The role of the side chain on the conformational and self-assembly patterns of C_2-symmetric Val and Phe pseudopeptidic derivatives

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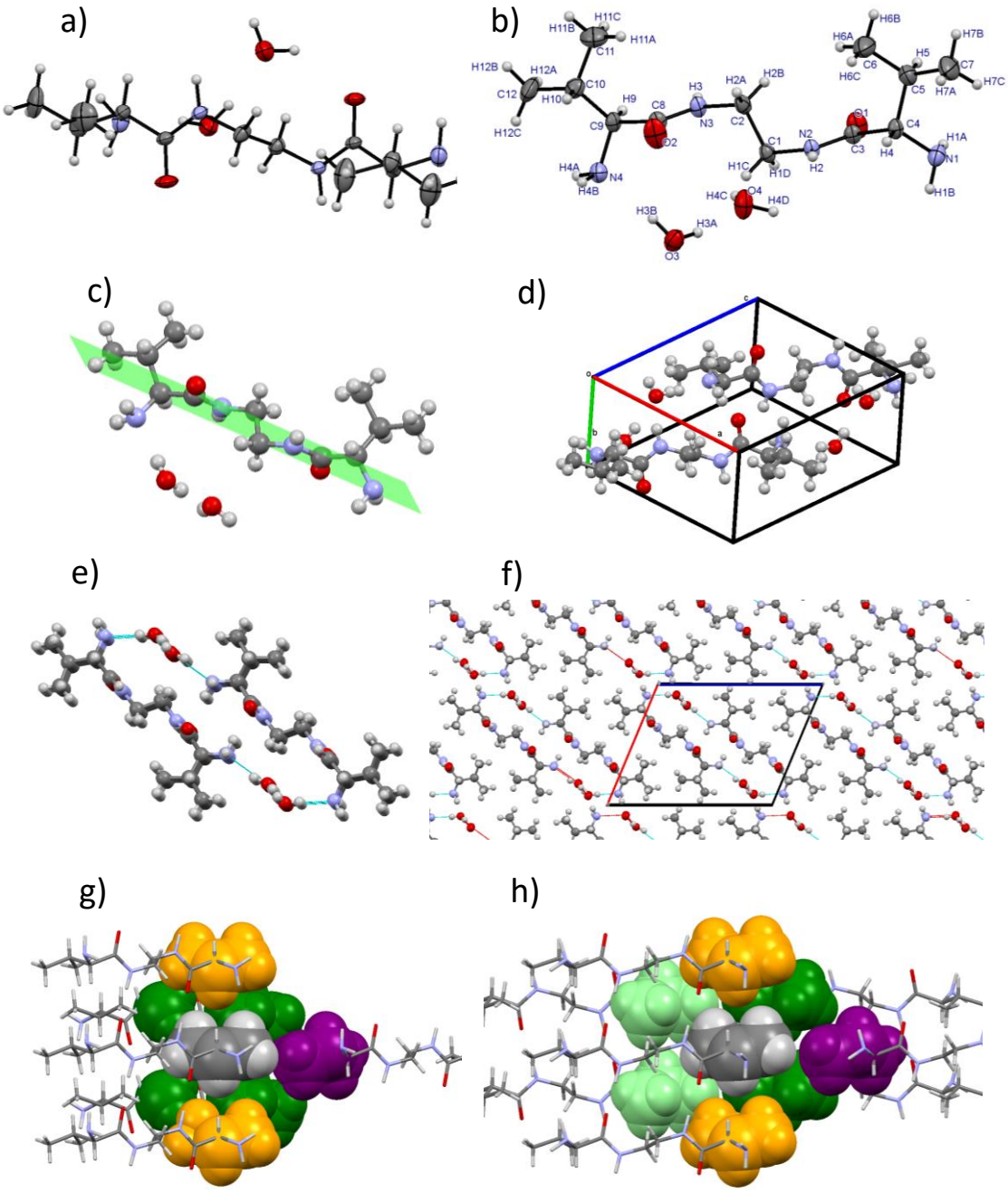

Figure S1 Conformational elements (a-c), unit cell (d) and packing motifs for **1a**: view along the b axis of the helical columnar assembly (e), packing observed in the crystal as seen along the b axis (f), KIH and KIK motifs for the two isopropyl groups in **1a** with the involved fragments in CPK (fragments in the same stack are represented in orange, those corresponding to a different helical columnar assembly on the same linear array are in purple, while those on a different linear array are in green with different colours for different stacks; g: C12-C10-C11, h: C6-C5-C7).

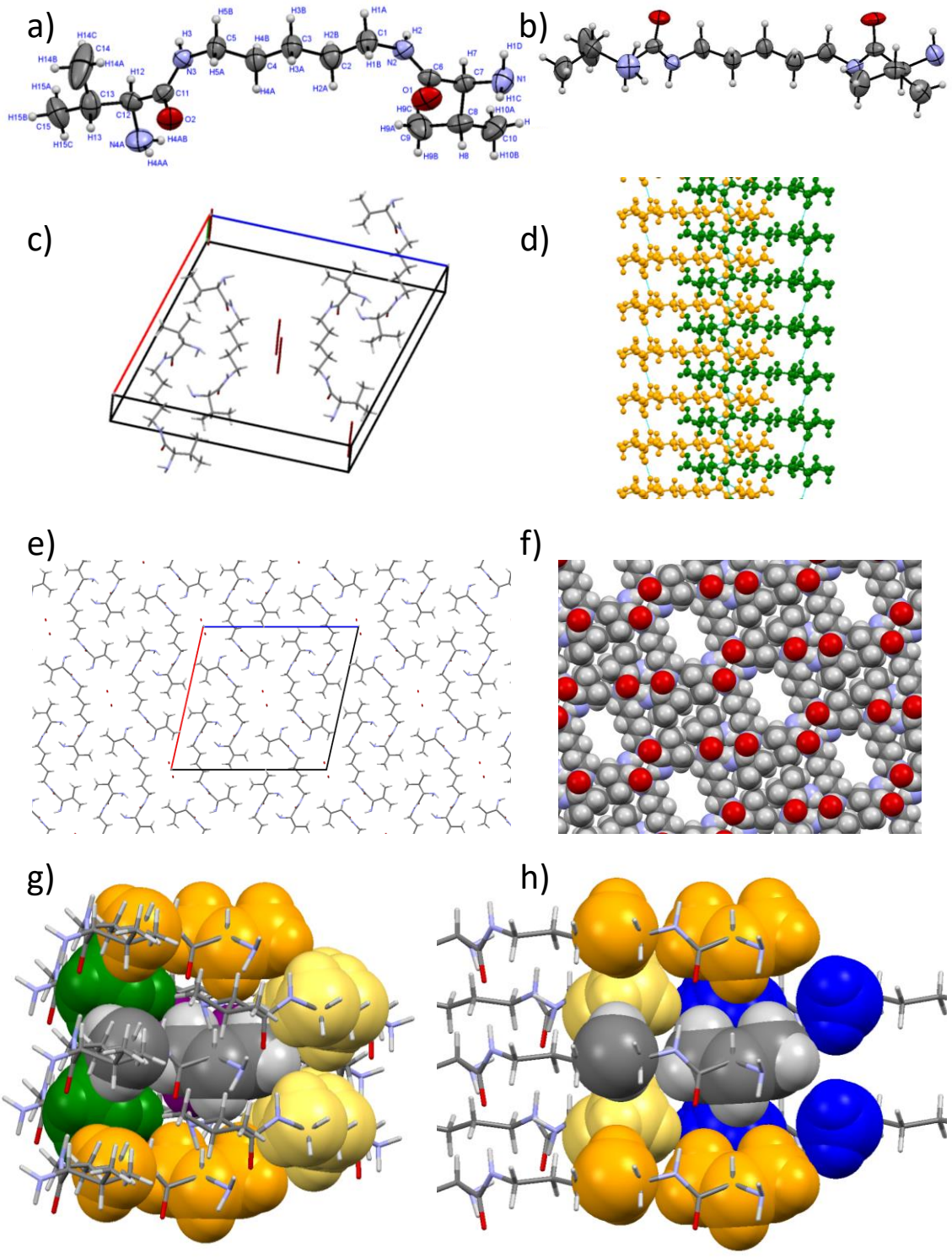

Figure S2 Conformational elements (a-b), unit cell (c) and packing motifs for **4a**: view along the c axis of an elongated columnar assembly (d), packing observed in the crystal as seen along the b axis (e), highlighting the formation of rectangular channels using CPK models (f), KIH and KIK motifs for the two isopropyl groups in **4a** with the involved fragments in CPK (fragments in the same stack are represented in orange, those corresponding to a different helical columnar assembly on a different linear array are in green, purple and blue; g: C14-C13-C15, h: C9-C8-C10).

