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Destabilization of Alzheimer's Aβ42 Protofibrils with a Novel Drug Candidate wgx-50 by Molecular Dynamics Simulations

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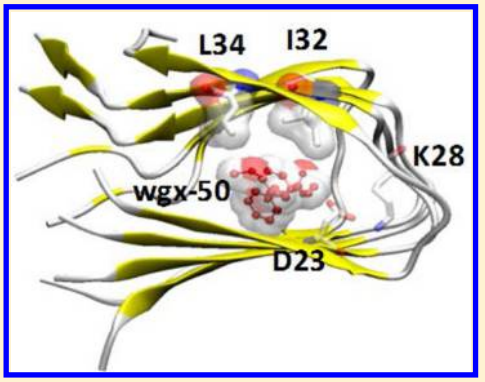
Supporting Information

ABSTRACT: Al heime ' di ea e (AD) i one of the mo t common dementia. The agg egation and depo ition of the am loid-β peptide (Aβ) in ne al ti e i it cha acte i tic mptom. To de tabili e and di ol e Aβ fib il , a n mbe of candidate molec le ha e been p opo ed. g -50 i a compo nd e t acted f om Sich an peppe (*Zanthoxylum bungeanum*) and a potential candidate d g fo t eating AD. O ea l e pe iment ho it i effecti e in di a embling Aβ42 agg egation . A e ie of molec la d namic im lation e e pe fo med in thi o k to e plain the molec la mechani m of the de tabili ation of Aβ42 p otofib il b g -50. It i fo nd that the e e th ee po ible table binding ite incl ding t o ite in h d ophobic g oo e on face of Aβ p otofib il that made no ignificant change in Aβ t ct e and one ite in the inte io that ca ed de tabili ation of the p otofib il. In thi ite, g -50 a packed again t the ide chain of I32 and L34, di pted the D23−K28 alt b idge , and pa tiall opened the tightl compacted t o β- heet . The e lt e e confi med b im lation at 320 K, he e deepe in e tion of g -50 into the hole p otofib il a ob e ed. The molec la mechani m of thi no el d g candidate g -50 to di agg egate Aβ p otofib il ma p o ide ome in ight into the t ateg of t ct e-ba ed d g de ign fo AD.



INTRODUCTION

Abno mal agg egate of mi folded p otein a e a ociated ith a n mbe of fatal ne odegene ati e di ea e , incl ding Al heime ' di ea e (AD), H ntington' di ea e (HD), Pa kin on' di ea e (PD), familial B iti h dementia (FED), familial Dani h dementia (FDD), and t pe II diabete .[1−6] In the e di ea e , AD i the mo t common dementia, ith apid inc ea ing incidence and demand fo t eatment .[7] The ph iological mechani m fo AD i not f ll nde tood et; one of the majo mptom of AD i the p e ence of am loid pla e in b ain, hich mainl con i t of fib il of the am loid-β peptide (Aβ).[8] The "am loid h pothe i " gge ted the agg egation and depo ition of the Aβ peptide in ne al ti e to be the ke of the AD.[9] Altho gh the mo t to ic pecie of Aβ i tho ght to be ol ble oligome ,[10,11] a e ie of t die al o gge ted po ible cont ib tion f om in ol ble fib il to the ne oto icit in a io a .[12−14]

Va io candidate ta geting on Aβ ha e been p opo ed, incl ding antibodie , peptidal inhibito , and nonpeptidal mall molec le . Fo e ample, ecent in it o t die ha e gge ted that ome pol phenolic compo nd f om ed ine and g een tea ma bind to Aβ, inhibit Aβ agg egation, and de tabili e p efo med fib il .[15,16] In i o e pe iment on the Al heime ' mo e model fo nd a lo e ed le el of am loid pla e and imp o ed memo and cogniti e abilit afte feeding of ed ine.[17,18] Enco aged b the e cce f l e lt , Ri ie e et al. p opo ed a h pothe i that the inte action bet een e e at ol de i ati e and Aβ co ld hift the e ilib ation of Aβ pol mo phi m f om β- heet into di o de ed monome .[19]

The ad ance in ea ching fo Aβ fib il ' inhibito a e enco aging; ho e e , the molec la detail of the inte action bet een the inhibito and the Aβ peptide e e often nkno n. Thi it ation a g ad all changed b p og e in in e tigation of the t ct e of Aβ fib il , e peciall afte a 3D t ct e a dete mined in 2005.[20] The nit of Aβ fib il a e gene ated b e ential clea age of β and γ ec eta e f om the am loid p ec o p otein (APP) into peptide of 40 o 42 amino acid , indicated b Aβ40 and Aβ42, e pecti el . Compa ed ith Aβ40, Aβ42 ha a t onge tendenc to agg egate and comp i e the dominant po tion of Aβ pla e in AD patient ;[21−24] ho e e , both of them ma ha e a common t ct al motif of t and-loop- t and, hich i aligned into t o tacked β- heet and f the a embled into c o -β t ct e in e e al h pothetical a .

