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Molecular Docking of Pepstatin (A) and Compounds with Structural Similarity to the Molecular Model of Human BACE-1 Enzyme

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ABSTRACT

Background and Objectives: Almost all known aspartic proteases are inhibited by pepstatin (A). One of the aspartic proteases enzymes, β-secretase, is a well-known enzyme in the process of Alzheimer's disease, and it plays a role in the progression of Alzheimer's disease by cleaving the amyloid precursor protein and forming the amyloid-β (Aβ) peptide. In the present study, we attempt to use pepstatin (A) and compounds with a similar structure as inhibitory ligand for β-secretase enzyme model [PDB ID: 6EQM]. **Materials and Methods:** We prepared the molecular model of pepstatin (A) and compounds with a similar structure, then calculated their physicochemical and pharmacological properties, and then performed molecular docking between the molecular model of human BACE-1 enzyme [PDB ID: 6EQM] with pepstatin (A) inhibitor and compounds with a similar structure. We perform molecular dynamics analysis to evaluate the deformation and fluctuation of the enzyme model with or without ligands during molecular dynamic simulation. **Results:** In this study, cyclic peptides and pseudo-peptides often have higher binding affinity for the active site of the enzyme in the molecular model of beta-secretase [PDB ID: 6EQM], but they have higher molecular weight than the rest of the compounds (400-700 Daltons), which consist of compounds with CID numbers: 10532731, 16084771, 122177562, 155209842, 155228360, 155228472, 155228476, 162667790, 163186155, and 164960792. Other compounds weighing between 300 and 400 Da with lower affinity were also investigated in this study, including the pseudo-peptide Ac-Ser-Sta (3R, 4R)-Val-OH with the CID numbers: 101039397 with a molecular weight of 402.4 and a docking score of -143.6, and compound 58057434 with a molecular weight of 386.4 and a docking score of -141.1, which had the highest affinity for the active site of the molecular model of human BACE-1 enzyme [PDB ID: 6EQM] in rang of 300-400 Da. **Conclusion:** The present study demonstrated that by using the molecular docking method and with a more comprehensive view, more effective compounds can be proposed to inhibit beta-secretase enzyme. As in our study based on molecular docking results, compounds such as pepstatin and compounds with structural similarity to it often have high affinity for the active site of beta-secretase enzyme.

Keywords: *Molecular docking, Pepstatin (A), Human BACE-1.*

INTRODUCTION

Protease enzymes are characterized by (EC 3.4) and belong to hydrolases. Among them, aspartate proteases are characterized by (EC 3.4.23). Aspartic acid proteases use a water molecule which bound to one or more amino acids of aspartic acid for catalysis of their substrate (peptide). Generally, they have two highly conserved aspartates in their active site (1, 2). Almost all known aspartic acid proteases are inhibited by pepstatin (A). Pepstatin (A) is a potent aspartic acid protease inhibitor and a hexapeptide with the unusual amino acid (statin) and the isovaleryl-Val-Val-Sta-Ala-Sta sequence, and its ability to inhibit pepsin is well known. Pepstatin (A) was originally isolated from the culture of various Actinomyces species (3, 4). β-secretase have a highly conserved two-domain structure, and each domain has a catalytic aspartic acid amino acid. The active site is like a gap between the two parts of the molecule. The amino acid sequence in the active site is highly conserved. The rest of the protein sequence differs among the different enzymes and the different species. A conserved disulfide bond is also found in the sequence of these enzymes [1, 2].

The most widely accepted mechanism for aspartic proteases is a general acid-base mechanism in which a water molecule interacts with two highly conserved aspartic acid amino acids. One aspartic acid activates the water by splitting off a proton, allowing the resulting hydroxyl group to make a nucleophilic attack on the carbonyl carbon atom of the peptide bond in the substrate, forming a tetrahedral oxanion intermediate. This complex is stabilized by hydrogen bonds with the second aspartic acid. Rearrangement of this reaction intermediate leads to protonation of the peptide amide, the amide group of the peptide bond get proton from the first aspartic acid and resulting in peptide bond breakage[1, 2].

