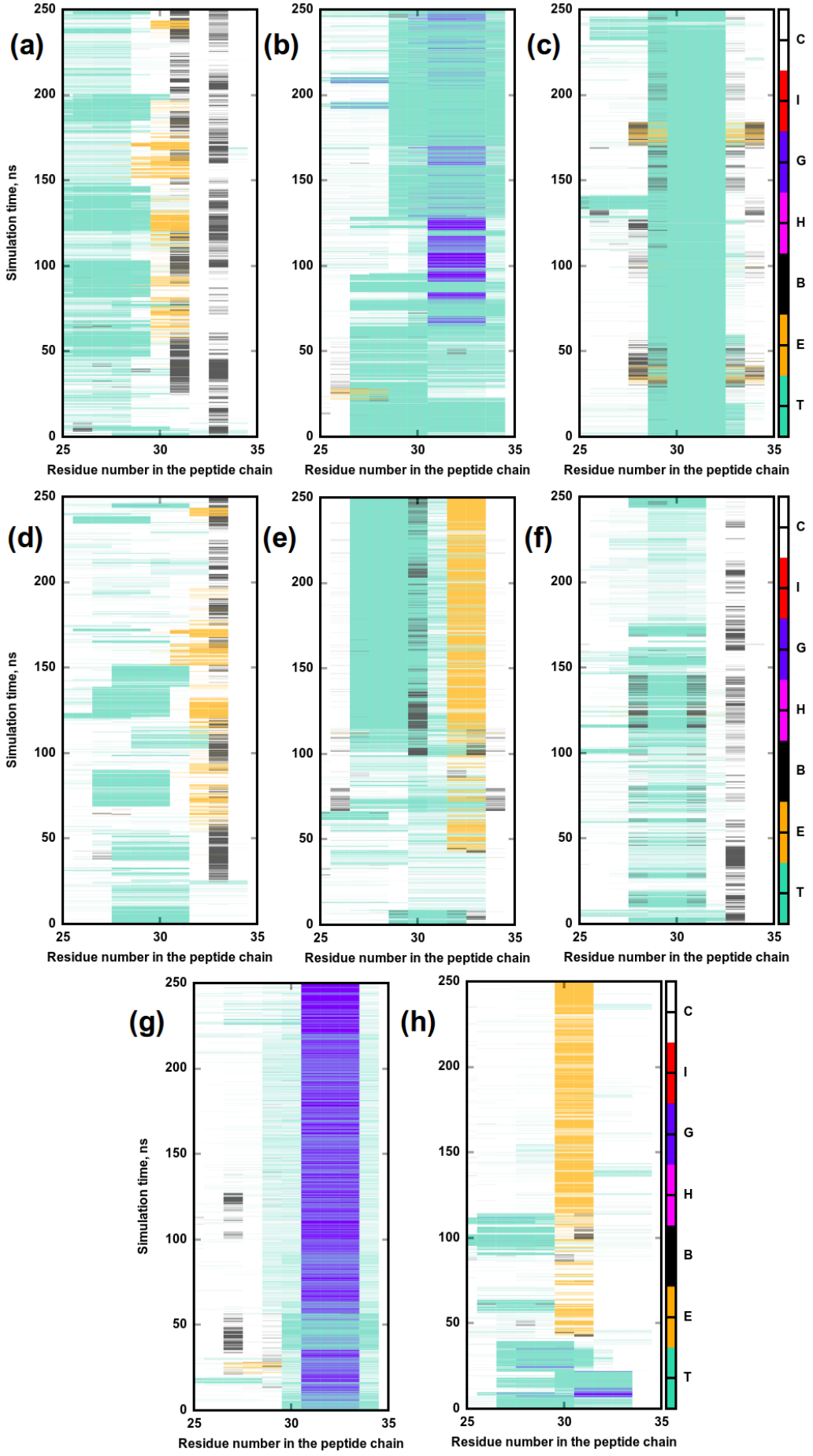

Figure S29: Secondary structures of A$\beta(25-35)$ for the system containing 8 peptides and 8 molecules of lovastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(h) are denoting separate peptides.