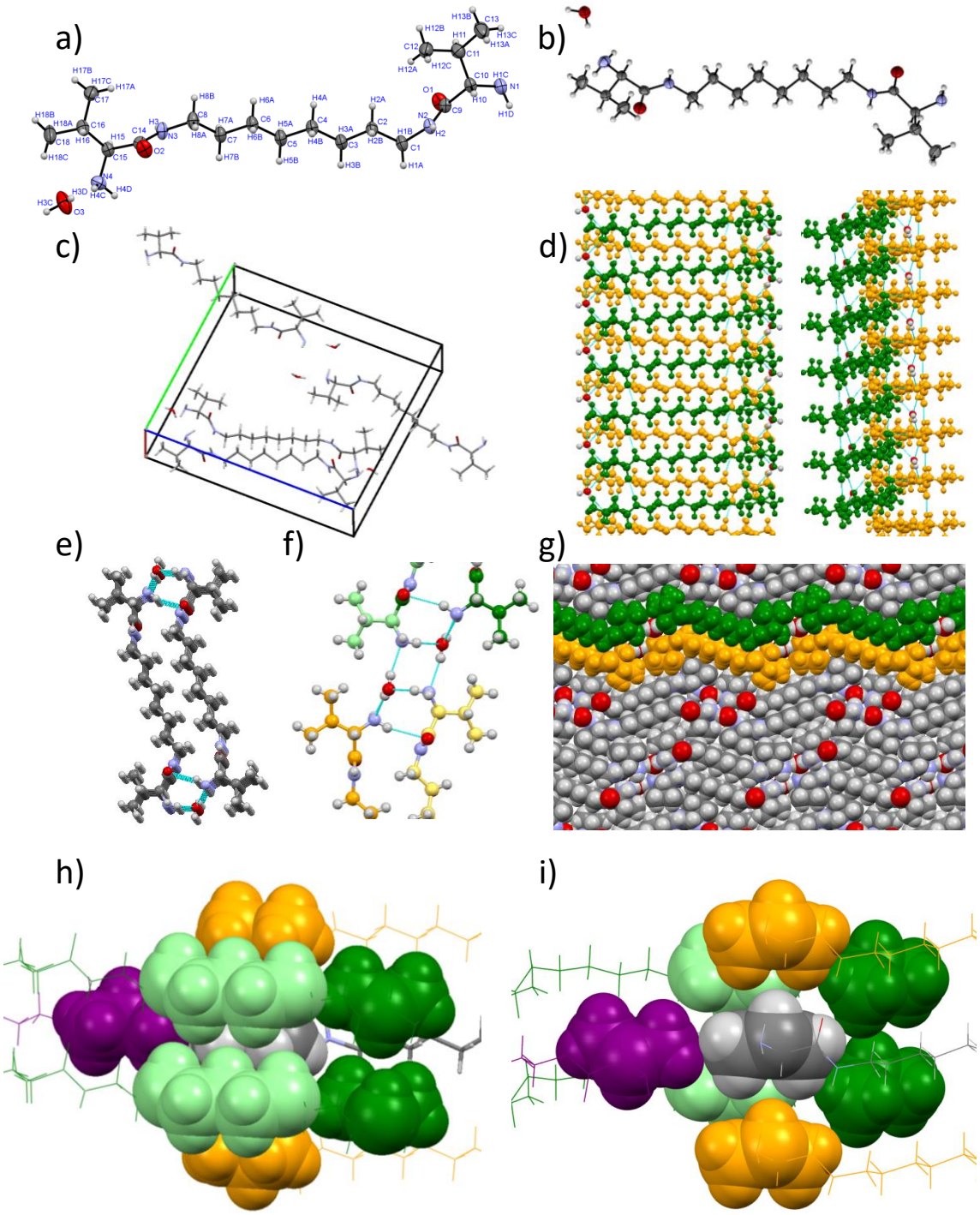

Figure S3 Conformational elements (a-b), unit cell (c) and packing motifs for **6a**: two perspectives of an elongated columnar assembly (d); hydrogen bonding network involving two columnar β-sheet like stacks and water molecules for the formation of an helical columnar assembly (e); hydrogen bonding network connecting two helical columnar assemblies through water molecules (f); CPK model of the packing observed in the crystal (a axis view), highlighting the compact packing of hydrophobic fragments (a linear array of columnar assemblies highlighted in orange and green) (g); KIH and KIK motifs for the isopropyl groups in **6a** with the involved fragments in CPK, fragments in the same stack represented in orange, those from a different helical columnar assembly are in green (different linear array) and purple (same linear array) , h: C17-C16-C18, i: C12-C11-C13; CH2 groups represented in light green.

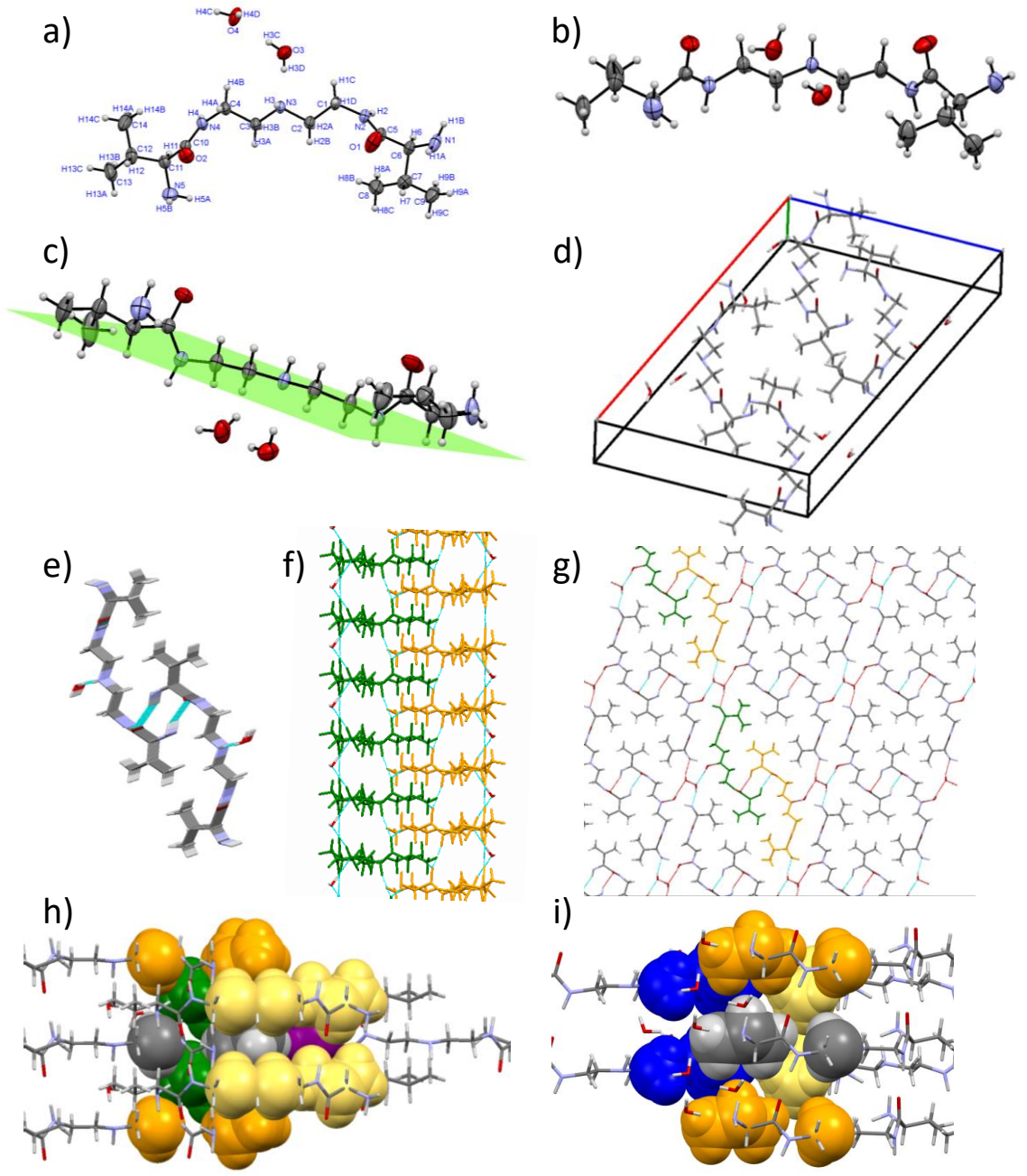

Figure S4 Conformational elements (a-c), unit cell (d) and packing motifs for **9a**: two perspectives of an elongated columnar assembly (e-f); b axis view of the packing highlighting the hydrogen bonding involving different β-sheet like stacks and water molecules (a linear array of columnar assemblies highlighted in orange and green) (g); KIH and KIK motifs for the isopropyl groups in **9a** (carbon atoms in grey); orange CPK fragments correspond to molecules on the same stack; yellow fragments to molecules on the same helical assembly (KIH) and purple (KIK), green (KIH) and blue (KIH) fragments to molecules in a different helical assembly; h: C13-C12-C14 isopropyl group; i: C8-C7-C9 isopropyl group.