The β-secretase, also known as β-amyloid precursor protein-cleaving enzyme 1 (BACE1), plays an important role in myelin sheath formation in peripheral neurons. BACE1 acts in the first step of the pathway leading to the production and deposition of amyloid-β (Aβ) peptide. BACE1 is an interesting therapeutic target for small molecule inhibitors that can alter the course of Alzheimer's disease. However, certain single amino acid mutations in the amyloid precursor protein APP reduce the ability of BACE1 to cleave it and produce amyloid beta, thereby reducing the risk of Alzheimer's disease and other cognitive impairments. In the present study, the tendency of compounds with the similar chemical structure as pepstatin (A) to interact with the active site of the enzyme was investigated [5].

MATERIAL AND METHODS

Molecular model of the beta-secretase enzyme

The 6EQM molecular model with a resolution of 1.35 Å is the molecular model of the human BACE-1 protein crystallized in interaction with the inhibitor CNP520 and is from the database www.rcsb.org. This model contains water molecules, the inhibitor CNP520, and a 385 amino acid sequence of the human BACE-1 enzyme. This enzyme was produced in an Escherichia coli BL21 (DE3) expression vector and its crystal was prepared for crystallography [6].

Molecular model of the ligands studied

We generated the molecular model of pepstatin (A) and similar compounds from PubChem database. These compounds are mostly penta- and hexa-peptides or cyclic and linear pseudo-peptides. These compounds are presented in the PubChem database based on their structural similarity to pepstatin (A) [7].

Structural and physicochemical properties of the individual ligands

The structural and physicochemical properties of each ligand were extracted from the PubChem online database and calculated using the XLogP (PubChem release 2019.06.18) and Cactvs 3.4.6.11 (PubChem release 2019.06.18) programs. XLOGP3- AA is an atomistic method that calculates log P by summing the contribution of each atom in the molecule. Log P is the basis for lipophilicity. Considering that the log P index is based on the dissolution of the compound in octane solution compared to its dissolution in aqueous solution, it can be said that compounds with higher log P have lower dissolution in blood plasma. In return, they can be better absorbed from the digestive system [7, 8]. To test the possibility of gastrointestinal absorption of compounds, we used A BOILED -Egg software to predict gastrointestinal absorption and blood brain barrier penetration of small molecules in the Swiss Adam database [9].

Perform molecular docking

We removed the CNP520 inhibitor compound and water molecules from the [PDB ID: 6EQM] molecular model. After preparing the molecule using molegro visual docker software (v5) and identifying the cavities in the protein model with a minimum size of 1 Angstrom, we did dock of the pepstatin (A) molecule and its similar compounds to the human BACE-1 protein model. The results of the highest affinity between the enzyme molecular model and each ligand were extracted[10].

Performance and analysis of molecular dynamics

We use iMODS at https://imods.iqfr.csic.es/ to perform a molecular dynamics simulation based on NMA in internal coordinates (torsion space) to determine the degree of stability within the active site of the enzyme model. We analyse our model extracted from the docking results to calculate the deformability, beta factors and other aspects of molecular dynamic analysis.

RESULTS AND DISCUSSION

Results

Pepstatin A has low absorption in the digestive tract and does not cross the blood-brain barrier. We investigated the compounds with a similar chemical structure to pepstatin (A). The compounds we studied often have a higher binding affinity for the active site of the enzyme model than pepstatin (A). Compared with pepstatin (A), all the compounds we studied have higher LE1 (ligand efficiency), an index of affinity based on the docking score versus the number of heavy atoms in a chemical compound. Thus, all of the compounds we studied bind more effectively to the human BACE-1 model than pepstatin (A). The polar surface area of pepstatin (A) is 223 Å² and has the most polar surface among the compounds studied. XLogP3- AA for pepstatin (A) is 3.0. This compound has moderate hydrophobicity.

Among the compounds studied, cyclic peptides and cyclic pseudo-peptides often have higher binding affinity for the active site of the enzyme in the molecular model of the enzyme, based on the results of molecular docking. Among them, compounds with CID numbers: 10532731, 16084771, 122177562, 155209842, 155228360, 155228472, 155228476, 162667790, 163186155, and 164960792, which have the highest affinity for the active site of human BACE-1 enzyme model (6EQM). These compounds exhibit high hydrophobicity. The binding site of these cyclic pseudo-peptides is located on beta-sheets and in interaction with aspartic acids 32 and 228. These compounds have a high molecular weight (400-700 Da) and are often poorly absorbed by the digestive tract and do not cross the blood-brain barrier.

