The effect of curcumin on the stability of Aβ dimers

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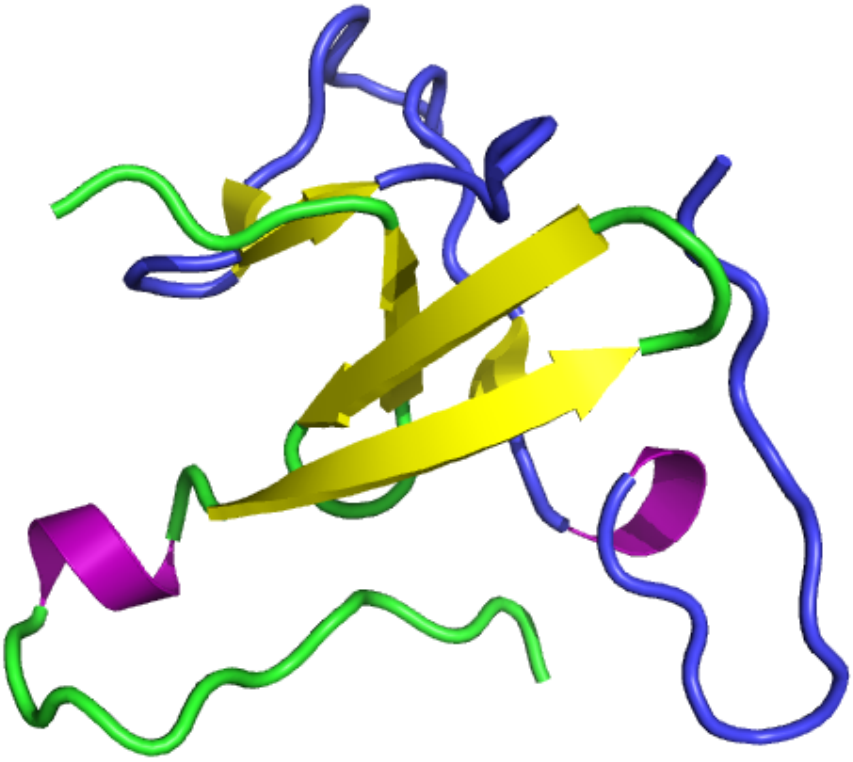

Figure S1: The snapshot of the dimer at the end of the set 2 simulation. The dimer was represented as cartoon (β-sheet: yellow; helix: purple; for the others from peptide A: tv_green; for the others from pepitde B: tv_blue).

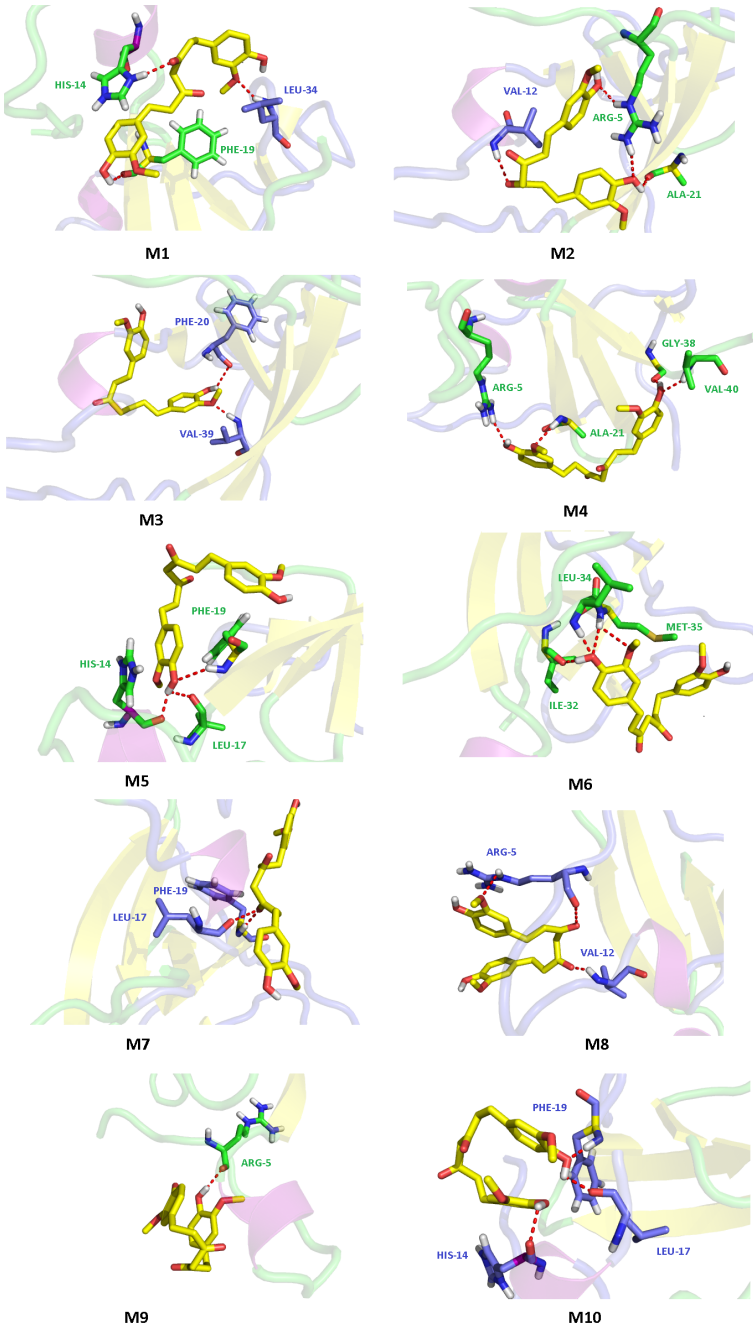

Figure S2: The initial M0-10 models. The secondary structure of dimer was represented as transparent cartoon (β-sheet: yellow; α-helix: purple; others for peptide A: tv_blue; others for peptide B: tv_green). The curcumin was shown as stick and colored by element (C: yellow; H: grey; O: red). For the residues from peptide A involved in the contacts with curcumin was represented as stick and colored by element (C: marine; N: blue; H: grey; O: red). For the residues from peptide B involved in the direct contact with curcumin was also represented as stick and colored by the similar element except C atom was colore as green to distinguish from peptide A. Please note for those C_α atom exits in the β-sheet part was colored as yellow, and purple for the Cα atom in α-helix part.