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The nde tanding in t ct e of Aβ fib il boo ted the t ct e-ba ed de ign of inhibito ta geting on them; ho e e, pa tiall d e to the pol mo phi m of Aβ oligome o thei highe o de pol me , man diffic ltie e e enco nte ed in the t die on molec la detail of the inte action bet een Aβ pol peptide and thei inhibito o on po ible de tabilization mechani m ing t aditional e pe imental method . On the cont a , comp tational method like molec la docking and molec la d namic im lation e hibited att acti e ad antage and ha e been cce f ll emplo ed in the de ign of Aβ agg egation inhibito in ecent ea . Fo e ample, ing molec la d namic im lation , W and co o ke cha acte ized the binding ite of a fl o e cent d e, Thiofla in T (ThT), and it de i ati e on p otofib il of both $A\beta_{9-40}$ and $A\beta_{17-42}$. A common binding motif con i t of g oo e fo med b h d ophobic o a omatic e id e on the β- heet face along the fib il a i .[25−27] The Klimo g o p t died anti-inflammato agent , ib p ofen and nap o en, hich ma bind to the end of am loid fib il to p e ent fib il g o th b a competiti e mechani m, itho t ignificant change in the t ct e of Aβ peptide .[28−30] Simila t die b Lemk l and Be an got e en mo e e citing e lt on mo in, an effecti e antiagg egation fla enoid. It a fo nd that mo in not onl bo nd to the end of $A\beta_{17-42}$ to block f the combination of incoming peptide b t al o int ded into the h d ophobic co e to di pt inte io inte action like D23−K28 alt b idge and backbone h d ogen bond .[31]

In addition to the inhibito abo e, *N*-[2-(3,4-dimetho phen l)eth l]-3-phen l-ac lamide, o named g -50 (ea lie a g -50), a de igned b Wei et al.[32] and fo nd in e t act of a nat al fla o ing egetation, Sich an pepe (*Zanthoxylum Bungeanum*) (Fig e 1). Thi no el d g candidate a gge ted to po ibl be an effecti e the ape tic agent fo AD ba ed on a e ie of biological e pe iment : in it o e pe iment demon t ated that g -50 co ld di a emble Aβ oligome , inhibit Aβ-ind ced ne onal apopto i and apoptotic gene e p e ion, and ed ce ne onal calci m to icit ; in i o e pe iment ho ed that g -50 co ld pa the blood b ain ba ie, dec ea e the acc m lation of Aβ oligome in the ce eb al co te , and imp o e the cogniti e abilitie of mice.[33] Fo nd in nat al food p od ct , nonto ic in clinicall ele ant do e , capable of pa ing th o gh the blood−b ain ba ie,[17,18] and effecti e in Aβ agg egate de tabilization in it o and in i o, g -50 ha man ad antage to be an att acti e the ape tic candidate; ho e e, the molec la mechani m fo g -50 to de tabilize the Aβ42 fib il i till nclea , hich i to be t died in thi o k ing molec la d namic im lation , o that f the t ct e-ba ed d g de ign and de elopment co ld be applied to thi t pe of inhibito ationall .

METHODS

Models of Aβ42 Protofibrils. The model fo im lation e e con t cted ba ed on the olid- tate NMR t ct e of Aβ p otofib il dete mined b L h et al. (PDB ent 2BEG).[20] Di tinct f om ol ble oligome ic pecie of Aβ, thi pentame ic t ct e i a epeat nit of the mat e Aβ fib il and a de c ibed a a p otofib il o a c o -β b nit.[34] In thi t ct e, each peptide monome ha the di o de ed N-te minal e id e 1−16 mi ing. The emaining e id e 17−42 e e gge ted to cont ib te the tabilit of the mat e fib il mo tl and e e incl ded in the im lation model he e. Thi ingle c o -β b nit contain fi e identical peptide of e id e 17−42, labeled a A−E (Fig e 2), ith a t and-loop- t and motif, con i ting of t o in- egi te tacked β- heet ho e ide chain zip again t each othe in an antipa allel a . In thi b nit, the di ection of backbone h d ogen bond pa alleled to the fib il a i , ith the β- t and pe pendic la to it. Each U- hape peptide con i t of an N-te minal β- t and (β1) incl ding e id e V18−S26, a C-te minal β- t and (β2) incl ding e id e I31−A42, and a loop (e id e N27−A30) connecting them (Fig e 2).