The compounds we studied exhibit a wide range of hydrophobicity. The compounds with CID numbers: 162667790 and 138479069 exhibit the highest hydrophobicity and have good binding affinity for the active site of the enzyme. However, due to their size, they are not well absorbed by digestive system. This is because the two requirements for good absorption of drugs are hydrophobicity and molecular weight. Compounds exhibit the lowest hydrophobicity with CID numbers: 58057445, 58057438, 58057434, 58057429, 58057428, and 88383428. These compounds are most soluble in water. These compounds have lower affinity for the active site of the enzyme in the molecular model than the other compounds studied. The question arises whether the hydrophobicity of the compounds studied is related to the affinity for the active site of the enzyme.

Compound with CID number: 156186536 has the strongest hydrogen bonds in the binding site with the active site of the human BACE-1 enzyme in the molecular model, and this ligand has 5 bond donors and 6 hydrogen ion acceptors and a polar surface area of 136 Å². This compound has low hydrophobicity and a molecular weight of 401 Da. This compound has moderate affinity in compare to the other compounds for the target enzyme with the docking score of -126.

In the present study, based on the number of heavy atoms, compounds with number of heavy atoms more than 30 have low digestive absorption, but most compounds with number of heavy atoms less than 30 have good digestive absorption.

Compounds with CID numbers: 88666410, 88665994, 88665450, 44383576, 129716927, 88665041, 88383428, 58952715, 58952713, 58057422, 9995915, 10064371, and 16084772 have approximately 400 Daltons. According to the results of the software Swiss Adam, these compounds have high digestive absorption. The binding affinity of some of them for the active site of the enzyme is sufficient as inhibitors for beta-secretase enzyme.

DISCUSSION

The peptide compound pepstatin (A) is a well-known aspartic acid inhibitor. We have studied 98 compounds that are similar to pepstatin (A). Although some of the compounds studied cannot cross the blood-brain barrier. But when the compound crosses this barrier, it is available in brain tissue to inhibit the enzyme beta-secretase in brain neurons. Therefore, compounds that do not cross the blood-brain barrier cannot act on neurons. In our study, the compounds that exhibited the highest affinity for the molecular model of beta-secretase enzyme were hydrophobic cyclic peptides. Investigation of the pharmacological properties of these chemical compounds using the online software Swiss Adam revealed that these compounds had low absorption in the digestive tract and did not cross the blood-brain barrier [8].

In our study, compounds smaller than 400 daltons have a high probability of gastrointestinal absorption and moderate binding affinity for the enzyme active site, but limited ability to cross the blood-brain barrier. Compounds with good hydrophobicity and a number of hydrogen bonds of less than 8 and a weight of less than 400 Da can pass the blood-brain barrier [11, 12].

Well-known beta-secretase inhibitors such as Cnp-520, Verubecestat, Elenbecestat, Atabecestat, LY3314814, LY2811376, LY2886721 and CTS21166 have been implicated in clinical trial studies.

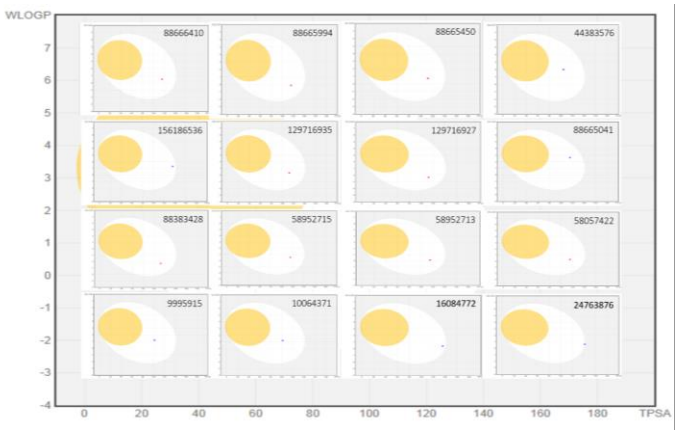

Figure 1. BOILED-Egg plot of studied compounds. The BOILED -egg diagram for each ligand (CID number). The vertical axis is the hydrophobicity index and the horizontal axis is the solubility index. White areas correspond to compounds with high absorption in the digestive tract, and yellow areas correspond to compounds with the ability to cross the blood-brain barrier. According to the BOILED -egg diagram of Swiss ADAM for each compound studied, none of the compounds can cross the blood-brain barrier. Only the compounds shown with blue dots in the BOILED egg diagram can be cleared from the central nervous system by p-glycoproteins. The red dots in the egg diagram correspond to the compounds that cannot be eliminated from the central nervous system by p-glycoproteins. The compounds whose graph is shown all have high gastrointestinal absorption. The remaining compounds are absorbed by the gastrointestinal tract only to a small extent and are not included in the white and yellow areas of the diagram.