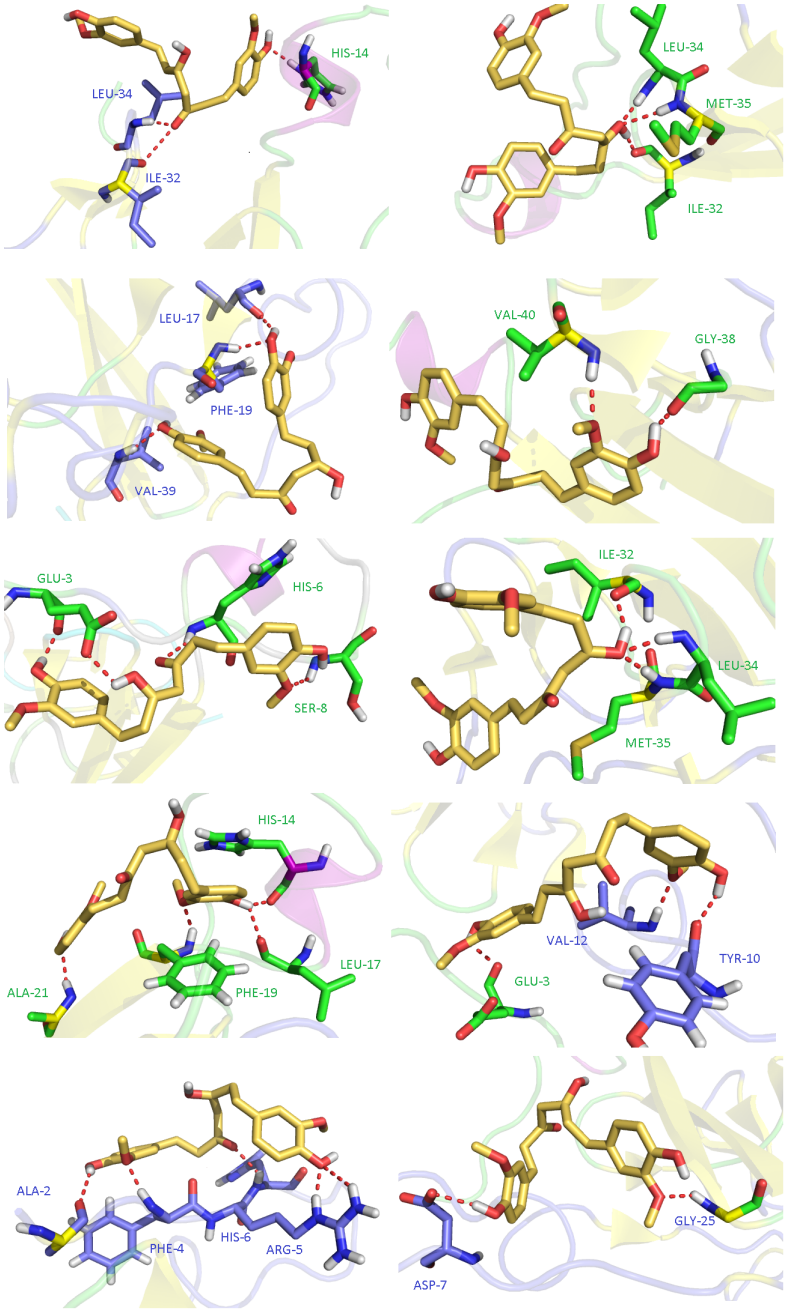

Figure S3: The initial M11-20 models. The secondary structure of dimer was represented as transparent cartoon (β-sheet: yellow; α-helix: purple; others for peptide A: tv_blue; others for peptide B: tv_green). The curcumin was shown as stick and colored by element (C: yellow; H: grey; O: red). For the residues from peptide A involved in the contacts with curcumin was represented as stick and colored by element (C: marine; N: blue; H: grey; O: red). For the residues from peptide B involved in the direct contact with curcumin was also represented as stick and colored by the similar element except C atom was colore as green to distinguish from peptide A. Please note for those C_α atom exits in the β-sheet part was colored as yellow, and purple for the Cα atom in α-helix part.

Table S1: Calculated pKa value for titratable residues.