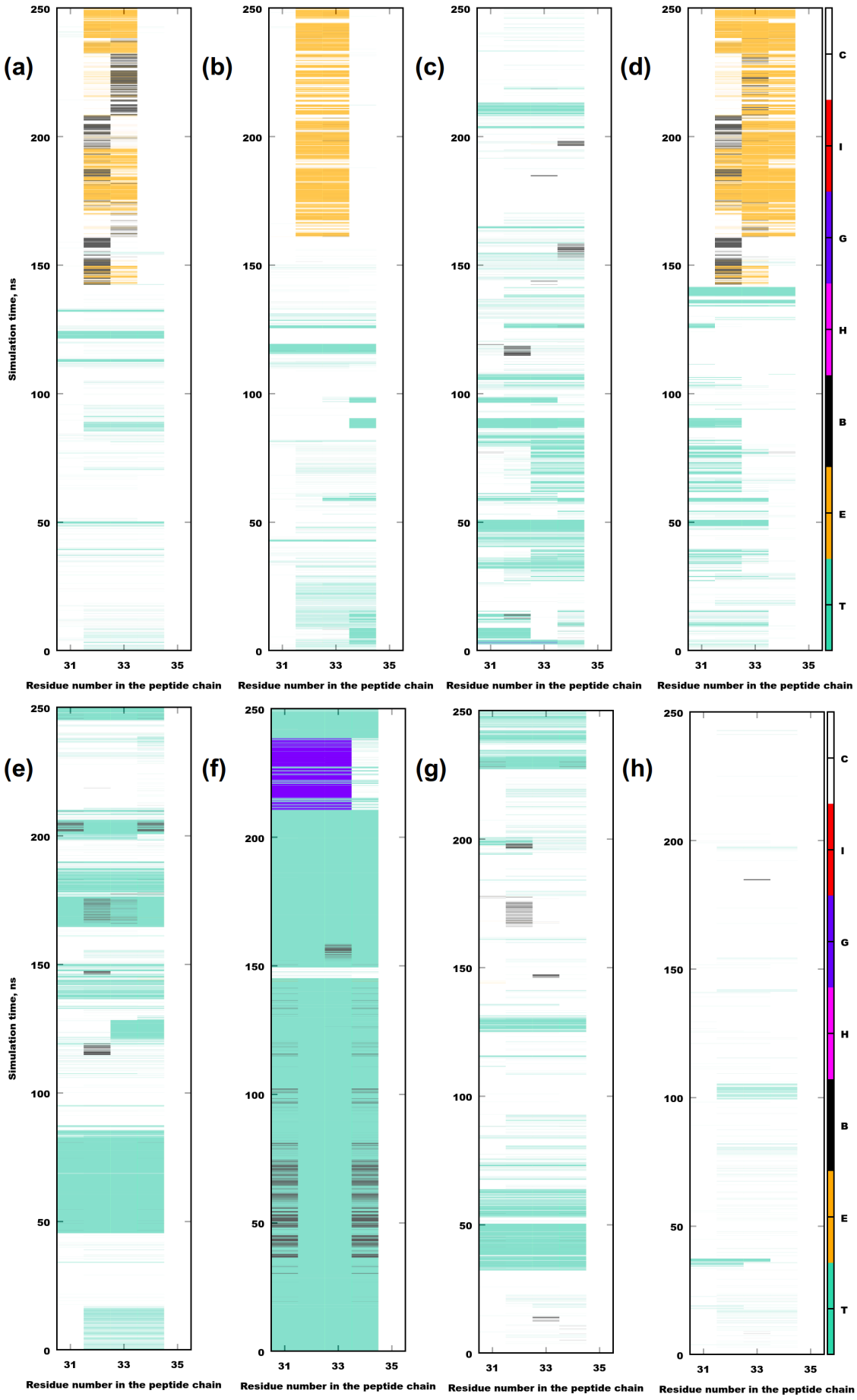

Figure S30: Secondary structures of A$\beta(31-35)$ for the system containing 8 peptides and 8 molecules of lovastatin. Secondary structures are coded as the following: T - turn, E - extended conformation, B - isolated β-bridge, H - α-helix, G - 3_{10}-helix, I - π-helix, C - coil. Letters (a)-(h) are denoting separate peptides.

5 Well-tempered metadynamics: potential of mean force profiles

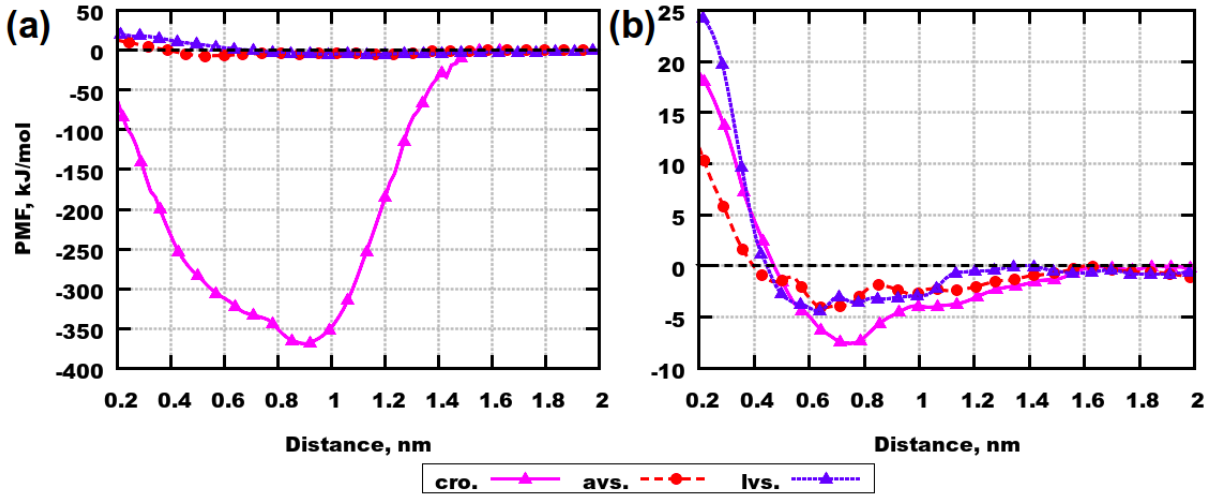

Figure S31: Potential of mean force profiles for CV2. (a) Systems with A$\beta(25-35)$. (b) Systems with A$\beta(31-35)$. Abbreviations mean the following: "cro." - systems containing cromolyn, "avs." - systems containing atorvastatin, "lvs." - systems containing lovastatin.