MD Simulation Protocol. All model of $A\beta_{17-42}$ molec le ith o itho t g -50 e e ol ated in a c bic bo incl ding abo t 11 000 ate molec le mo e than 11 A a a f om the model bo de . The ol ent ate molec le e e e plicitl ep e ented b the TIP3P model.[35] Fi e po iti e odi m ion (Na^+) e e added to ne t alize the tem. Pe iodic bo nda condition e e applied in all di ection . Follo ing teepe t de cent minimization , each of the tem a e ilib ated ith po itional e t aint applied to peptide hea atom . With all of the po itional e t aint 14a . of po itio-322.8(oe o9

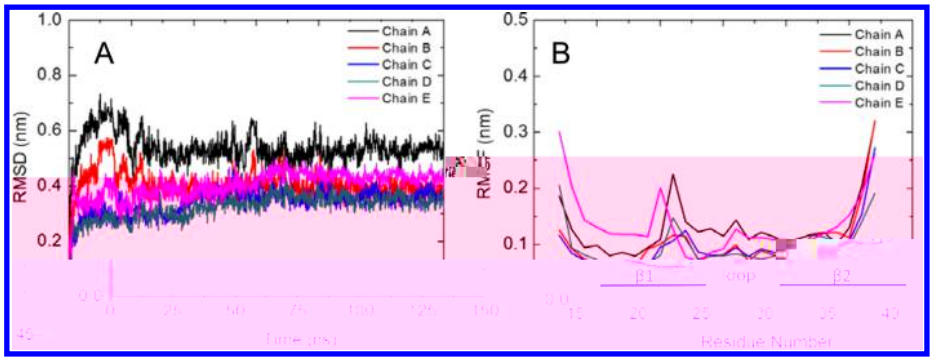

Figure 3. (A) Root-mean- a.e de iation (RMSD) al e and (B) .oot-mean- a.e fl ct ation (RMSF) of the fi e chain d .ing the im lation ith Aβ p.otofib.il alone. The colo. of the fi e chain a.e ame to tho e in Fig .e 2.

integ.ation time tep to 2 f . The t.ajecto.ie e.e a ed e e. 10 p fo. the follo ing anal e . The ho.t-.ange an de. Waal (VDW) inte.action e.e t.eated ing a 1.4 nm c toff, and long-.ange elect.o tatic fo.ce e.e calc lated b the Pa.ticle Me h E ald (PME) method.[41] The pa.amete. of the g -50 molec le e.e f.om the AMBER GAFF pa.amete. et.[42]

Analysis Details. Binding f.ee ene.gie e.e calc lated ing molec la. mechanic /gene.alized Bo.n .face a.ea (MM-GBSA) in the AMBER package.[43] The global t. ct .al tabilit of the pentame. i mea .ed b .oot-mean- a.e de iation (RMSD) of the backbone atom ith .e pect to initial minimized t. ct .e, hile the .oot mean- a.e atomic fl ct ation (RMSF) a calc lated fo. Cα atom of each indi id al .e id e. The D23−K28 alt-b.idge di tance e.e calc lated bet een the ma cente. of the Nζ-amino g.o p and co. e ponding Cγ-ca.bo late . The a e.age int.achain and inte.chain di tance of β1 and β2 e.e calc lated b the ma cente. of the .e id e A21 and V36. The a e.age inte.chain di tance e.e calc lated a the a e.age of di tance of the ma cente. of all the Cα atom of neighbo.ing chain . The h d.ophobic inte.action bet een g -50 and Aβ p.otofib.il e.e e al ated b the n mbe. of h d.ophobic contact , hich a defined a an contact bet een a ide chain ca.bon atom and an ca.bon atom in g -50 ithin a di tance of 0.6 nm. The t. ct .e e.e i ali ed and fig .ed b the VMD package.[44]