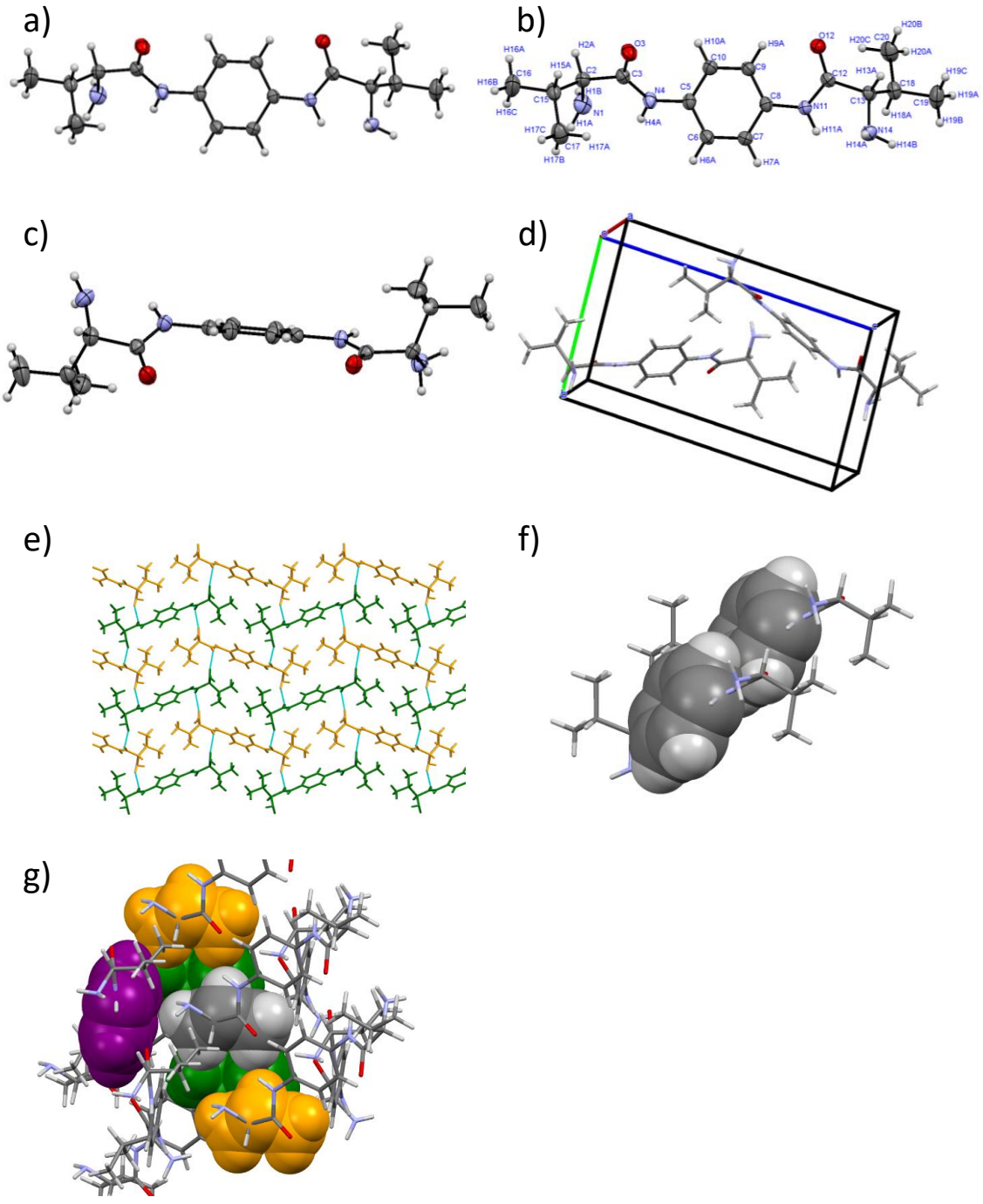

Figure S5 Conformational elements (a-c), unit cell (d) and packing motifs for **11a**: hydrogen bonding network for the formation of β-sheet like stacks (d); b axis view of the packing highlighting the hydrogen bonding between different β-sheet like stacks (e); aromatic displaced face-to-face interactions present in the β-sheet like stacks (f); KIH motifs for the isopropyl groups (C19-C18-C20) in **11a** (carbon atoms in grey); orange CPK fragments correspond to molecules on the same stack, the close contact of this isopropyl with an benzene ring (purple) is also highlighted (g). Crystallographic data taken from ref. 23a.

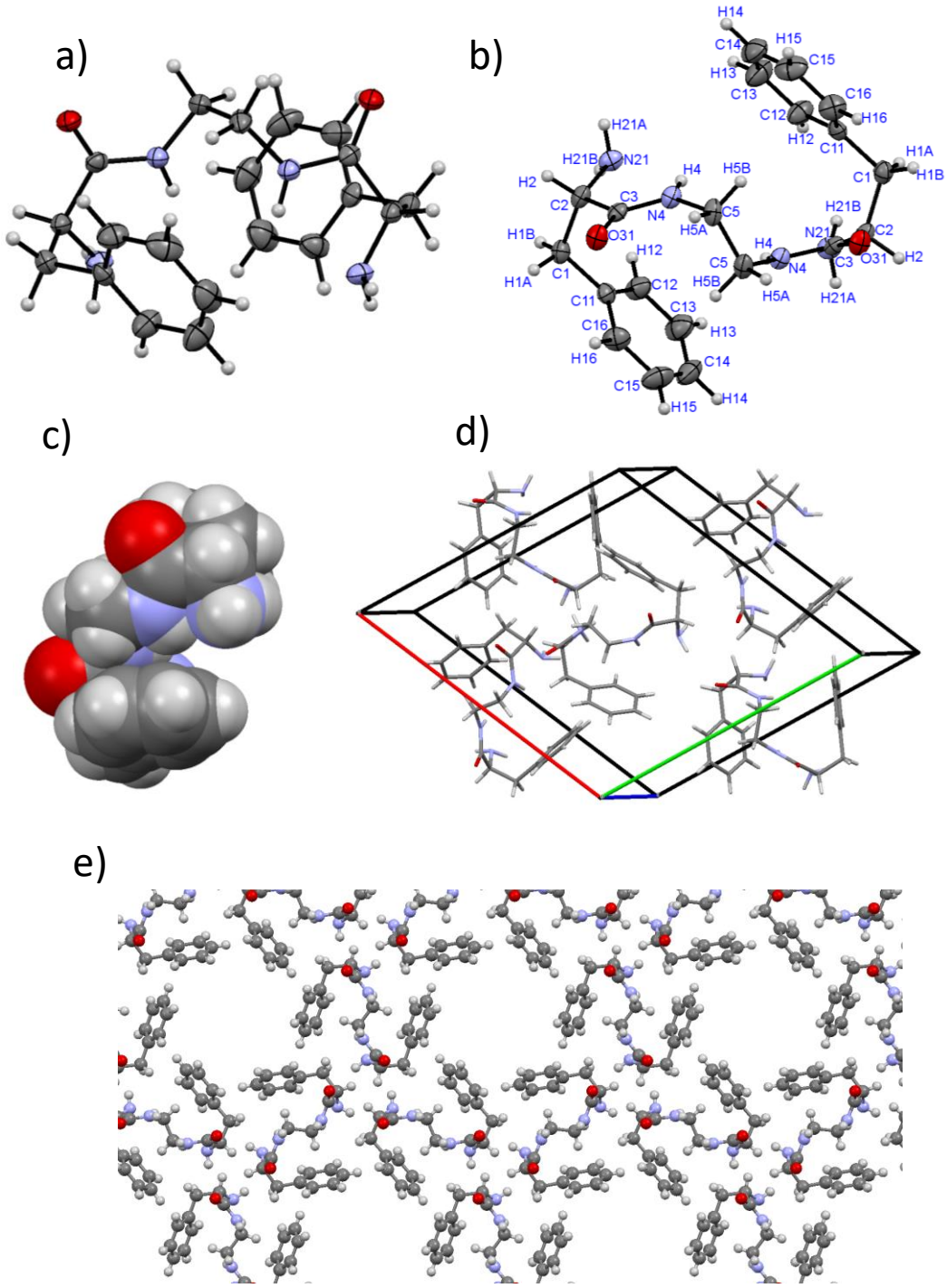

Figure S6 Conformational elements for **1b** (a-c), highlighting the shielding of the amide N-H and one HC-H by the aromatic side chain (c), unit cell (d) and packing observed in the crystal as seen along the c axis (e). Crystallographic data taken from ref. 22b.