Residues	pKa values
N-terminus	7.9
AspNT	2.4
Glu-3	4.2
Arg-5	12.2
His-6	6.0
Asp-7	4.2
Tyr-10	11.0
Glu-11	4.6
His-13	5.5
His-14	7.6
Lys-16	9.7
Glu-22	4.5
Asp-23	4.4
Lys-28	10.3
C-terminus	4.4

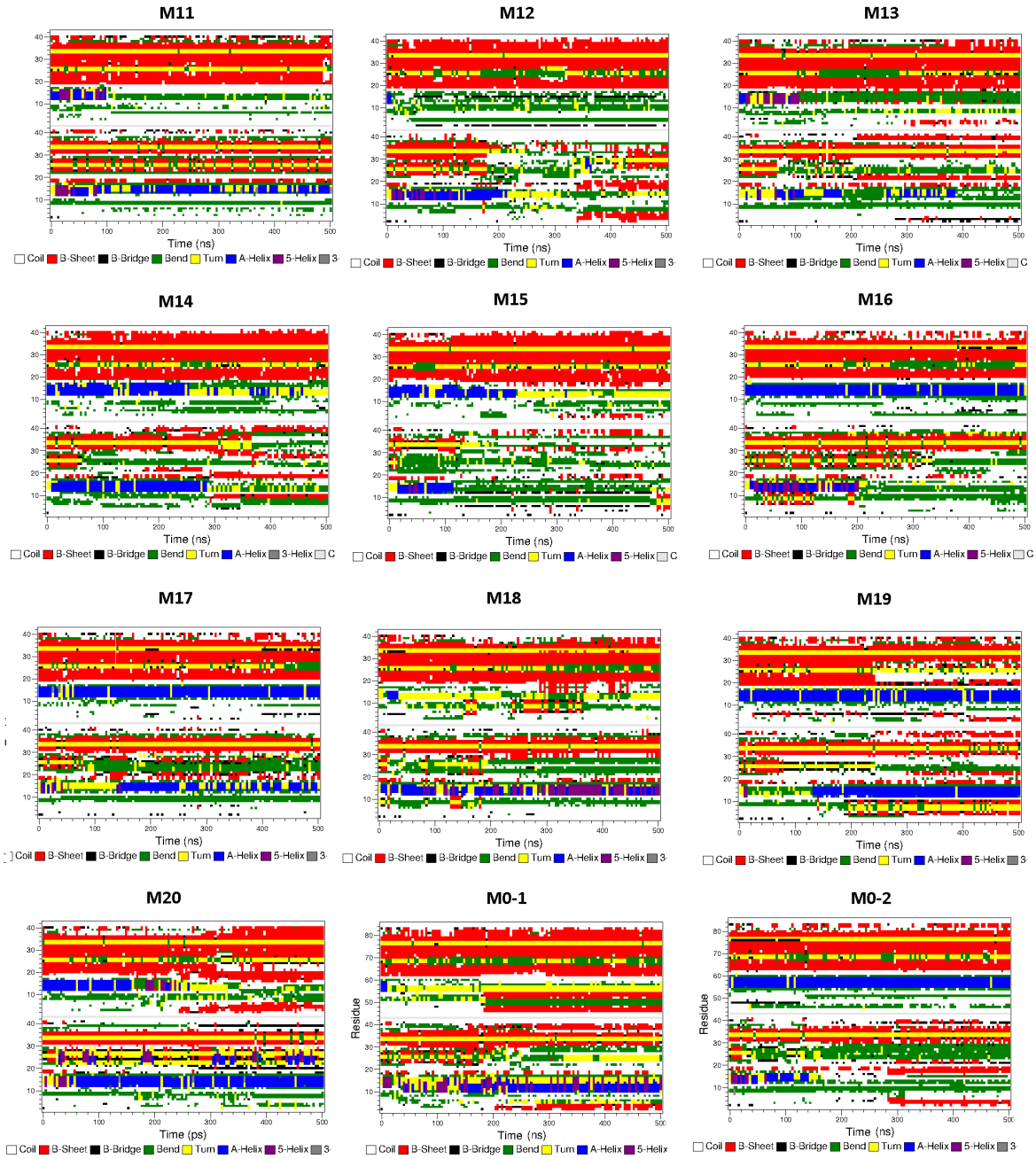

Figure S4: Evolution of the secondary structure of protein in the presence of keto-enol conformers and the controlled group M0.

Table S2: Simulation System

β-diketone tautomers					keto-enol tautomers				
Model ID	Potential binding sites	Binding Energy kcal/mol	Rank	Water molecules	Model ID	Potential binding sites	Binding Energy kcal/mol	Rank	Water molecules
M1	A: LEU-34 B :HIS-14$^{\alpha}$, PHE-19$^{\beta}$	-3.84	5	7475	M11	A: LEU-34, ILE-32 B: HIS-14$^{\alpha}$	-4.38	1	8111
M2	A: VAL-12 B: ARG-5, ALA-21$^{\beta}$	-5.30	1	7471	M12	B: ILE-32$^{\beta}$, LEU-34 MET-35$^{\beta}$	-4.14	2	7472
M3	A: PHE-20, VAL-39	-2.82	9	7477	M13	A: LEU-17, PHE-19$^{\beta}$ VAL-39	-3.74	3	7474
M4	B: ARG-5, ALA-21$^{\beta}$ GLY-38$^{\beta}$, VAL-40	-3.04	8	7480	M14	B: GLY-38, VAL-40$^{\beta}$	-3.71	4	7478
M5	B: HIS-14$^{\alpha}$, LEU-17 PHE-19	-4.37	3	7478	M15	B: GLU-3, HIS-6 SER-8	-3.55	5	7468
M6	B: ILE-32$^{\beta}$, LEU-34 MET-35$^{\beta}$	-3.08	7	7474	M16	B: ILE-32$^{\beta}$, LEU-34 MET-35$^{\beta}$	-3.53	6	7479
M7	A: LEU-17, PHE-19$^{\beta}$	-4.79	2	7469	M17	A: HIS-14$^{\alpha}$, LEU-17 PHE-19$^{\beta}$, ALA-21$^{\alpha}$	-2.97	7	7475
M8	A: ARG-5, VAL-12	-2.76	10	7472	M18	A: TYR-10, VAL-12 B: GLU-3	-2.88	8	7471
M9	B: ARG-5	-4.04	4	7466	M19	A: ALA-2$^{\beta}$, PHE-4 ARG-5, HIS-16	-2.77	9	7475
M10	A: HIS-14, LEU-17 PHE-19	-3.66	6	7469	M20	A: ASP-7 B: GLY-25$^{\beta}$	-2.50	10	7471
M0	-	-	-	7495					

- indicates NULL.
$^{\alpha}$ indicates residue sites on α-helix.
$^{\beta}$ indicates residue sites on β-sheet.