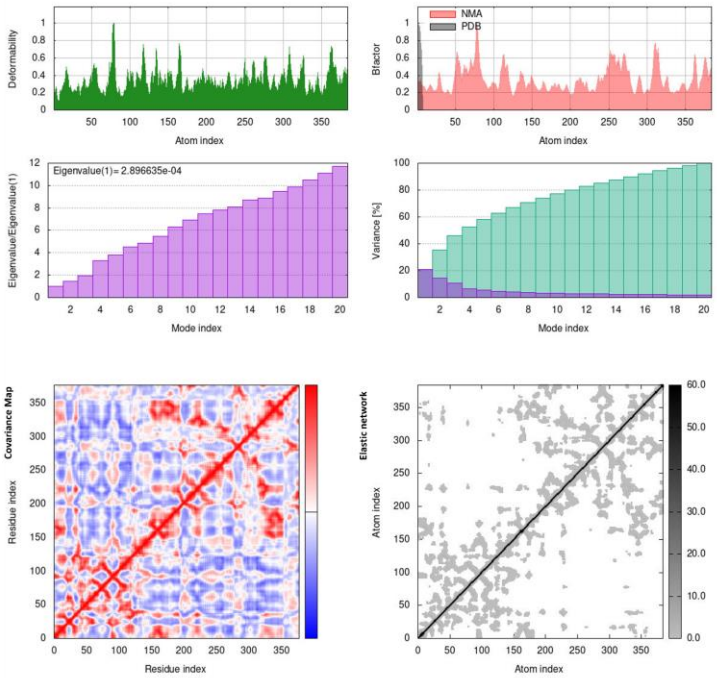

Figure 2. Molecular dynamic simulation analysis result of beta secretase-1 enzyme model. In the deformability model, the deformity of the backbone of protein chains is measured by the deformation potential of the molecular model of enzyme on each of its residues. The hinges Residues of chain signed by high deformability. In the B-factor model, experimental B-factor calculated with NMA method; the B-factor is index of the fluctuation in each residue of the enzyme. Eigenvalues model, the eigenvalue is directly related to the energy expended to deform the protein model structure. The lower the eigenvalue, the easier the deformation. Variance model, The variance index is associated with each mode and inversely correlates with the eigenvalue. Each variance model is colored red, but the cumulative variances are green. Covariance Map, It is a representation of the convergence of motions between pairs of amino acids. If the movements converge, it is shown in red, if there is no convergence, it is shown in white. and if the movements are in the opposite direction, this is shown in blue. The movements in each domain are often convergent. Elastic network model, it represents the contact between amino acids that is convergent, and the more convergent motions they have, the darker it is represented.

Table 1. Molecular docking results and ligand feature.

IUPAC Name	(3S,6R,9S,12S,15R,19R)-3-[(2S)-butan-2-yl]-19-heptyl-9-[(1R)-1-hydroxyethyl]-12-(hydroxymethyl)-6,15-bis(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,6S,13S,16S)-3,16-bis(hydroxymethyl)-6,13-bis(2-methylpropyl)-10,20-dipentyl-1,11-dioxa-4,7,14,17-tetrazacycloicosane-2,5,8,12,15,18-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,4S)-3-hydroxy-4-[[(2S)-2-[[(3S,4S)-3-hydroxy-6-methyl-4-[[(2S)-3-methyl-2-[[(2S)-3-methyl-2-(3-methylbutanoylamino)butanoyl]amino]butanoyl]amino]heptanoyl]amino]-6-methylheptanoic acid
CID code	88666410	138479032	16084771	508501	508500	5478883
MolDock Score	-111.56	-201.64	-195.26	-174.78	-142.17	-100.13
Torsions	9	14	14	13	11	5
HBond	-6.02	-6.15	-2.5	-9.57	-6.10	-2.25
Heavy Atoms	22	49	48	48	46	48
MW	315.38	697.90	684.86	683.87	655.82	659.68
LE1	-5.07	-4.11	-4.06	-3.64	-3.09	-2.08
XLogP3-AA	0.9	5.4	5.1	5	3.9	3
Hydrogen Bond Donor Count	4	7	6	6	6	8
Hydrogen Bond Acceptor Count	5	9	10	9	9	9
Topological Polar Surface	116 Å²	212 Å²	210 Å²	204 Å²	204 Å²	223 Å²
Gastrointestinal absorption	High	Low	Low	Low	Low	Low