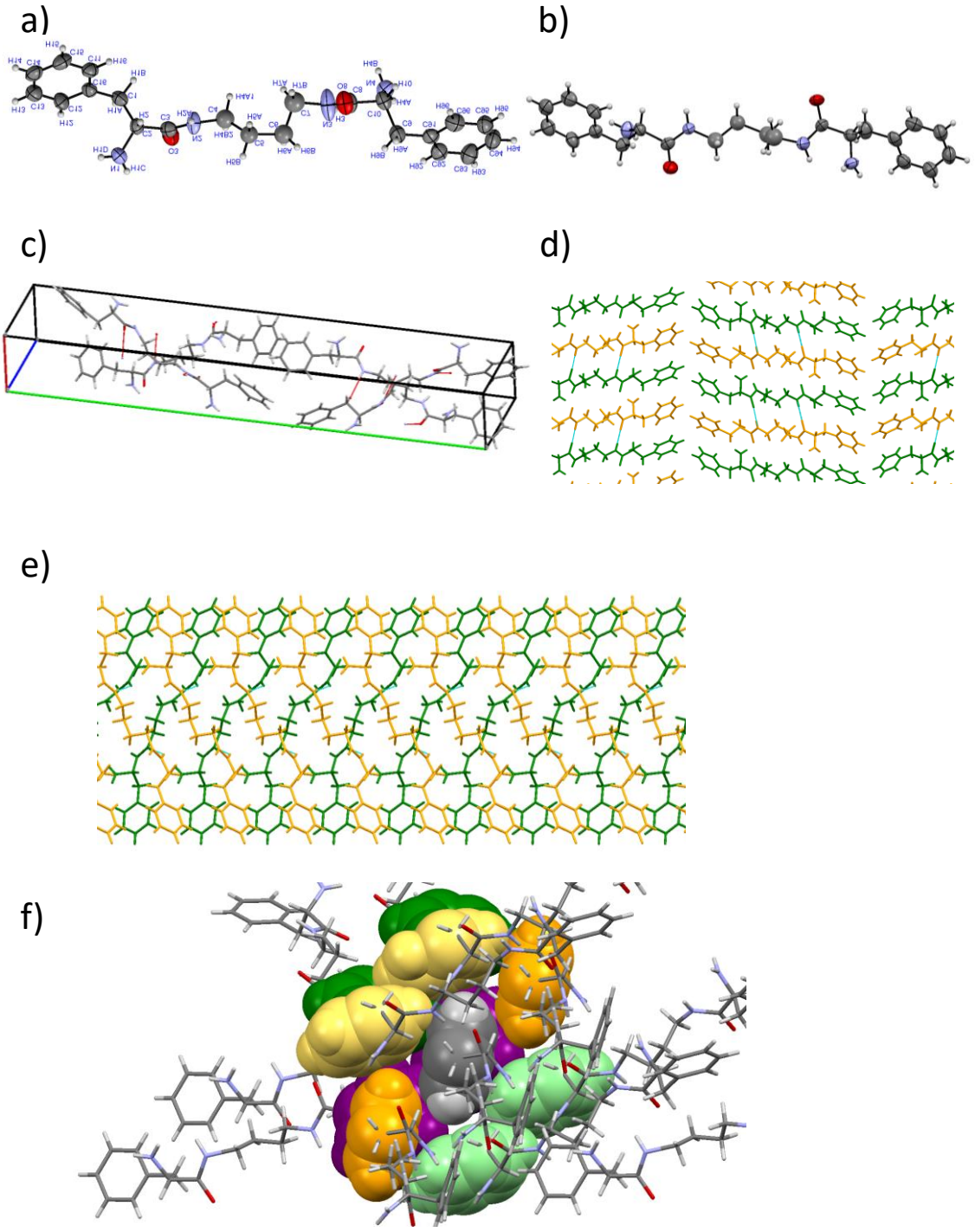

Figure S7 Conformational elements (a-b), unit cell (c) and packing motifs for **3b**: hydrogen bonding between stacks based on face-to-face aromatic arrangements (d); view of the packing highlighting the hydrogen bonding between two stacks based on face-to-face aromatic interactions (e); aromatic-aromatic arrangements present for each aromatic ring in the packing; face-to-face contacts correspond to molecules in the same stack; interactions with aromatic rings corresponding to different stacks are always edge-to-face (f). Crystallographic data taken from ref. 22b.

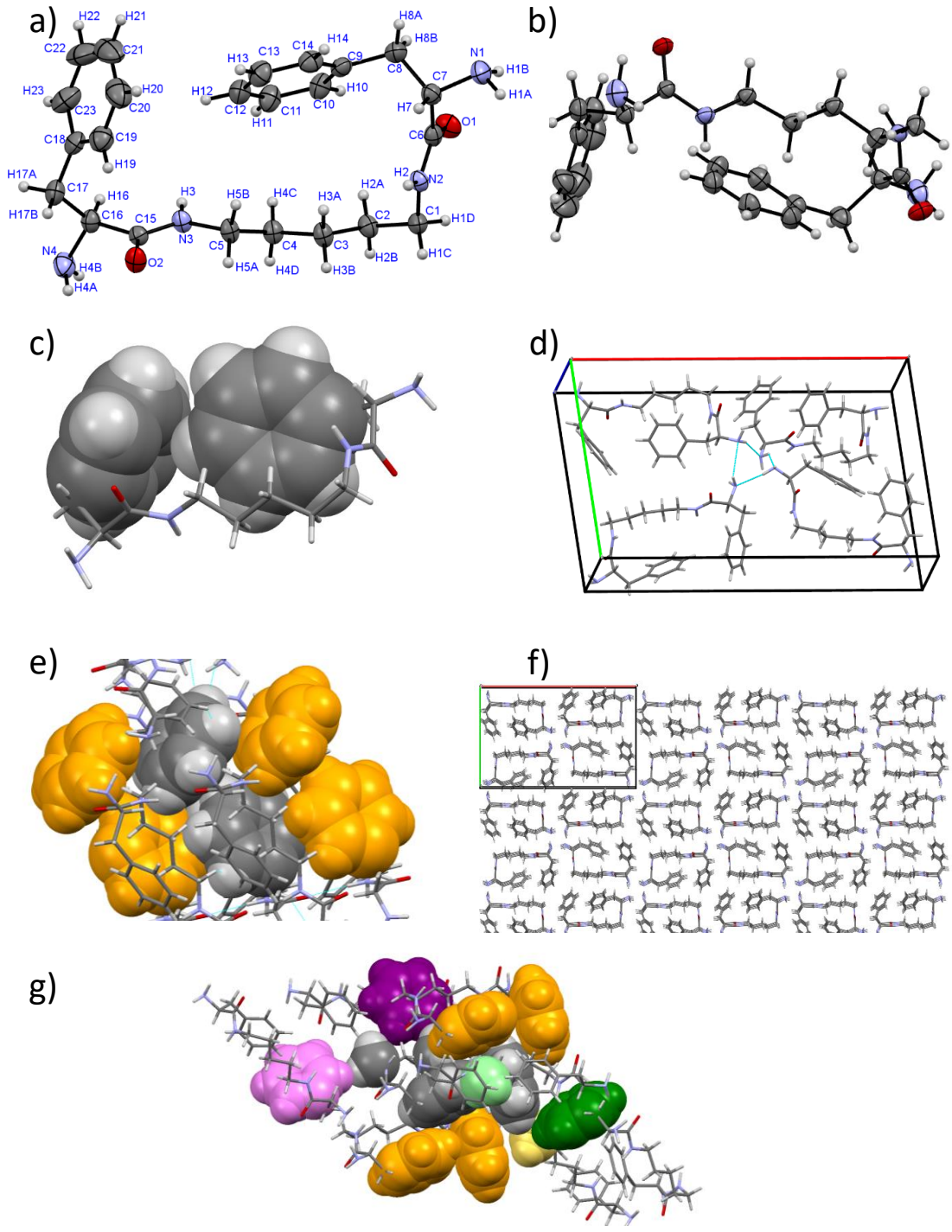

Figure S8 Conformational elements (a-c) highlighting the intramolecular edge-to-face aromatic interaction (c), unit cell displaying $NH_2\cdots NH_2$ intermolecular hydrogen bonds (d) and packing motifs for **4b**: face-to-face aromatic arrangements observed in the stacks (e); view along c axis (d); aromatic arrangements for a given molecule (carbon atoms in grey), different colours correspond to different molecules; close contacts between aromatic rings and some methylene groups have also been represented (g).

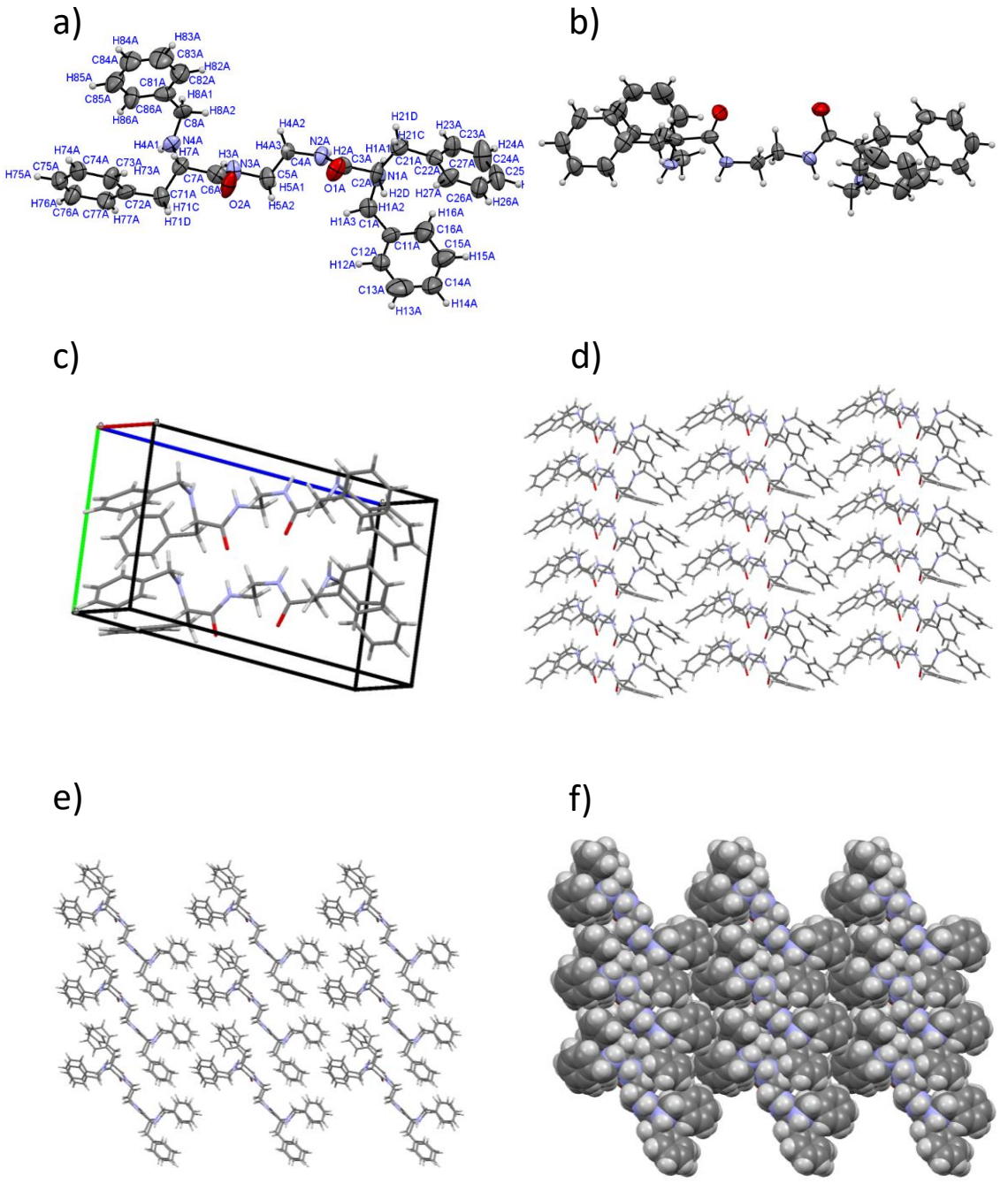

Figure S9 Conformational elements (a-b), unit cell (c) and packing motifs for **7b**: view along a axis (d); view along the b axis highlighting the aromatic contacts between stacks based on edge-to-face aromatic arrangements (e and f). Crystallographic data taken from ref. 24.