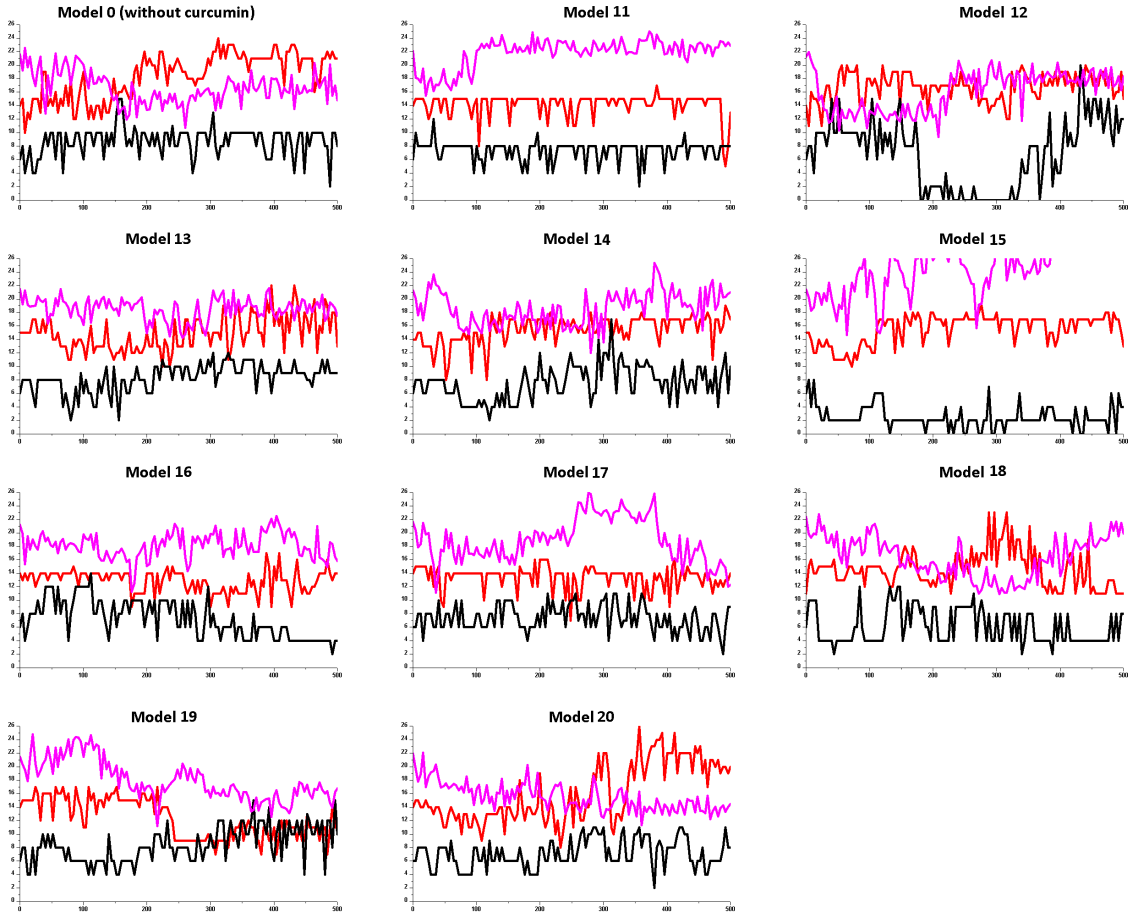

Figure S5: Time evolution of the number of residues in β-structure (β-sheet and β-bridge) of peptide A (black line) and B (colored by red) and the contact numbers between peptide A and B (colored by magenta). The data were extracted from each 11 model trajectories and averaged per 4 *ns*. The contact number were divided by 100.

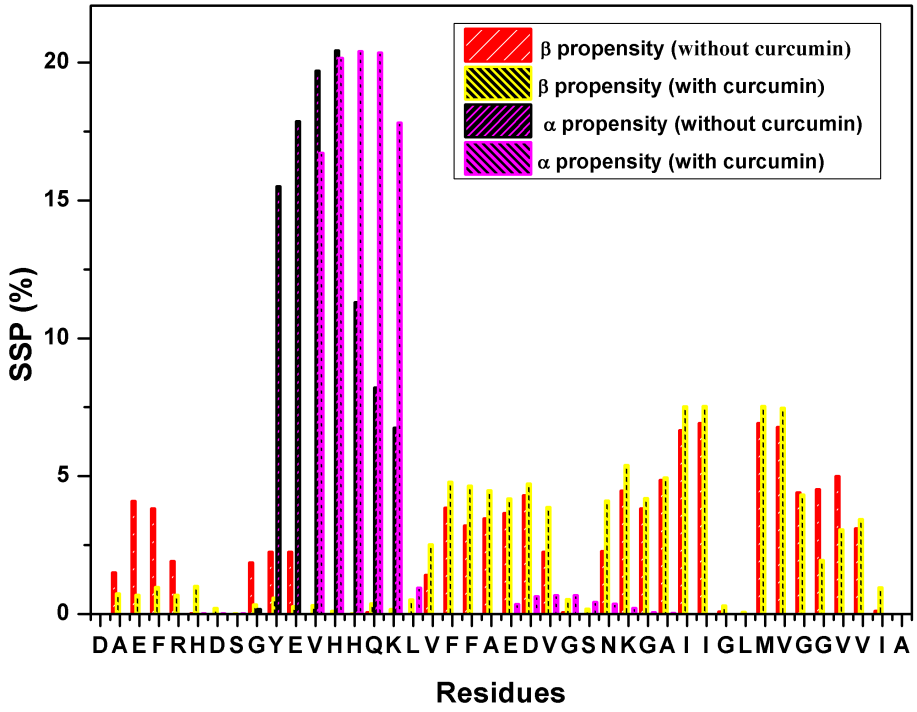

Figure S6: The secondary structure propensity of Aβ residues in the presence and absence of curcumin.