RESULTS AND DISCUSSION

Simulations of Aβ Protofibril Alone at 300 K. Vi al in pection of the 150 n t.ajecto. of the model fo. Aβ p.otofib.il alone gge ted that the o e.all Aβ t. ct .e e.e ite table; onl mall de iation f.om the initial t. ct .e e.e ob e. ed. The majo. pa.t of the β- t.and e.e tightl packed to each othe. itho t di ociation, and the econda t. ct .e of the t.and-loop- t.and motif e.e ell-p.e e. ed. In the t o open end of the β- t.and , mino. t i ting made the fi e chain not enti el coplana., optimized ide-chain packing, h d.ogen bond , and elect.o tatic inte.action , and ome hat cont.ib ted to am loid fib.il tabilit a p.opo ed p.e io l [45] (Fig .e S1 in the S ppo.ting Info.mation (SI)).

The o e.all t. ct .al tabilit of the fib.il a mea .ed b RMSD of the backbone atom ith .e pect to initial model of the minimized c. tal t. ct .e. The fi e peptide chain e.e all gene.all table, ith the RMSD al e a ~0.5 nm, indicating a e. lo le el of o e.all t. ct .al a iation (Fig .e 3A). F.om the RMSF p.ofile (Fig .e 3B), it i clea. that thi tabilit mainl come f.om the t o β- t.and , he.e the h d.ophobic ide chain of F19, A21, I32, L34, V36, and o on packed tightl . The mo t fle ible .egion of each peptide e.e the .e id e at the N- and C-te.minal a ell a the .e id e S26 and I31 connecting the β- t. and and the loop. In thi model, the te.minal .e id e in the open end of β- t.and e.e mo tl e po ed to the ol ent and .e lted in la.ge fl ct ation . E peciall on the β1- t.and at C-te.minal, t o .e id e I41 and A42 be ond the β2- t.and at N-te.minal a.e e en mo.e e po ed and .e lted in e en highe. fle ibilitie . Anothe. cont.ib tion to the o e.all tabilit of Aβ p.otofib.il i the tabili ation of the loop .egion b the inte.chain alt-b.idge bet een .e id e D23 and K28, imila. to man t die that gge ted the impo.tance of the D23−K28 alt b.idge.[45,46] Mo t of the D23−K28 alt b.idge e.e maintained d .ing the hole im lation , ith the a e.age di tance bet een the Nζ-amino g.o p and co. e ponding Cγ-ca.bo late being ~0.35 ± 0.05 nm.

Binding of wgx-50 to Aβ Protofibril at 300 K. The ame p.oced .e of 150 n im lation of Aβ alone a .epeated fo . time at 300 K fo. the model of Aβ fib.il ith a g -50 molec le, in hich th.ee po ible binding ite e.e fo nd, ho n a ite A, B, and C (Fig .e 4). Binding ite A and B

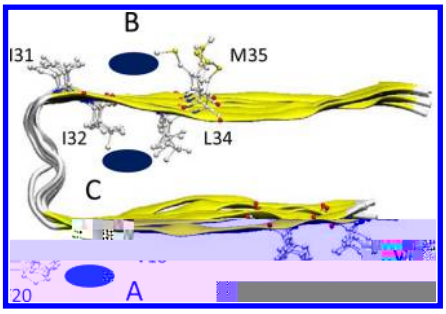

Figure 4. Th.ee binding ite of g -50 on Aβ p.otofib.il at 300 K: (A) V18−F20 g.oo e on .face of the β1 heet la e.. (B) I31−M35 g.oo e on .face of the β2 heet la e.. (C) In e.ted ite in the h d.ophobic inte.io. again t the I32 and L34 ide chain . Fo. cla.it , he.e the Aβ p.otofib.il i impl ill t.ated b the initial model, and the po ition of the th.ee binding ite a.e indicated b bl e ellip e .