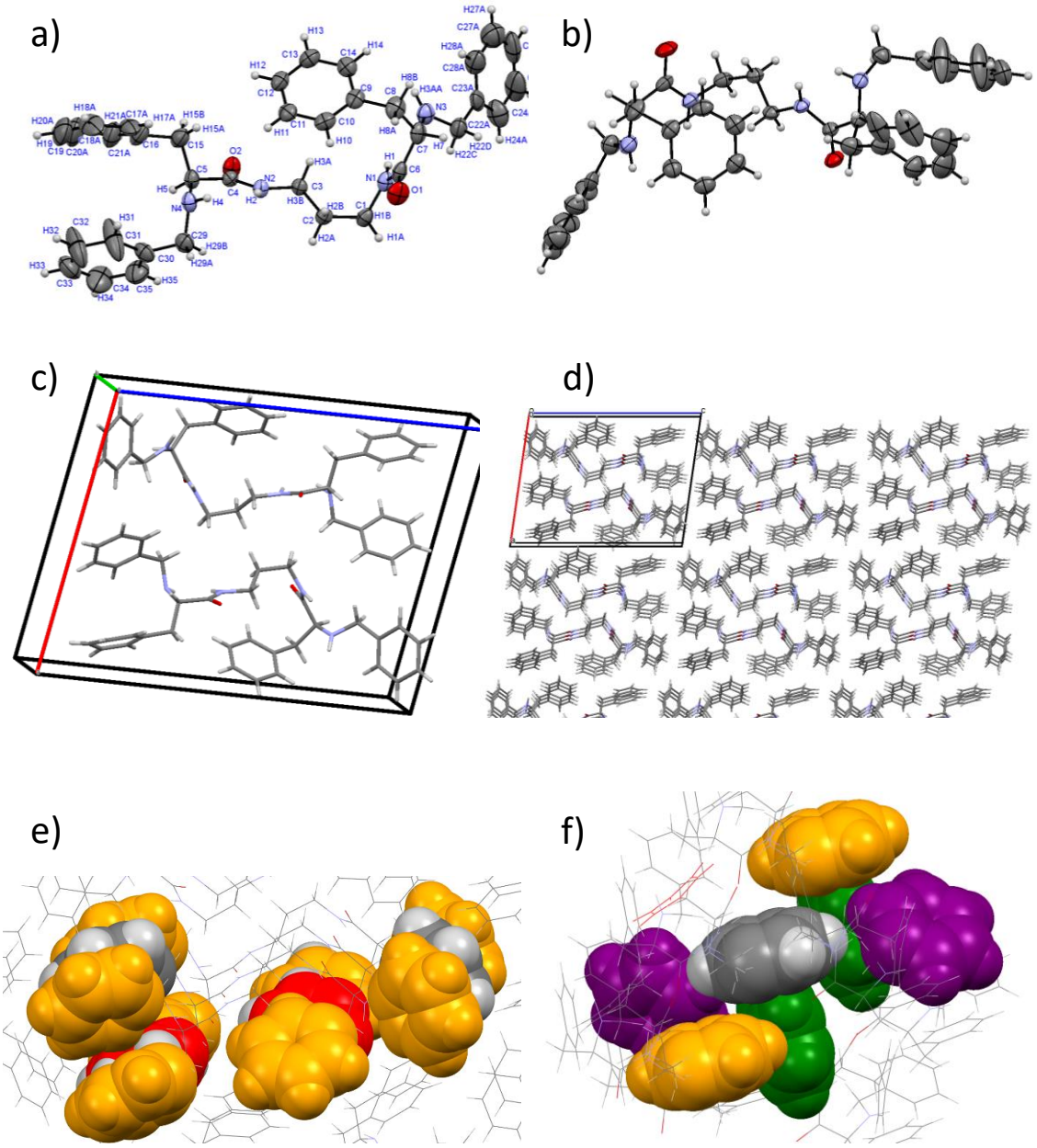

Figure S10 Conformational elements (a-b), unit cell (c) and packing motifs for **8b**: view along b axis (d); CPK representation of aromatic arrangements present in stacks; for the central molecule, aromatic rings from the amino acid side chain are represented in red and those from the N-benzyl groups in grey (e); CPK representation of the intermolecular aromatic contacts involving an aromatic ring (grey carbon atoms) from an N-benzyl group (f). Crystallographic data taken from ref. 23c.

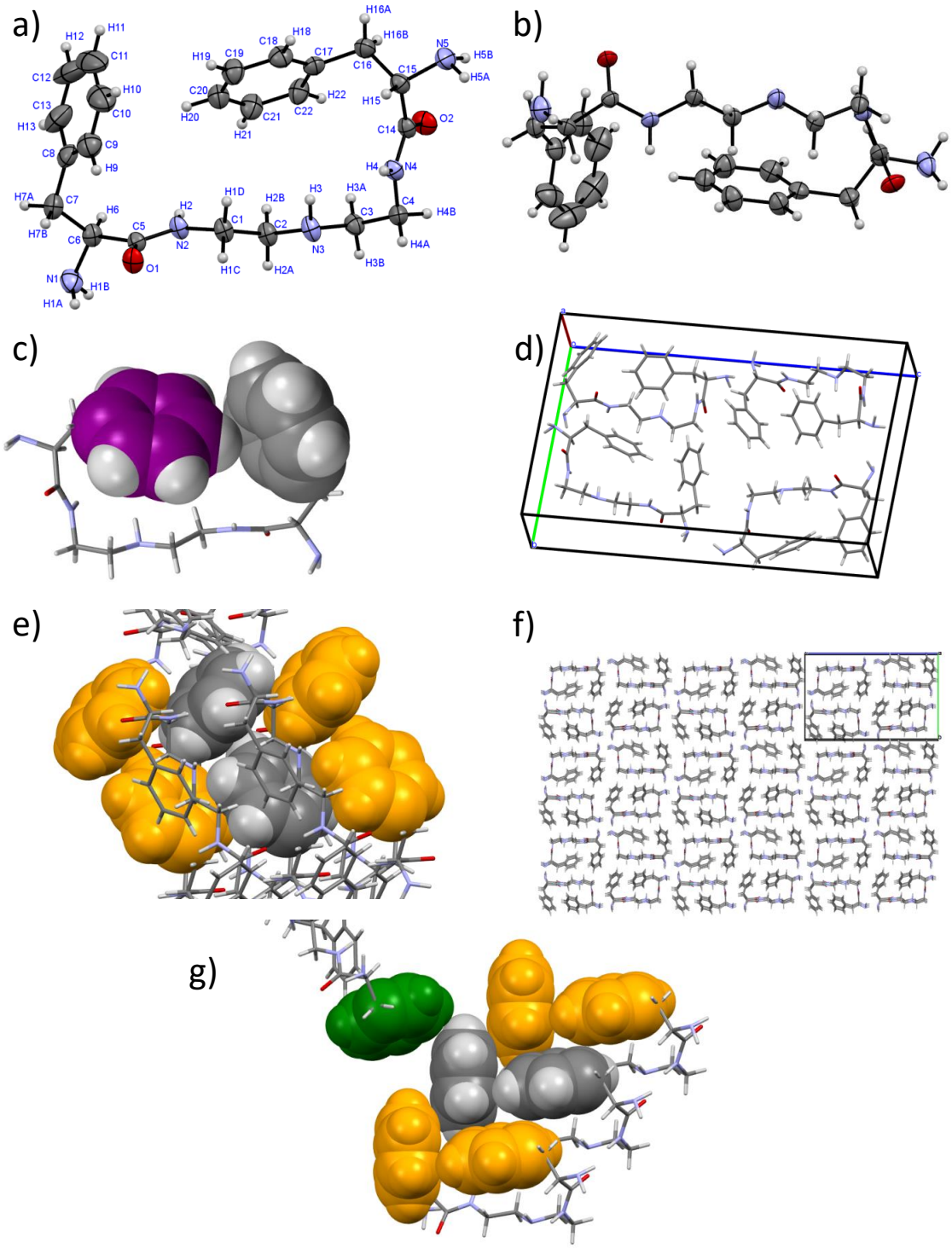

Figure S11 Conformational elements (a-c) highlighting the intramolecular edge-to-face aromatic interaction (c), unit cell (d) and packing motifs for **9b**: face-to-face aromatic arrangements observed in the stacks (e); view along a axis (d); aromatic interactions for a given molecule (carbon atoms in grey), orange colour indicates molecules in the same stack, green colour indicates a molecule in a different stack.