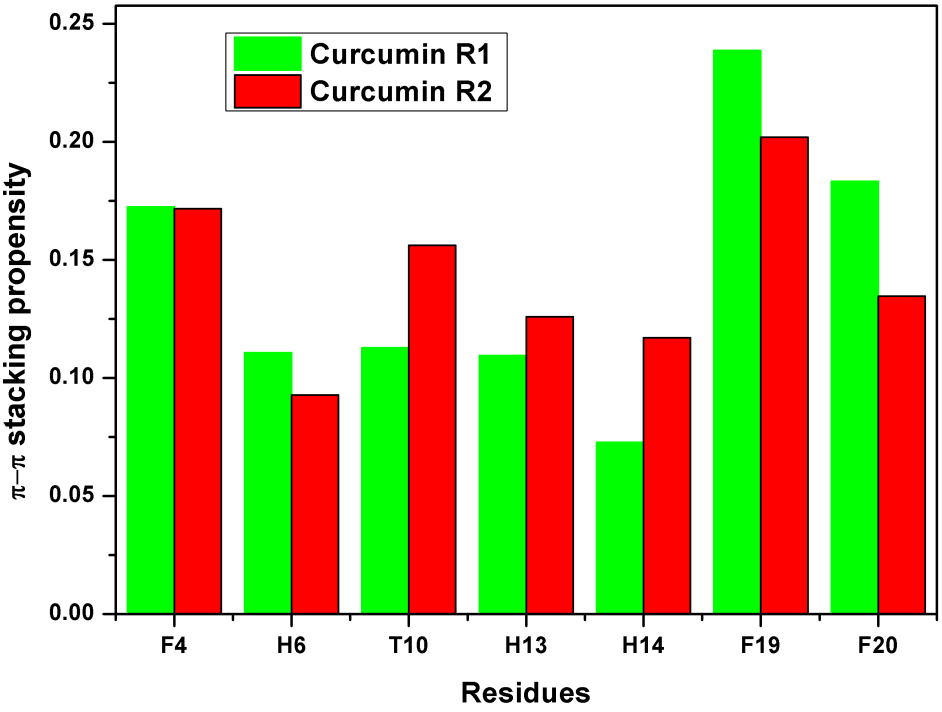

Figure S7: The π-π stacking propensity of Aβ residues His, Tyr and Phe with curcumin R1 and R2 respectively.

Table S3: The occurence of dehydron.

The occurence of dehydron	
pairs	occurence
B: (24V, 27N)	292
A: (24V, 27N)	222
B: (11E, 15Q)	157
B: (34L, 41I)	150
(A: 40V, B: 28K)	133
A:(30A, 37G)	124
A:(11E, 15Q)	110
B:(12V, 16K)	98
A:(22E, 29G)	89
A:(12V, 16K)	53
B:(22E, 29G)	52
A:(6H, 12V)	51
(A:38G, B:41I)	49
A:(23D, 27N)	45
A:(23D, 28K)	44
A:(5R, 9D)	42
(A:36V, B:39V)	37
B:(1D, 15Q)	35
A:(22E, 27N)	35
(A:3E, B:24V)	34
(A:41I, B:28K)	33
(A:1D, B:26S)	32
(A:1D, B:27N)	31
A:(7D, 10Y)	31
A:(28K, 35G)	31
...	< 30

Table S4: The curcumin topology

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[ moleculetype ]
; Name nrexcl
CUR      3

[ atoms ]
;   nr       type  resnr resid  atom  cgnr    charge      mass
     1       CH3      1  CUR     C21     1    0.200  15.0350
     2        OA      1  CUR      O4     1   -0.400  15.9994
     3         C      1  CUR     C19     1    0.200  12.0110
     4       CR1      1  CUR     C20     1   -0.060  12.0110
     5        HC      1  CUR     H20     1    0.060   1.0080
     6         C      1  CUR     C18     1    0.265  12.0110
     7        OA      1  CUR      O5     1   -0.683  15.9994
     8         H      1  CUR     H52     1    0.418   1.0080
     9       CR1      1  CUR     C17     2   -0.060  12.0110
    10        HC      1  CUR     H17     2    0.060   1.0080
    11       CR1      1  CUR     C16     2   -0.060  12.0110
    12        HC      1  CUR     H16     2    0.060   1.0080
    13         C      1  CUR     C15     2   -0.000  12.0110
    14         C      1  CUR     C14     3    0.000  13.0190
    15         C      1  CUR     C13     3    0.000  13.0190
    16         C      1  CUR     C12     3    0.265  12.0110
    17        OA      1  CUR      O3     3   -0.683  15.9994
    18         H      1  CUR     H32     3    0.418   1.0080
    19         C      1  CUR     C11     3    0.000  13.0190
    20         C      1  CUR     C10     3    0.265  12.0110
    21         O      1  CUR      O6     3   -0.265  15.9994
    22         C      1  CUR      C9     4    0.000  13.0190
    23         C      1  CUR      C8     4    0.000  13.0190
    24         C      1  CUR      C4     4   -0.000  12.0110
    25       CR1      1  CUR      C3     4   -0.060  12.0110
    26        HC      1  CUR     H31     4    0.060   1.0080
    27       CR1      1  CUR      C5     5   -0.060  12.0110
    28        HC      1  CUR     H51     5    0.060   1.0080
    29       CR1      1  CUR      C6     6   -0.060  12.0110
    30        HC      1  CUR      H6     6    0.060   1.0080
    31         C      1  CUR      C7     6    0.265  12.0110
    32        OA      1  CUR      O2     6   -0.683  15.9994
    33         H      1  CUR     H22     6    0.418   1.0080
    34         C      1  CUR      C2     6    0.200  12.0110
    35        OA      1  CUR      O1     6   -0.400  15.9994
    36       CH3      1  CUR      C1     6    0.200  15.0350