.e ide in the V18−F20 g.oo e on the .face of the β1 heet la e. and the I31−M35 g.oo e on the .face of the β2 heet la e., .e pecti el (Fig .e S2 in the SI). The e t o g.oo e a.e bet een ide chain of h d.ophobic/a.omatic .e id e , mo.e fa o.able fo. the h d.ophobic g -50 to bind. P.e io im lation al o gge ted that h d.ophobic/a.omatic and te.ic inte.action a.e tabili ing fo.ce fo. binding of e e.al

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ligand .[25] Site C i in the inte io of the pentame ic Aβ fib il, bet een the ide chain of I32 and L34 and the alt b idge bet een D23 and K28. All th ee binding ite fo g -50 e e al o ob e ed in p e io im lation on othe Aβ–ligand comple e . Cook p edicted the h d ophobic cleft bet een V18 and F20 a a pla ible binding ite fo [R (bp)$_2$dppz]$^{2+}$.[47] Both ite on the face e e cha acte ized in the binding of ThT and it de i ati e on Aβ fib il.[25] Pa tial in e tion of mo in into the h d ophobic co e a al o fo nded in Lemk l' im lation .[48]

In the e e al epeat of 150 n MD im lation at 300 K and al o at an ele ated tempe at e 320 K a di c ed late , onl binding to the th ee ite he e a ob e ed to be table eno gh to keep the ligand f om e caping a a . On the ba i of MM/GBSA calc lation , the in e tion ite ha a binding ene g of −35.5 kcal/mol, hich i m ch t onge than the −12.3 kcal/mol of ite A and −20.5 kcal/mol of ite B. The a e not g a anteed to be the onl po ible binding mode , b t ba ed on the e lt e ha e, e o ld belie e that the a e the mo t po ible one . In the fo epeat of im lation at 300 K, one ha g -50 tabl bo nd at ite A, one at ite B, and t o ha e it in e ted into ite C. The highe binding ene g and the highe f e enc to be ob e ed in limited time of im lation ma gge t the highe po ibilit fo g -50 to be in e ted into ite C, and the infl ence of in e tion to ite C i al o diffe ent ith binding to ite A o B. RMSD p ofile gge ted that the binding of g -50 to the ite A and B on the face of the Aβ p otofib il had little effect on it global tabilit , hile the in e tion into ite C e lted in ignificant de tabilization. (Fig e S3 in the SI). The efo e, it i ea onable to a me t o po ible ole of g -50 in antiagg egation of Aβ fib il: (1) It bind to the t o ite on face to hinde tacking of m ltila e of the fib il into c o -β comple e and hence to ea e agg egation; (2) it i in e ted into the inte io ite C, ca e ignificant defo mation of the c o -β b nit, and top a embl of the Aβ fib il.

It i inte e ting to notice that all th ee binding ite abo e e e not p edicted b a p elimina emifle ible docking ing A todock 4.2. When fle ible g -50 a docked onto the igid initial model of Aβ p otofib il f om the PDB t ct e 2BEG, the top p edicted binding ite e e mainl along the edge at chain A of the c o -β b nit, e te io to the binding ite C, b t in the initial model the e i not eno gh pace to accommodate the ligand. The efo e, it i impo ible to find ite C b docking it onto the igid initial model. In MD im lation , the ligand a al o ob e ed to be tempo a il a o nd tho e ite , b t finall it a g ad all in e ted into ite C, ith e pan ion of the inte io pace and pa tial defo mation of the c o -β b nit a de c ibed late . Altho gh the g oo e at ite A o B e e not li ted a top binding ite in docking, the binding ene gie co ld be eno gh fo them to hold the ligand, in hich nece a confo mational change and fo mation of t ong h d ophobic inte action ith o nding e id e ma help to tabili e the bo nd tate. The e d namic "ind ced fit" binding to the th ee ite e i e MD im lation to de c ibe the nece a confo mational change in Aβ p otofib il and co ld not be impl p edicted b gene al emifle ible docking p oced e ing a igid ta get. O in othe o d , o MD p otocol i e i alent to an e ten i e docking ith f ll fle ibilit con ide ed fo both the ligand and the ta get.

Destabilization of Aβ Protofibril by wgx-50 Insertion. In all im lation ith g -50 in e ted into the inte io of Aβ p otofib il, the ent of g -50 a al a f om the edge of chain A, ome hat imila to the binding p efe ence of ib p ofen to the conca e (CV) edge im lated b Klimo et al.[30] In one im lation, g -50 a apidl in e ted into the h d ophobic inte io of the Aβ p otofib il ithin 40 n , e tabli hing a la ge n mbe of h d ophobic contact ith ide chain in ide the t o β- heet of the p otofib il. The e h d ophobic inte action might be the ea on to allo the in e tion of g -50 into the inte io of Aβ p otofib il , imila to the p efe ed binding to the h d ophobic g oo e of ite A and B. The mo t impo tant h d ophobic inte action i bet een the a omatic ing of g -50 and the ide chain of I32 and L34 on chain A–C (Fig e 5), hich fo ced the la e of β2 heet