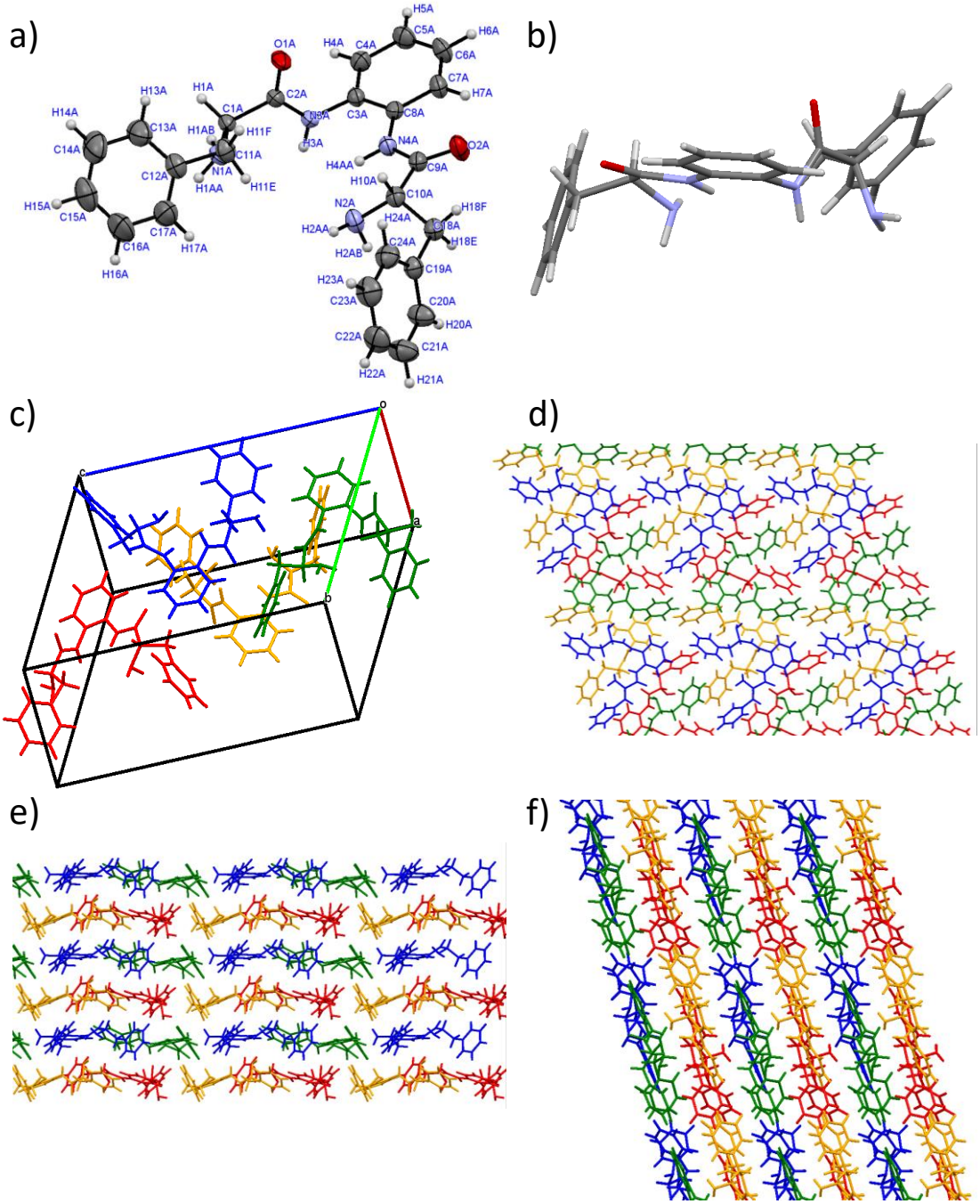

Figure S12 Conformational elements for one of the four conformers present in the asymmetric unit (a-b), unit cell (d) and packing motifs for **10b**: view along a axis (d); view along b axis (e); .view along c axis (f). Crystallographic data taken from ref. 23b.

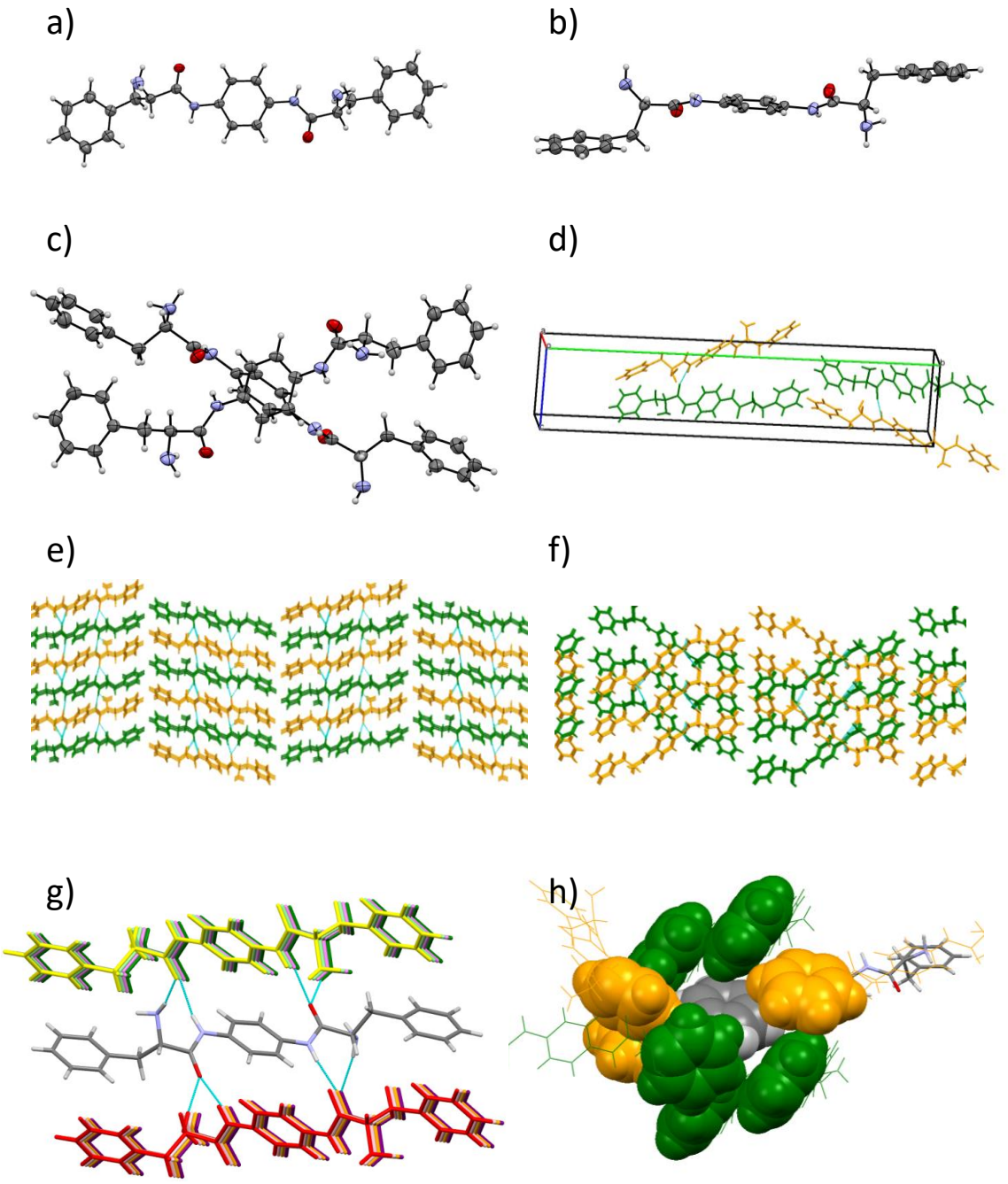

Figure S13 Conformational elements (a-c), including the asymmetric unit (c), unit cell (d) and packing motifs for **11b**: a axis view of the packing highlighting the hydrogen bond between stacks based on face-to-face aromatic contacts; orange and green indicate the two different conformations present at the asymmetric unit (e); c axis view of the packing highlighting the hydrogen bonding network (f); Hydrogen bonding network for a single molecule involving amide-amide or amide-amine interactions with eight molecules in the second conformation from two different stacks based on face-to-face aromatic interactions (g) aromatic contacts present for each aromatic unit (side chain); the selected molecule is represented with the carbon atoms in grey; orange indicates a molecule with the same conformation; green indicates a molecule with the second conformation (h). Crystallographic data taken from ref. 23a.

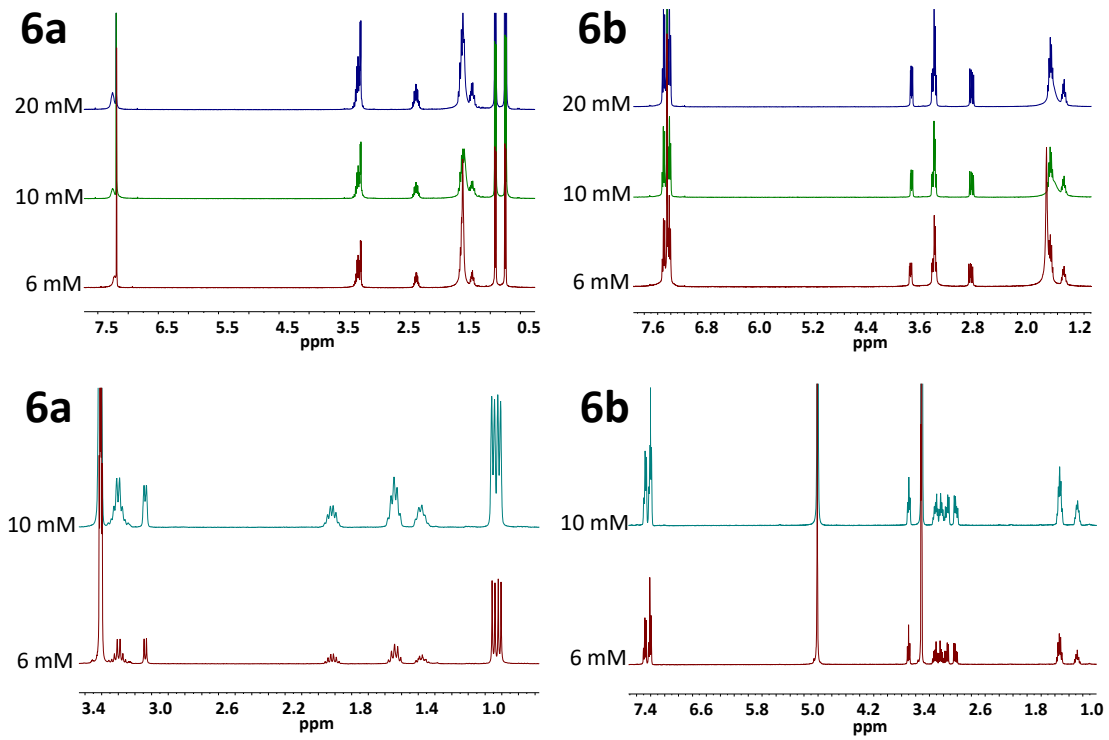

Figure S14 Partial ^{1}H NMR spectra of **6a** and **6b** in $CDCl_3$ (top) and CD_3OD (bottom) at different concentrations