(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-18-ethyl-19-heptyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-4,16-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S)-3-hydroxy-4-[[(2S)-2-[[(3S)-3-hydroxy-4,6-dimethylheptanoyl] amino] propanoyl] amino]-6-methylheptanoic acid	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9,16,18-trimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,6R,10R,13R,16R,20R)-3,16-bis(hydroxymethyl)-6,13-bis(2-methylpropyl)-10,20-dipentyl-1,11-dioxa-4,7,14,17-tetrazacycloicosane-2,5,8,12,15,18-hexone	(6S,9S,12S,15S,18R,19R)-19-decyl-14-hydroxy-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,17-pentone	ethyl 3-hydroxy-6-methyl-4-[[3-methyl-2-(3-methylbutanoylamino) butanoyl] amino] heptanoate	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,4S)-4-[[(2S)-2-amino-4-methylpentanoyl] amino]-3-hydroxy-6-methylheptanoic acid	(3S,4S)-4-[[(2S)-2-acetamidopropanoyl] amino]-3-hydroxy-6-methylheptanoic acid
155628361	156186536	162667790	163186155	164960792	44383576	76328341	88665450	88665994
-168.18	-127.06	-192.65	-203.52	-202.80	-126.64	-169.60	-95.92	-103.46
13	13	14	14	15	13	15	9	8
-9.65	-12.50	-7.23	-4.06	-2.5	-9.27	-9.01	-4.40	-5.07
49	28	49	48	49	27	50	20	20
697.90	401.51	695.93	684.86	697.90	386.52	711.92	287.37	287.33
-3.43	-4.53	-3.93	-4.24	-4.13	-4.69	-3.39	-4.79	-5.17
5	1.7	6.6	5.1	5.4	2.8	6.1	-1.3	-0.1
5	5	5	6	7	3	6	4	4
9	6	8	10	10	5	9	5	5
195 Å ²	136 Å ²	183 Å ²	210 Å ²	207 Å ²	105 Å ²	204 Å ²	113 Å ²	116 Å ²
Low	Low	Low	Low	Low	High	Low	High	High

(6S,9S,12S,15S,18R,19R)-12-butan-2-yl-19-decyl-6-(1-hydroxyethyl)-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,15S,18R,19R)-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-18-ethyl-19-heptyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16-methyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,8,11,14,17-pentone	(6S,9S,12S,15S,18R,19R)-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,1 5S,18R,19R)-19-decyl-9-(hydroxymethyl)-6,16,18-trimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,1 8R,19R)-19-decyl-9-(hydroxymethyl)-6-(2-hydroxypropan-2-yl)-16,18-dimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,1 5S,18R,19R)-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,1 7-hexone	(6S,9S,12S,15S, 18R,19R)-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-12,15-dipropyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,6S,9S,12S,15S,18R,19R)-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-3,16,18-trimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
155210110	155228360	155228373	155228401	155228449	155228472	155228476	155228502	155228518
-176.61	-190.10	-168.36	-174.47	-178.31	-196.59	-196.12	-180.83	-179.69
15	14	13	14	14	15	15	15	15
1.09	-1.88	-3.20	-10.55	0	-6.71	-4.49	-7.43	-0.57
49	48	47	48	47	50	48	48	50
697.90	683.87	669.89	683.87	667.87	711.92	683.87	683.87	711.92
-3.60	-3.96	-3.58	-3.63	-3.79	-3.93	-4.08	-3.76	-3.59
5.7	5.3	4.5	5.3	5.7	5.8	5.2	5.2	6.1
6	6	6	6	5	6	6	6	6
9	9	9	9	8	9	9	9	9
204 Å ²	204 Å ²	186 Å ²	204 Å ²	183 Å ²	204 Å ²	204 Å ²	204 Å ²	204 Å ²
Low	Low	Low	Low	Low	Low	Low	Low	Low