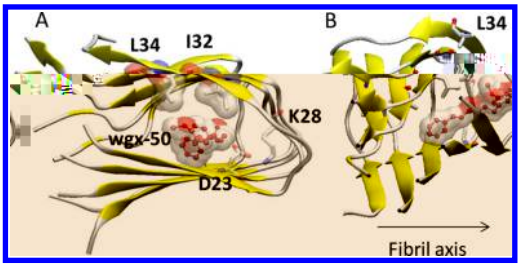

Figure 5. In e tion of g -50 into ite C at 300 K ho n b the final nap hot f om top ie (A) and alte nate ie (B). The packing of g -50 (in ball and tick) again t the ide chain of I32 and L34 (in tick) i i ali ed b face ende ing. The po ition of D23 and K28 a e al o indicated b tick .

to be conto ted, and pa tiall opened the tightl compacted t ct e of the c o -β b nit. The compactne of the h d ophobic co e comp i ing the β2 po tion of the fib il ma be a c cial tabilization element in agg egation and elongation of Aβ agg egate .[49,50]

The pa tial opening of the c o -β- b nit b g -50 in e tion de tabilized the p otofib il. The RMSD of the backbone atom inc ea ed to almo t 0.75 nm, gge ting an impo tant de tabilization of the Aβ p otofib il. The RMSF of the e id e e e lightl inc ea ed, meaning highe fle ibilitie of the chain afte the g -50 in e tion. Thi in e tion al o affected local confo mation . The a e age di tance bet een the cha ged moietie of the D23–K28 alt b idge e e g eate than 0.53 nm, fa longe than the al e of 0.35 nm in im lation of Aβ p otofib il alone (Fig e 6C). The integ it of the inte chain alt b idge ha been p opo ed to be an impo tant cont ib tion in the tabilit of the Aβ fib il, e peciall fo the loop egion.

In addition to co ption of the alt b idge , the n mbe of the backbone h d ogen bond bet een chain A and chain B a lo e ed to a o nd 14 in the im lation afte g -50 a in e ted at ite C, ell belo the cont ol al e of 19 h d ogen bond in the im lation of Aβ p otofib il alone (Fig e S5 in the SI). The binding ene g bet een chain A and chain B al o dec ea ed f om −116.2 to −104.5 kcal/mol. The a e age inte chain di tance e e calc lated b the ma cente of all the Cα atom of each chain. The di tance of Aβ p otofib il alone i in good ag eement ith the e pe imental al e a 0.48 ± 0.05 nm of the pa allel β- heet epo ted b Balbach et al.[51] At the ame time, Aβ p otofib il ith g -50 in e ted ha thi di tance lightl inc ea ed to 0.53 nm, gge ting a tendenc of detachment bet een the peptide . (Fig e 6D)

The in e tion of g -50 into ite C ca ed conto tion of the c o -β- b nit and d amatic ea angement of t o t and β1 and β2. With g -50 in e ted, the t o β- t and of the ame

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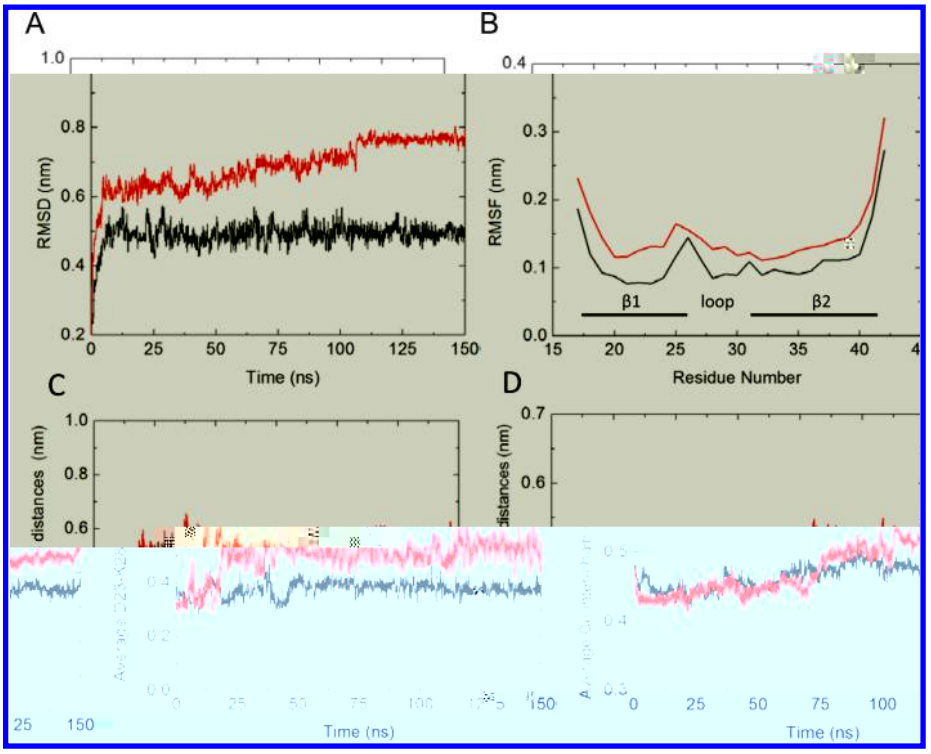