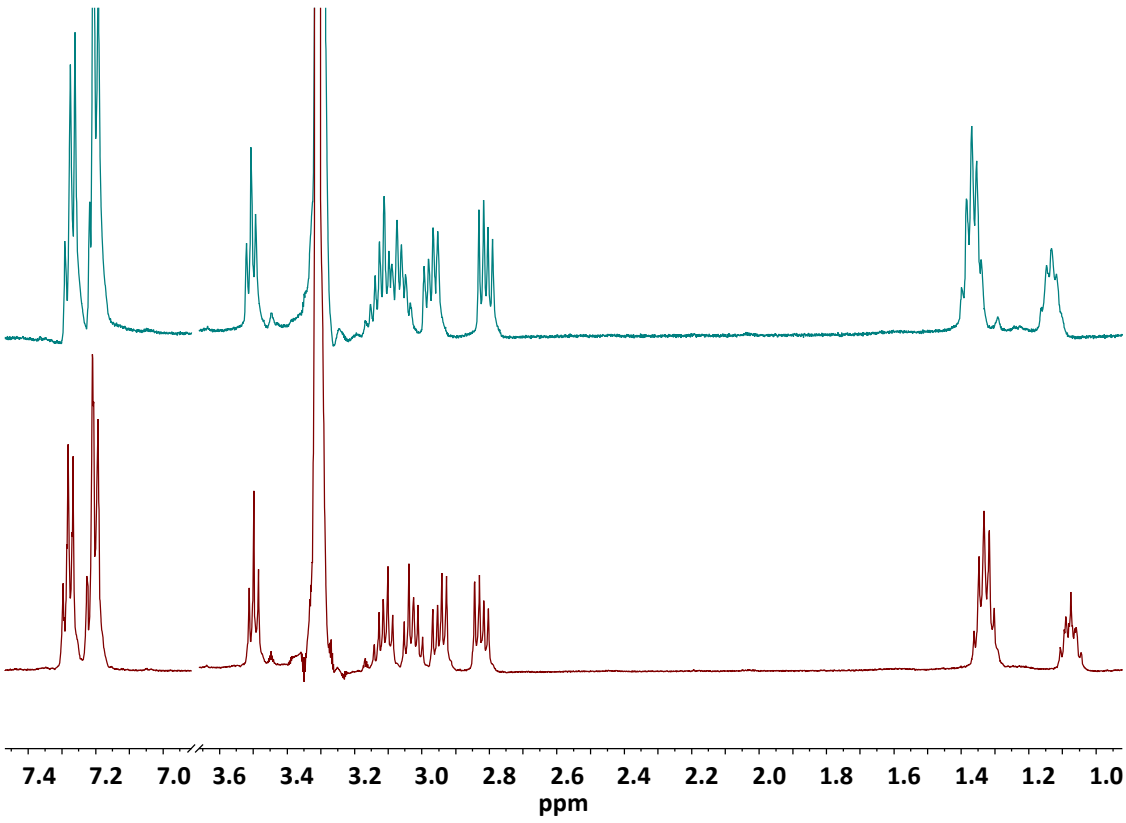

Figure S15 Partial ^{1}H NMR spectra of **4b** (6 mM in CD_3OD) at 58^{o}C (top) and 30^{o}C (bottom)