[ bonds ]
; ai  aj  fu    c0, c1, ...
   2   1   2    0.143   8180000.0    0.143   8180000.0 ;    O4  C21
   3   2   2    0.136  10200000.0    0.136  10200000.0 ;   C19   O4
   3   4   2    0.139  10800000.0    0.139  10800000.0 ;   C19  C20
   3   6   2    0.139  10800000.0    0.139  10800000.0 ;   C19  C18
   4   5   2    0.109  12300000.0    0.109  12300000.0 ;   C20  H20
  13   4   2    0.139  10800000.0    0.139  10800000.0 ;   C15  C20
   6   7   2    0.136  10200000.0    0.136  10200000.0 ;   C18   O5
   6   9   2    0.139  10800000.0    0.139  10800000.0 ;   C18  C17
   7   8   2    0.100  15700000.0    0.100  15700000.0 ;    O5  H52
   9  10   2    0.109  12300000.0    0.109  12300000.0 ;   C17  H17
   9  11   2    0.139  10800000.0    0.139  10800000.0 ;   C17  C16
  11  12   2    0.109  12300000.0    0.109  12300000.0 ;   C16  H16
  13  11   2    0.139  10800000.0    0.139  10800000.0 ;   C15  C16
  13  14   2    0.139  10800000.0    0.139  10800000.0 ;   C15  C14
  14  15   2    0.153   7150000.0    0.153   7150000.0 ;   C14  C13
  16  15   2    0.153   7150000.0    0.153   7150000.0 ;   C12  C13
  16  17   2    0.136  10200000.0    0.136  10200000.0 ;   C12   O3
  16  19   2    0.153   7150000.0    0.153   7150000.0 ;   C12  C11
  17  18   2    0.100  15700000.0    0.100  15700000.0 ;    O3  H32
  20  19   2    0.153   7150000.0    0.153   7150000.0 ;   C10  C11
  20  21   2    0.123  16600000.0    0.123  16600000.0 ;   C10   O6
  20  22   2    0.153   7150000.0    0.153   7150000.0 ;   C10   C9
  22  23   2    0.153   7150000.0    0.153   7150000.0 ;    C9   C8
  24  23   2    0.139  10800000.0    0.139  10800000.0 ;    C4   C8
  24  25   2    0.139  10800000.0    0.139  10800000.0 ;    C4   C3
  24  27   2    0.139  10800000.0    0.139  10800000.0 ;    C4   C5
  25  26   2    0.109  12300000.0    0.109  12300000.0 ;    C3  H31
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   34  25   2    0.139  10800000.0    0.139  10800000.0 ;    C2   C3
   27  28   2    0.109  12300000.0    0.109  12300000.0 ;    C5  H51
   27  29   2    0.139  10800000.0    0.139  10800000.0 ;    C5   C6
   29  30   2    0.109  12300000.0    0.109  12300000.0 ;    C6   H6
   31  29   2    0.139  10800000.0    0.139  10800000.0 ;    C7   C6
   31  32   2    0.136  10200000.0    0.136  10200000.0 ;    C7   O2
   31  34   2    0.139  10800000.0    0.139  10800000.0 ;    C7   C2
   32  33   2    0.100  15700000.0    0.100  15700000.0 ;    O2  H22
   34  35   2    0.136  10200000.0    0.136  10200000.0 ;    C2   O1
   35  36   2    0.143   8180000.0    0.143   8180000.0 ;    O1   C1