Figure 6. De tabili ation of Aβ p otofib il b g -50 in e tion at 300 K. (A) RMSD of the backbone atom . (B) Root-mean- a e fl ct ation (RMSF). (C) D23−K28 di tance bet een the ma cente of the Nζ-amino g o p and co e ponding Cγ-ca bo late . (D) A e age inte chain di tance bet een the ma cente of all the Cα atom of neighbo ing chain a e compa ed bet een the im lation ith Aβ p otofib il alone (black) and ith g -50 in e ted in ite C (ed).

chain ignificantl mo ed a a f om each othe , e lting in a mall t an lational hift bet een the t o heet la e and pa tial opening of the U- hape t ct e of the β- t and-loop-β- t and motif, e peciall at the chain A, B, and C (Fig e 5). The lo of h d ophobic contact bet een A21 and V36 a ob e ed b calc lating the di tance bet een the cente of ma of A21 and V36. All inte chain di tance bet een A21 and V36 inc ea ed ob io l . In pa tic la , bet een chain A and B and bet een chain B and C, the di tance e e inc ea ed b 0.42 and 0.70 nm, e pecti el (Fig e 7). Al o, the a e age int achain A21−V36 di tance a inc ea ed b 0.31 nm compa ed ith the model of Aβ alone. (Fig e S4 in the SI) The a iation in the A21−V36 di tance a e ob io

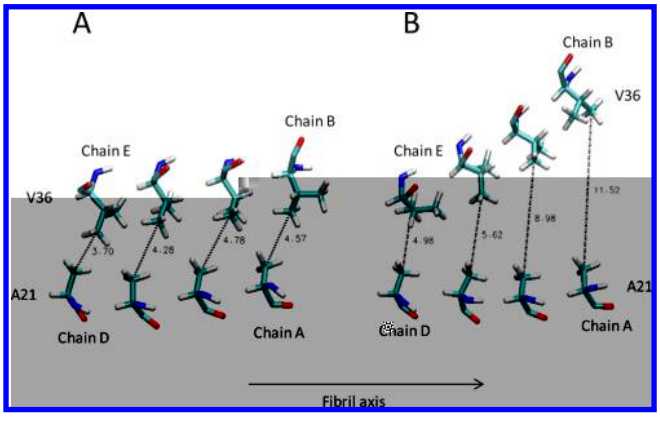

Figure 7. Rea angement of the β1 and β2 t and indicated b the inc ea ed inte chain di tance of A21 and V36 in the final nap hot of the im lation of Aβ p otofib il alone (A) and ith g -50 in e ted at 300 K (B) f om the ie ame to Fig e 5B.

indication of the ea angement of the pa allel, in- egi te , tightl compacted β- t and-loop-β- t and motif , hich a e the ba i of a c o -β b nit,[52] and a po ible binding inte mediate Aβ fib il elongation.[53]

Simulations of Aβ Protofibril with wgx-50 at 320 K. The im lation of Aβ p otofib il ith g -50 e e epeated at 320 K, lightl ele ated f om 300 K to compa e the infl ence of t onge h d ophobic inte action . The e lt e e imila to tho e at 300 K. The onl diffe ence a that he e g -50 penet ated mo e deepl into the h d ophobic inte io of Aβ p otofib il and packed again t the ide chain of I32 and L34 of chain A, B, C, and e en D (Fig e S6A in the SI). The inte chain A21−V36 di tance e e al o inc ea ed. Diffe ent f om the im lation at 300 K, the A21−V36 di tance of chain C−D and chain D−E al o inc ea ed ignificantl d e to the deepe in e tion (Fig e 8).