(6S,9S,12S,15S,18R,19R)-12-butan-2-yl-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-19-decyl-6-(1-hydroxyethyl)-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-butan-2-yl-19-decyl-6-(1-hydroxyethyl)-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-butan-2-yl-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-butan-2-yl-18-ethyl-19-heptyl-6-(1-hydroxyethyl)-9-(hydroxymethyl)-16-methyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-6-(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
155209837	155209842	155209873	155209881	155209882	155209917	155209962	155209977	155210109
-179.61	-206.37	-178.16	-171.85	-181.28	-165.54	-168.78	-180.16	-180.10
15	15	15	15	15	14	13	14	15
-2.72	-7.19	-9.63	-6.46	-2.55	-1.39	-6.81	-4.73	-8.00
49	49	50	48	48	48	48	48	49
697.90	697.90	711.92	683.87	683.87	681.90	683.87	683.87	697.90
-3.66	-4.21	-3.56	-3.58	-3.77	-3.44	-3.51	-3.75	-3.67
5.7	5.7	6.1	5.2	5.2	6.2	4.8	5.3	5.7
6	6	6	6	6	5	6	6	6
9	9	9	9	9	8	9	9	9
204 Å ²	204 Å ²	204 Å ²	204 Å ²	204 Å ²	183 Å ²	204 Å ²	204 Å ²	204 Å ²
Low	Low	Low	Low	Low	Low	Low	Low	Low

(6S,9S,12S,15S,18R,19R)-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-9-(hydroxymethyl)-6,16,18-trimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclonadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6,9-bis[(1S)-1-hydroxyethyl]-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-6-ethyl-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-18-ethyl-19-heptyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16-methyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-butan-2-yl-19-hexyl-6,9-bis(1-hydroxyethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-decyl-6,9-bis(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
138478588	138478788	138478852	138479069	153531700	153531702	155209727	155209835
-178.73	-152.45	-162.91	-163.05	-185.22	-170.58	-171.41	-172.06
15	14	11	15	15	13	11	15
-5.69	-6.61	0	-0.95	-4.32	-6.88	-6.54	-4.34
49	48	47	49	49	48	47	49
697.90	681.90	669.85	695.93	697.90	683.87	669.85	697.90
-3.64	-3.17	-3.46	-3.32	-3.78	-3.55	-3.64	-3.51
5.7	6.2	4.4	6.7	5.7	4.8	4.4	5.7
6	5	6	6	6	6	6	6
9	8	9	8	9	9	9	9
204 Å ²	183 Å ²	204 Å ²	183 Å ²	204 Å ²	204 Å ²	204 Å ²	204 Å ²
Low	Low	Low	Low	Low	Low	Low	Low

(3S,4S)-4-[[(2S)-5-(diaminomethylideneamino)-2-(propanoylamino)pentanoyl]amino]-3-hydroxy-6-methylheptanoic acid	[(3S)-4-[[(2S,3S)-1-carboxy-2-hydroxy-5-methylhexan-3-yl] amino]-4-oxo-3-(propanoylamino)butanoyl]azanium	(3S,4S)-4-[[(2S)-4-amino-2-(propanoylamino)butanoyl] amino]-3-hydroxy-6-methylheptanoic acid	(3S,4S)-4-[[(2S)-6-amino-2-(propanoylamino)hexanoyl] amino]-3-hydroxy-6-methylheptanoic acid	3-hydroxy-6-methyl-4-[[2-(2-methylpropanoylamino)acetyl]amino]heptanoic acid	4-[[(2S)-2-aminopropanoyl] amino]-3-hydroxy-6-methylheptanoic acid	methyl (3S,4S)-3-hydroxy-6-methyl-4-[[(2S)-4-methyl-2-[(2-methylpropan-2-yl)oxycarbonylamino]pentanoyl]heptanoate	(3S,4S)-4-[[(2S)-2-aminopropanoyl] amino]-3-hydroxy-6-methylheptanoic acid	(3S,4S)-4-[[(2S)-2-amino-3-methylbutanoyl] amino]-3-hydroxy-6-methylheptanoic acid	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-decyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
58057434	58057438	58057439	58057445	58952713	88383428	88665041	129716927	129716935	134141339
-141.11	-113.99	-107.687	-127.77	-106.09	-94.75	-121.01	-101.03	-105.99	-168.56
13	11	11	13	10	7	14	7	8	15
-4.15	-3.15	-4.05639	-2.90	-3.51	-4.34	-10.21	-8.22	-7.48	-6.95
27	23	23	25	22	17	28	17	19	50
386.46	331.40	331.408	359.46	315.38	245.29	401.51	245.29	274.35	711.92
-5.22	-4.95	-4.68206	-5.11	-4.82	-5.57	-4.32	-5.94	-5.57	-3.37
-0.8	-2.8	-2.8	-2.1	0.9	-2.6	3	-2.6	-1.7	6.1
6	5	5	5	4	4	3	4	4	6
6	5	6	6	5	5	6	5	5	9
180 Å ²	143 Å ²	142 Å ²	142 Å ²	116 Å ²	113 Å ²	114 Å ²	113 Å ²	113 Å ²	204 Å ²
Low	Low	Low	Low	High	High	High	High	High	Low