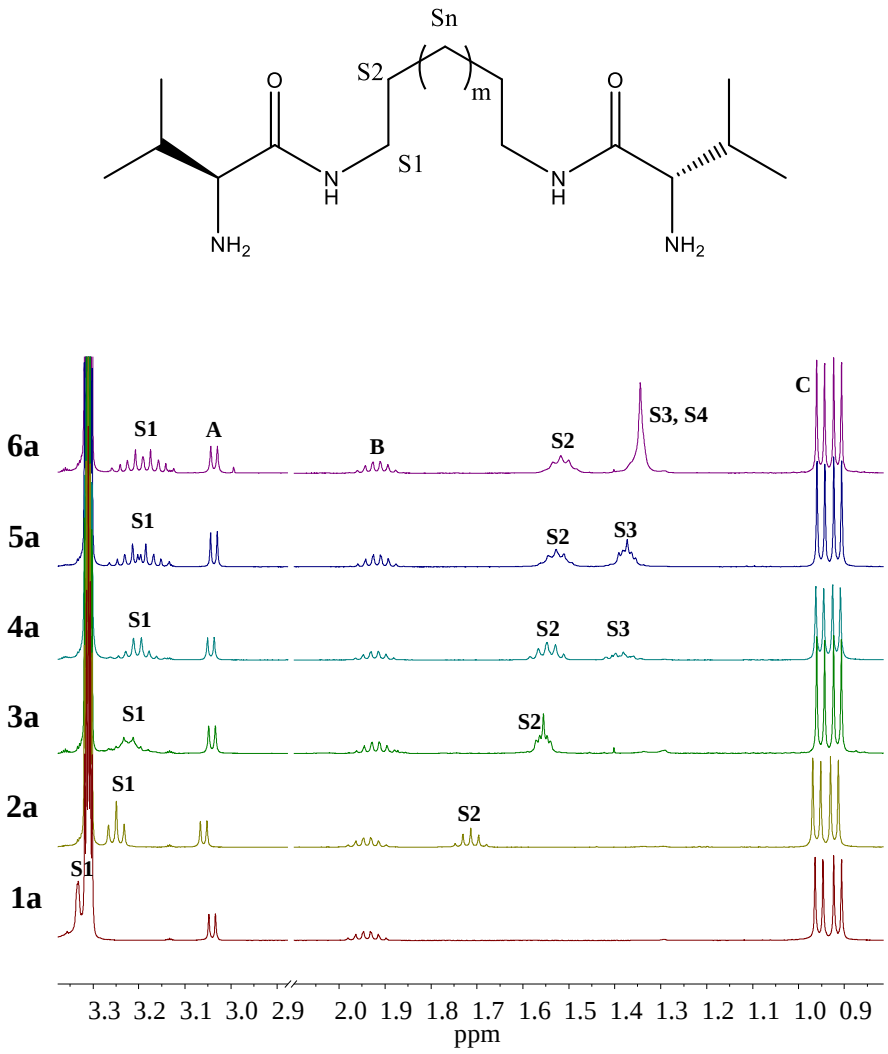

Figure S16 Partial ^{1}H NMR spectra for Val-derived pseudopeptides in CD_3OD

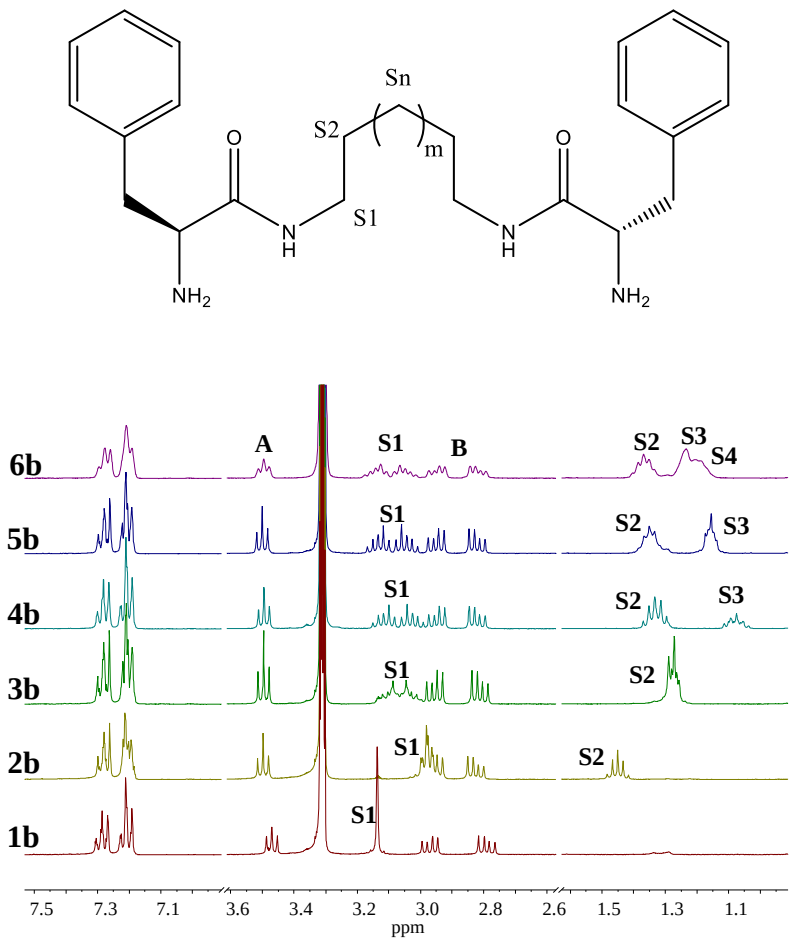

Figure S17 Partial ^{1}H NMR spectra for Phe-derived pseudopeptides in CD_3OD

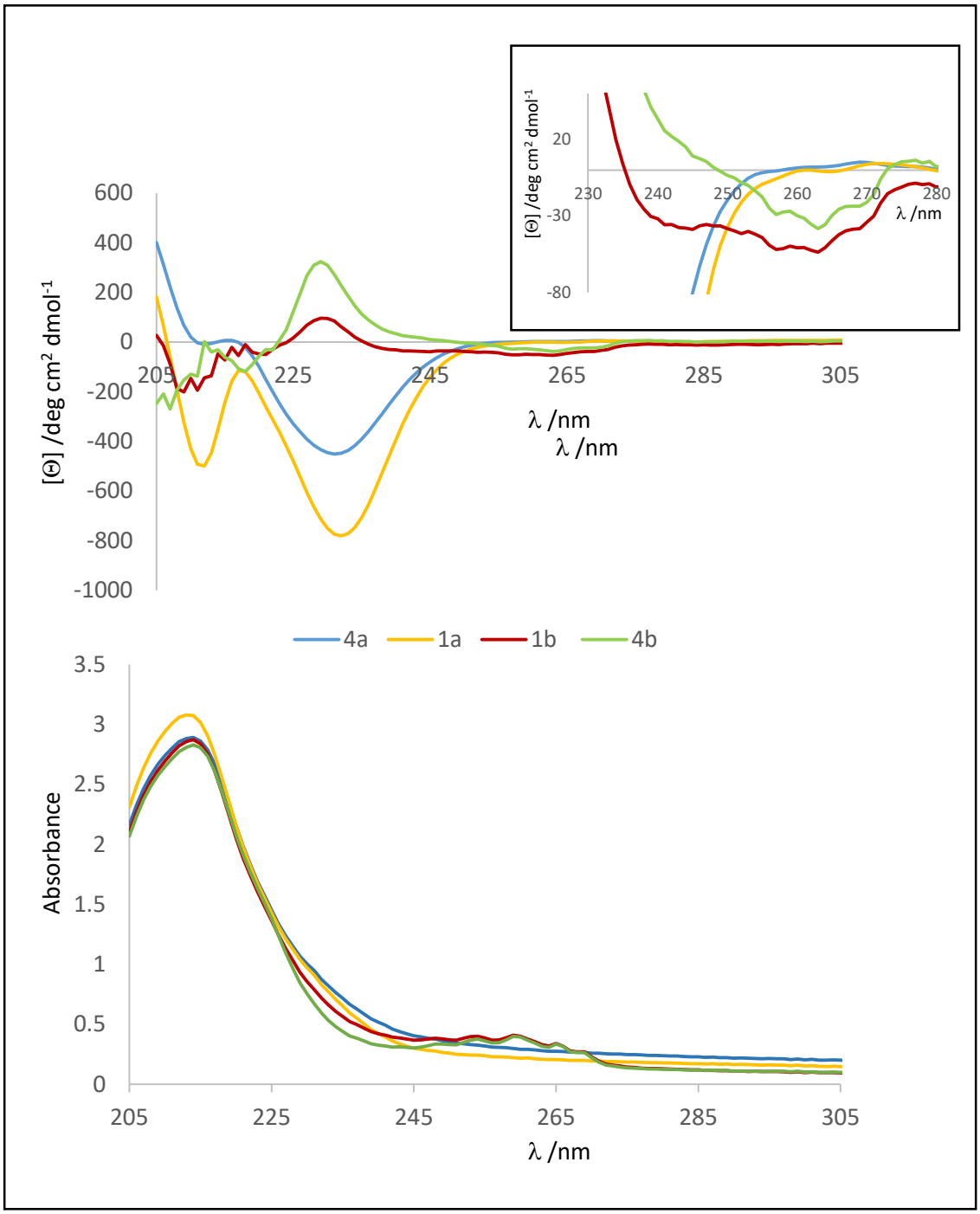

Figure S18 Partial CD (top) and UV (bottom) spectra for **1a, 1b, 4a** and **4b** 4 mM in CH_3OH. The inset shows an expansion of the 230-280 nm region.

Table S1 Crystallographic and structural refinements data for compounds **1a**, **4a** and **4b**

Identification code	**1a**	**4a**	**4b**
CCDC file	1880517	1880519	1880521
Empirical formula	$C_{12}H_{30}N_4O_4$	$C_{15}H_{31.61}N_4O_{4.25}$	$C_{23}H_{32}N_4O_2$
Formula weight	294.40	336.05	396.52
Temperature/K	293(2)	293(2)	293(2)
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	$P2_1$	I2	$P2_12_12$
a/Å	12.5640(3)	20.4259(4)	25.6360(3)
b/Å	4.80981(7)	4.79492(9)	16.5436(2)
c/Å	15.8319(3)	21.6606(5)	5.05085(6)
α/°	90	90	90
β/°	112.756(3)	102.636(2)	90
γ/°	90	90	90
Volume/$Å^3$	882.26(4)	2070.08(8)	2142.12(4)
Z	2	4	4
$\rho_{calc}g/cm^3$	1.108	0.963	1.230
μ/mm^{-1}	0.682	0.516	0.633
F(000)	324.0	662.0	856.0
Crystal size/mm^3	0.3977 × 0.1078 × 0.0509	0.7711 × 0.0913 × 0.0542	0.3512 × 0.0585 × 0.0346
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.63 to 131.998	6.728 to 131.978	6.896 to 145
Index ranges	$-14 \le h \le 12$, $-5 \le k \le 5$, $-18 \le l \le 18$	$-24 \le h \le 24$, $-5 \le k \le 5$, $-25 \le l \le 25$	$-31 \le h \le 31$, $-20 \le k \le 19$, $-5 \le l \le 6$
Reflections collected	8173	9488	19750
Independent reflections	3066 [R_{int} = 0.0762, R_{sigma} = 0.0748]	3413 [R_{int} = 0.0422, R_{sigma} = 0.0384]	4201 [R_{int} = 0.0391, R_{sigma} = 0.0223]
Data/restraints/parameters	3066/7/215	3413/21/228	4201/6/286
Goodness-of-fit on F^2	1.078	1.040	1.033
Final R indexes [I>=2σ(I)]	R_1 = 0.0459, wR_2 = 0.1216	R_1 = 0.0613, wR_2 = 0.1716	R_1 = 0.0385, wR_2 = 0.1030
Final R indexes [all data]	R_1 = 0.0542, wR_2 = 0.1244	R_1 = 0.0639, wR_2 = 0.1774	R_1 = 0.0400, wR_2 = 0.1059
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.22	0.30/-0.18	0.14/-0.16
Flack parameter	-0.1(3)	-0.11(19)	-0.03(10)

Table S2 Crystallographic and structural refinements data for compounds **6a**, **9a** and **9b**

Identification code	**6a**	**9a**	**9b**
CCDC file	1880520	1880518	1880522
Empirical formula	$C_{18}H_{40}N_4O_3$	$C_{14}H_{35}N_5O_4$	$C_{22}H_{31}N_5O_2$
Formula weight	360.54	337.47	397.52
Temperature/K	293(2)	293(2)	293(2)
Crystal system	orthorhombic	monoclinic	orthorhombic
Space group	$P2_12_12_1$	C2	$P22_12_1$
a/Å	4.84556(10)	26.1681(6)	5.01883(14)
b/Å	20.5154(5)	4.81178(18)	16.5007(5)
c/Å	21.9450(4)	16.5261(5)	25.5451(7)
α/°	90	90	90
β/°	90	105.807(3)	90
γ/°	90	90	90
Volume/$Å^3$	2181.51(8)	2002.20(11)	2115.49(10)
Z	4	4	4
$\rho_{calc}g/cm^3$	1.098	1.120	1.248
μ/mm^{-1}	0.596	0.672	0.656
F(000)	800.0	744.0	856.0
Crystal size/mm^3	0.383 × 0.067 × 0.05	0.9442 × 0.0931 × 0.0382	0.6174 × 0.0395 × 0.0248
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.058 to 131.994	7.022 to 129.942	6.92 to 140.994
Index ranges	$-5 \le h \le 4$, $-24 \le k \le 24$, $-26 \le l \le 26$	$-30 \le h \le 30$, $-5 \le k \le 5$, $-19 \le l \le 19$	$-6 \le h \le 1$, $-18 \le k \le 20$, $-21 \le l \le 30$
Reflections collected	19233	16100	6701
Independent reflections	3808 [R_{int} = 0.0405, R_{sigma} = 0.0285]	3249 [R_{int} = 0.0695, R_{sigma} = 0.0432]	3869 [R_{int} = 0.0379, R_{sigma} = 0.0488]
Data/restraints/parameters	3808/0/262	3249/9/246	3869/7/290
Goodness-of-fit on F^2	1.042	1.077	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0507, wR_2 = 0.1230	R_1 = 0.0548, wR_2 = 0.1514	R_1 = 0.0404, wR_2 = 0.1084
Final R indexes [all data]	R_1 = 0.0561, wR_2 = 0.1279	R_1 = 0.0592, wR_2 = 0.1564	R_1 = 0.0451, wR_2 = 0.1119
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.20	0.24/-0.21	0.16/-0.15
Flack parameter	0.09(11)	0.2(3)	-0.13(19)