A p e io l gge ted, the h d ophobic inte action a e po ibl the majo cont ib tion fo the binding of g -50 to Aβ p otofib il. Th , the n mbe of h d ophobic contact bet een g -50 and Aβ p otofib il e e compa ed bet een the in e tion im lation at 300 and 320 K. A ho n in (Fig e S6B in the SI), the n mbe of atomic contact bet een the peptide and g -50 inc ea ed to the ma im m ha pl ithin the fi t 5 n at 320 K, m ch fa te than in the im lation at 300 K, he e it took 45 n to each the ma im m and became table. Beca e the g -50 a in e ted into the h d ophobic co e deepe at 320 K, the total n mbe of h d ophobic contact a gene all 100 highe than in the im lation at 300 K.

CONCLUSIONS

In thi o k, the binding of g -50 onto Aβ p otofib il a im lated b molec la d namic im lation , he e de tabi-

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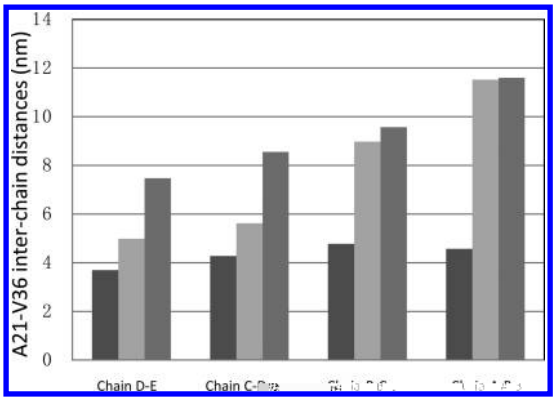

Figure 8. A e age A21−V36 inte chain di tance in im lation of Aβ p otofib il alone (da k g a) a ell a ith g -50 in e ted at 300 (light g a) and at 320 K (g a).

li ation of the p otofib il a ob e ed and it molec la mechani m a di c ed. Repeat of 150 n MD im lation fo nd th ee po ible table binding ite , in hich t o e e in h d ophobic g oo e on face of Aβ p otofib il and one a in the inte io . Onl in e tion of g -50 into the inte io ite ca ed ignificant de tabili ation of the p otofib il. The a omatic ing of g -50 a packed again t the ide chain of I32 and L34, pa tiall di pted the D23−K28 alt b idge c itical to tabili e the loop egion, and e tended the di tance of A21−V36, hich a e cha acte i tic of the tacked β- t and-loop-β- t and motif . The conto tion of the pa allel β- heet and the pa tial opening of the t o tightl compacted β- heet of the c o -β- b nit al o de tabili ed the inte action bet een the peptide : the n mbe of inte chain backbone h d ogen bond a dec ea ed, the a e age di tance bet een the peptide chain e e enla ged, and the inte chain binding ene gie e e lo e ed. The e lt e e confi med b im lation epeated at 320 K, he e deepe in e tion of g -50 into the hole p otofib il a ob e ed. The molec la d namic im lation fo g -50 to de tabili e the Aβ p otofib il ma p o ide ome in ight into the mechani m of thi no el d g candidate to di agg egate Aβ fib il and gi e ome hint on the t ateg of t ct e-ba ed d g de ign fo AD.

■ ASSOCIATED CONTENT

Supporting Information

Final nap hot of the im lation of Aβ p otofib il alone at 300 K f om ide ie , binding of g -50 at ite A f om the ide ie of β1 heet and at ite B f om the ide ie of β2 heet, RMSD of the backbone atom in all im lation at 300 K, a e age int achain A21−V36 di tance in the im lation of Aβ alone and ith g -50 in e ted at 300 K, n mbe of the backbone h d ogen bond bet een chain A and chain B in the im lation of Aβ alone and ith g -50 in e ted at 300 K, in e tion of g -50 into the inte io of Aβ p otofib il at 320 K, and compa i on of the n mbe of h d ophobic inte action bet een g -50 and the Aβ p otofib il d ing the im lation ith g -50 in e ted at 300 and 320 K. The S ppo ting Info mation i a ailable f ee of cha ge on the ACS P blication eb ite at DOI: 10.1021/ac .jpcb.5b03116.

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Notes

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