(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-18-methyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-6-ethyl-19-hexyl-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-9-(hydroxymethyl)-6-[(1S)-1-methoxyethyl]-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,4S)-3-hydroxy-6-methyl-4-[[(2S)-2-(propanoylamino)propanoyl] amino] heptanoic acid	[(4S)-5-[[(2S,3S)-1-carboxy-2-hydroxy-5-methylhexan-3-yl] amino]-5-oxo-4-(propanoylamino)pentyl] azanium	(3S,4S)-4-[[(2S)-5-amino-2-(propanoylamino) pentanoyl] amino]-3-hydroxy-6-methylheptanoic acid
44314019	44314057	44314119	44314377	44314378	44314379	58057422	58057428	58057429
-188.08	-162.30	-165.69	-171.93	-164.91	-175.99	-106.589	-118.233	-130.757
11	11	11	11	11	12	9	12	12
-2.65	-3.85	-1.74	-4.51	-7.18	-4.18	-8.41	-6.69	-10.21
45	46	45	46	46	47	21	24	24
641.79	655.82	639.82	655.82	655.82	669.85	301.35	345.43	345.43
-4.17	-3.52	-3.68	-3.73	-3.58	-3.74	-5.07	-4.92	-5.44
3.7	3.9	4.5	3.9	3.9	3.9	0.4	-2.5	-2.5
7	6	5	6	6	5	4	5	5
9	9	8	9	9	9	5	5	6
212 Å ²	204 Å ²	183 Å ²	204 Å ²	204 Å ²	193 Å ²	116 Å ²	143 Å ²	142 Å ²
Low	Low	Low	Low	Low	Low	High	Low	Low

(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-6-ethyl-19-hexyl-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,19R)-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-9-(hydroxymethyl)-6-[(1S)-1-methoxyethyl]-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(3S,6R,9S,12S,15R)-3-[(2S)-butan-2-yl]-19-heptyl-9-[(1R)-1-hydroxyethyl]-12-(hydroxymethyl)-6,15-bis(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
508506	508508	508510	5495863	9831660	10532731	12096747	12096748
-138.17	-170.52	-163.80	-141.06	-169.54	-207.50	-150.32	-162.21
11	11	12	12	15	14	11	13
-9.32	-7.33	-3.44	-3.29	-0.11	-6.50	-2.46	-0.74
45	45	47	47	50	49	46	48
639.82	641.79	669.85	669.85	711.92	697.90	655.82	683.87
-3.07	-3.78	-3.48	-3.00	-3.39	-4.23	-3.26	-3.37
4.5	3.7	4.7	3.9	6.1	5.4	3.9	5
5	7	6	5	6	7	6	6
8	9	9	9	9	9	9	9
183 Å ²	212 Å ²	204 Å ²	193 Å ²	204 Å ²	212 Å ²	204 Å ²	204 Å ²
Low	Low	Low	Low	Low	Low	Low	Low

(6R,9S,12S,15S,18R,19S)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	ethyl (4S)-4-[[(2S)-2-amino-3-methylpentanoyl] amino]-3-hydroxy-6-methylheptanoate	(6R,9S,12S,15S,18R,19S)-12-[(2R)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	ethyl (3R,4S)-4-[[(2S)-2-amino-3-methylpentanoyl] amino]-3-hydroxy-6-methylheptanoate	(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
10372433	10064371	10010038	9995915	508502	508503	508504	508505
-183.47	-122.24	-173.91	-121.12	-161.23	-151.48	-161.08	-164.48
13	11	15	11	15	11	11	11
-3.52	-6.81	-5.20	-6.85	-4.05	-6.36	-8.61	-2.5
48	22	50	22	50	46	46	46
683.87	316.43	711.92	316.43	711.92	655.82	655.82	655.82
-3.82	-5.55	-3.47	-5.50	-3.22	-3.29	-3.50	-3.57
5	1.7	6.1	1.7	6.1	3.9	3.9	3.9
6	3	6	3	6	6	6	6
9	5	9	5	9	9	9	9
204 Å ²	102 Å ²	204 Å ²	102 Å ²	204 Å ²	204 Å ²	204 Å ²	204 Å ²
Low	High	Low	High	Low	Low	Low	Low