[ pairs ]
; ai  aj  fu    c0, c1, ...
    1   4   1                                            ;   C21  C20
    1   6   1                                            ;   C21  C18
    2   5   1                                            ;    O4  H20
    2   7   1                                            ;    O4   O5
    2   9   1                                            ;    O4  C17
    2  13   1                                            ;    O4  C15
    3   8   1                                            ;   C19  H52
    3  10   1                                            ;   C19  H17
    3  11   1                                            ;   C19  C16
    3  14   1                                            ;   C19  C14
    4   7   1                                            ;   C20   O5
    4   9   1                                            ;   C20  C17
    4  12   1                                            ;   C20  H16
    4  15   1                                            ;   C20  C13
    5   6   1                                            ;   H20  C18
    5  11   1                                            ;   H20  C16
    5  14   1                                            ;   H20  C14
    6  12   1                                            ;   C18  H16
    6  13   1                                            ;   C18  C15
    7  10   1                                            ;    O5  H17
    7  11   1                                            ;    O5  C16
    8   9   1                                            ;   H52  C17
    9  14   1                                            ;   C17  C14
   10  12   1                                            ;   H17  H16
   10  13   1                                            ;   H17  C15
   11  15   1                                            ;   C16  C13
   12  14   1                                            ;   H16  C14
   13  16   1                                            ;   C15  C12
   14  17   1                                            ;   C14   O3
   14  19   1                                            ;   C14  C11
   15  18   1                                            ;   C13  H32
   15  20   1                                            ;   C13  C10
   16  21   1                                            ;   C12   O6
   16  22   1                                            ;   C12   C9
   17  20   1                                            ;    O3  C10
   18  19   1                                            ;   H32  C11
   19  23   1                                            ;   C11   C8
   20  24   1                                            ;   C10   C4
   21  23   1                                            ;    O6   C8
   22  25   1                                            ;    C9   C3
   22  27   1                                            ;    C9   C5
   23  26   1                                            ;    C8  H31
   23  28   1                                            ;    C8  H51
   23  29   1                                            ;    C8   C6
   23  34   1                                            ;    C8   C2
   24  30   1                                            ;    C4   H6
   24  31   1                                            ;    C4   C7
   24  35   1                                            ;    C4   O1
   25  28   1                                            ;    C3  H51
   25  29   1                                            ;    C3   C6
   25  32   1                                            ;    C3   O2
   25  36   1                                            ;    C3   C1
   26  27   1                                            ;   H31   C5
   26  31   1                                            ;   H31   C7
   26  35   1                                            ;   H31   O1
   27  32   1                                            ;    C5   O2
   27  34   1                                            ;    C5   C2
   28  30   1                                            ;   H51   H6
   28  31   1                                            ;   H51   C7
   29  33   1                                            ;    C6  H22
   29  35   1                                            ;    C6   O1
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  30  32   1                                          ;    H6   O2
  30  34   1                                          ;    H6   C2
  31  36   1                                          ;    C7   C1
  32  35   1                                          ;    O2   O1
  33  34   1                                          ;   H22   C2

[ angles ]
; ai  aj  ak  fu    c0, c1, ...
   1   2   3   2    109.5       380.0    109.5       380.0 ;   C21   O4  C19
   2   3   4   2    120.0       560.0    120.0       560.0 ;    O4  C19  C20
   2   3   6   2    115.0       610.0    115.0       610.0 ;    O4  C19  C18
   4   3   6   2    120.0       560.0    120.0       560.0 ;   C20  C19  C18
   3   4   5   2    120.0       505.0    120.0       505.0 ;   C19  C20  H20
   3   4  13   2    120.0       505.0    120.0       505.0 ;   C19  C20  C15
   5   4  13   2    120.0       505.0    120.0       505.0 ;   H20  C20  C15
   3   6   7   2    115.0       610.0    115.0       610.0 ;   C19  C18   O5
   3   6   9   2    120.0       560.0    120.0       560.0 ;   C19  C18  C17
   7   6   9   2    120.0       560.0    120.0       560.0 ;    O5  C18  C17
   6   7   8   2    109.5       450.0    109.5       450.0 ;   C18   O5  H52
   6   9  10   2    120.0       505.0    120.0       505.0 ;   C18  C17  H17
   6   9  11   2    120.0       505.0    120.0       505.0 ;   C18  C17  C16
  10   9  11   2    120.0       505.0    120.0       505.0 ;   H17  C17  C16
   9  11  12   2    120.0       505.0    120.0       505.0 ;   C17  C16  H16
   9  11  13   2    120.0       505.0    120.0       505.0 ;   C17  C16  C15
  12  11  13   2    120.0       505.0    120.0       505.0 ;   H16  C16  C15
   4  13  11   2    120.0       560.0    120.0       560.0 ;   C20  C15  C16
   4  13  14   2    120.0       560.0    120.0       560.0 ;   C20  C15  C14
  11  13  14   2    120.0       560.0    120.0       560.0 ;   C16  C15  C14
  13  14  15   2    115.0       610.0    115.0       610.0 ;   C15  C14  C13
  14  15  16   2    115.0       610.0    115.0       610.0 ;   C14  C13  C12
  15  16  17   2    115.0       610.0    115.0       610.0 ;   C13  C12   O3
  15  16  19   2    115.0       610.0    115.0       610.0 ;   C13  C12  C11
  17  16  19   2    115.0       610.0    115.0       610.0 ;    O3  C12  C11
  16  17  18   2    109.5       450.0    109.5       450.0 ;   C12   O3  H32
  16  19  20   2    115.0       610.0    115.0       610.0 ;   C12  C11  C10
  19  20  21   2    121.0       685.0    121.0       685.0 ;   C11  C10   O6
  19  20  22   2    115.0       610.0    115.0       610.0 ;   C11  C10   C9
  21  20  22   2    121.0       685.0    121.0       685.0 ;    O6  C10   C9
  20  22  23   2    115.0       610.0    115.0       610.0 ;   C10   C9   C8
  22  23  24   2    115.0       610.0    115.0       610.0 ;    C9   C8   C4
  23  24  25   2    120.0       560.0    120.0       560.0 ;    C8   C4   C3
  23  24  27   2    120.0       560.0    120.0       560.0 ;    C8   C4   C5
  25  24  27   2    120.0       560.0    120.0       560.0 ;    C3   C4   C5
  24  25  26   2    120.0       505.0    120.0       505.0 ;    C4   C3  H31
  24  25  34   2    120.0       505.0    120.0       505.0 ;    C4   C3   C2
  26  25  34   2    120.0       505.0    120.0       505.0 ;   H31   C3   C2
  24  27  28   2    120.0       505.0    120.0       505.0 ;    C4   C5  H51
  24  27  29   2    120.0       505.0    120.0       505.0 ;    C4   C5   C6
  28  27  29   2    120.0       505.0    120.0       505.0 ;   H51   C5   C6
  27  29  30   2    120.0       505.0    120.0       505.0 ;    C5   C6   H6
  27  29  31   2    120.0       505.0    120.0       505.0 ;    C5   C6   C7
  30  29  31   2    120.0       505.0    120.0       505.0 ;    H6   C6   C7
  29  31  32   2    120.0       560.0    120.0       560.0 ;    C6   C7   O2
  29  31  34   2    120.0       560.0    120.0       560.0 ;    C6   C7   C2
  32  31  34   2    115.0       610.0    115.0       610.0 ;    O2   C7   C2
  31  32  33   2    109.5       450.0    109.5       450.0 ;    C7   O2  H22
  25  34  31   2    120.0       560.0    120.0       560.0 ;    C3   C2   C7
  25  34  35   2    120.0       560.0    120.0       560.0 ;    C3   C2   O1
  31  34  35   2    115.0       610.0    115.0       610.0 ;    C7   C2   O1
  34  35  36   2    109.5       380.0    109.5       380.0 ;    C2   O1   C1

[ dihedrals ]
; ai  aj  ak  al  fu    c0, c1, m, ...
   3   2   4   6   2      0.0  167.4        0.0  167.4   ; imp   C19   O4  C20  C18
   4   3  13   5   2      0.0  167.4        0.0  167.4   ; imp   C20  C19  C15  H20
   6   9   7   3   2      0.0  167.4        0.0  167.4   ; imp   C18  C17   O5  C19
   9   6  11  10   2      0.0  167.4        0.0  167.4   ; imp   C17  C18  C16  H17
  11   9  13  12   2      0.0  167.4        0.0  167.4   ; imp   C16  C17  C15  H16
  13  14  11   4   2      0.0  167.4        0.0  167.4   ; imp   C15  C14  C16  C20
  16  19  17  15   2      0.0  167.4        0.0  167.4   ; imp   C12  C11   O3  C13
  20  22  21  19   2      0.0  167.4        0.0  167.4   ; imp   C10   C9   O6  C11
  24  23  27  25   2      0.0  167.4        0.0  167.4   ; imp    C4   C8   C5   C3
  25  24  34  26   2      0.0  167.4        0.0  167.4   ; imp    C3   C4   C2  H31
  27  24  29  28   2      0.0  167.4        0.0  167.4   ; imp    C5   C4   C6  H51
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29  27  31  30   2      0.0  167.4        0.0  167.4   ; imp    C6   C5   C7   H6
31  29  32  34   2      0.0  167.4        0.0  167.4   ; imp    C7   C6   O2   C2
34  25  35  31   2      0.0  167.4        0.0  167.4   ; imp    C2   C3   O1   C7
 3   4  13  11   2      0.0  209.3        0.0  209.3   ; imp   C19  C20  C15  C16
 4  13  11   9   2      0.0  209.3        0.0  209.3   ; imp   C20  C15  C16  C17
13  11   9   6   2      0.0  209.3        0.0  209.3   ; imp   C15  C16  C17  C18
11   9   6   3   2      0.0  209.3        0.0  209.3   ; imp   C16  C17  C18  C19
 9   6   3   4   2      0.0  209.3        0.0  209.3   ; imp   C17  C18  C19  C20
 6   3   4  13   2      0.0  209.3        0.0  209.3   ; imp   C18  C19  C20  C15
24  25  34  31   2      0.0  209.3        0.0  209.3   ; imp    C4   C3   C2   C7
25  34  31  29   2      0.0  209.3        0.0  209.3   ; imp    C3   C2   C7   C6
34  31  29  27   2      0.0  209.3        0.0  209.3   ; imp    C2   C7   C6   C5
31  29  27  24   2      0.0  209.3        0.0  209.3   ; imp    C7   C6   C5   C4
29  27  24  25   2      0.0  209.3        0.0  209.3   ; imp    C6   C5   C4   C3
27  24  25  34   2      0.0  209.3        0.0  209.3   ; imp    C5   C4   C3   C2
 6   3   2   1   1    180.0   16.7 2    180.0   16.7 2 ; dih   C18  C19   O4  C21
 3   6   7   8   1    180.0    7.1 2    180.0    7.1 2 ; dih   C19  C18   O5  H52
15  14  13   4   1    180.0    5.9 2    180.0    5.9 2 ; dih   C13  C14  C15  C20
16  15  14  13   1    180.0    5.9 2    180.0    5.9 2 ; dih   C12  C13  C14  C15
19  16  15  14   1    180.0    5.9 2    180.0    5.9 2 ; dih   C11  C12  C13  C14
15  16  17  18   1    180.0   16.7 2    180.0   16.7 2 ; dih   C13  C12   O3  H32
20  19  16  15   1    180.0    5.9 2    180.0    5.9 2 ; dih   C10  C11  C12  C13
22  20  19  16   1    180.0    5.9 2    180.0    5.9 2 ; dih    C9  C10  C11  C12
23  22  20  19   1    180.0    5.9 2    180.0    5.9 2 ; dih    C8   C9  C10  C11
24  23  22  20   1    180.0    5.9 2    180.0    5.9 2 ; dih    C4   C8   C9  C10
27  24  23  22   1    180.0    5.9 2    180.0    5.9 2 ; dih    C5   C4   C8   C9
29  31  32  33   1    180.0    7.1 2    180.0    7.1 2 ; dih    C6   C7   O2  H22
25  34  35  36   1    180.0   16.7 2    180.0   16.7 2 ; dih    C3   C2   O1   C1
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