(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(2S)-2-[[(3S,4S)-4-[[(2S)-2-amino-4-methylpentanoyl] amino]-3-hydroxy-6-methylheptanoyl] amino] butanoic acid	(6R,9R,12S,15S,18R,19S)-12-[(2R)-butan-2-yl]-19-decyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6R,9R,12S,15S,18R,19S)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(2S)-3-hydroxy-2-[[(2R)-2-(3-hydroxyoctanoylamino)-4-methylpentanoyl] amino] propanoic acid	(6S,9R,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(2S)-2-[[(3S,4S)-4-[[(2S)-2-acetamido-3-hydroxypropanoyl] amino]-3-hydroxy-6-methylheptanoyl] amino]-3-methylbutanoic acid	(6S,9S,12S,15S)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
73351724	24763876	23327181	20704753	16084772	11388203	11365949	10549158	10461975
-166.14	-132.83	-168.01	-148.05	-131.03	-177.49	-171.28	-136.16	-162.89
11	12	15	13	13	11	13	12	11
-3.50	-4.42	-4.94	-6.95	-5.97	-5.66	-5.19	-8.02	-0.62
46	26	50	48	25	46	48	28	46
655.82	372.48	711.92	683.87	359.43	655.82	683.87	402.46	655.82
-3.61	-5.10	-3.36	-3.08	-5.24	-3.85	-3.56	-4.86	-3.54
3.9	-1	6.1	5	1.2	3.9	5	-0.4	3.9
6	5	6	6	5	6	6	6	6
9	6	9	9	6	9	9	7	9
204 Å ²	142 Å ²	204 Å ²	204 Å ²	136 Å ²	204 Å ²	204 Å ²	165 Å ²	204 Å ²
Low	High	Low	Low	High	Low	Low	Low	Low

(6S,9S,12S,15S)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S)-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S)-12-[(2R)-butan-2-yl]-19-heptyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1R)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(6S,9S,12S,15S,18R,19R)-12-[(2S)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	(2S)-2-[[(3R,4R)-4-[[(2S)-2-acetamido-3-hydroxypropanoyl] amino]-3-hydroxy-6-methylheptanoyl] amino]-3-methylbutanoic acid	(6S,9S,12S,15S)-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-12-propan-2-yl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone
102060402	101982286	101982285	101341132	101341131	101341130	101039397	90475794
-176.82	-167.28	-164.41	-151.00	-163.16	-163.34	-143.62	-162.33
13	12	12	11	11	11	12	10
-3.25	-5.99	-1.60	-4.70	-3.23	-7.53	-9.76	0
48	47	47	45	46	46	28	45
683.87	669.85	669.85	641.79	655.82	655.82	402.46	641.79
-3.68	-3.55	-3.49	-3.35	-3.54	-3.55	-5.12	-3.60
5	4.7	4.5	3.5	3.9	3.9	-0.4	3.6
6	6	6	6	6	6	6	6
9	9	9	9	9	9	7	9
204 Å ²	204 Å ²	204 Å ²	204 Å ²	204 Å ²	204 Å ²	165 Å ²	204 Å ²
Low	Low	Low	Low	Low	Low	Low	Low

(6S,9R,12S,15S,18S,19R)-12-[(2R)-butan-2-yl]-19-hexyl-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	162936024	-153.47	11	-3.49	46	655.82	-3.33	3.9	6	9	204 Å²	Low
(6R,9R,12R,15R,18R,19R)-12-[(2R)-butan-2-yl]-6-[(1S)-1-hydroxyethyl]-9-(hydroxymethyl)-16,18-dimethyl-15-(2-methylpropyl)-19-octyl-1-oxa-4,7,10,13,16-pentazacyclononadecane-2,5,8,11,14,17-hexone	163054762	-181.18	13	-7.11	48	683.87	-3.77	5	6	9	204 Å²	Low
(3S,6S,10S,13S,16S,20S)-3,16-bis(hydroxymethyl)-6,13-bis(2-methylpropyl)-10,20-dipentyl-1,11-dioxa-4,7,14,17-tetrazacycloicosane-2,5,8,12,15,18-hexone	163064313	-172.573	14	-4.49	48	684.86	-3.59	5.1	6	10	210 Å²	Low

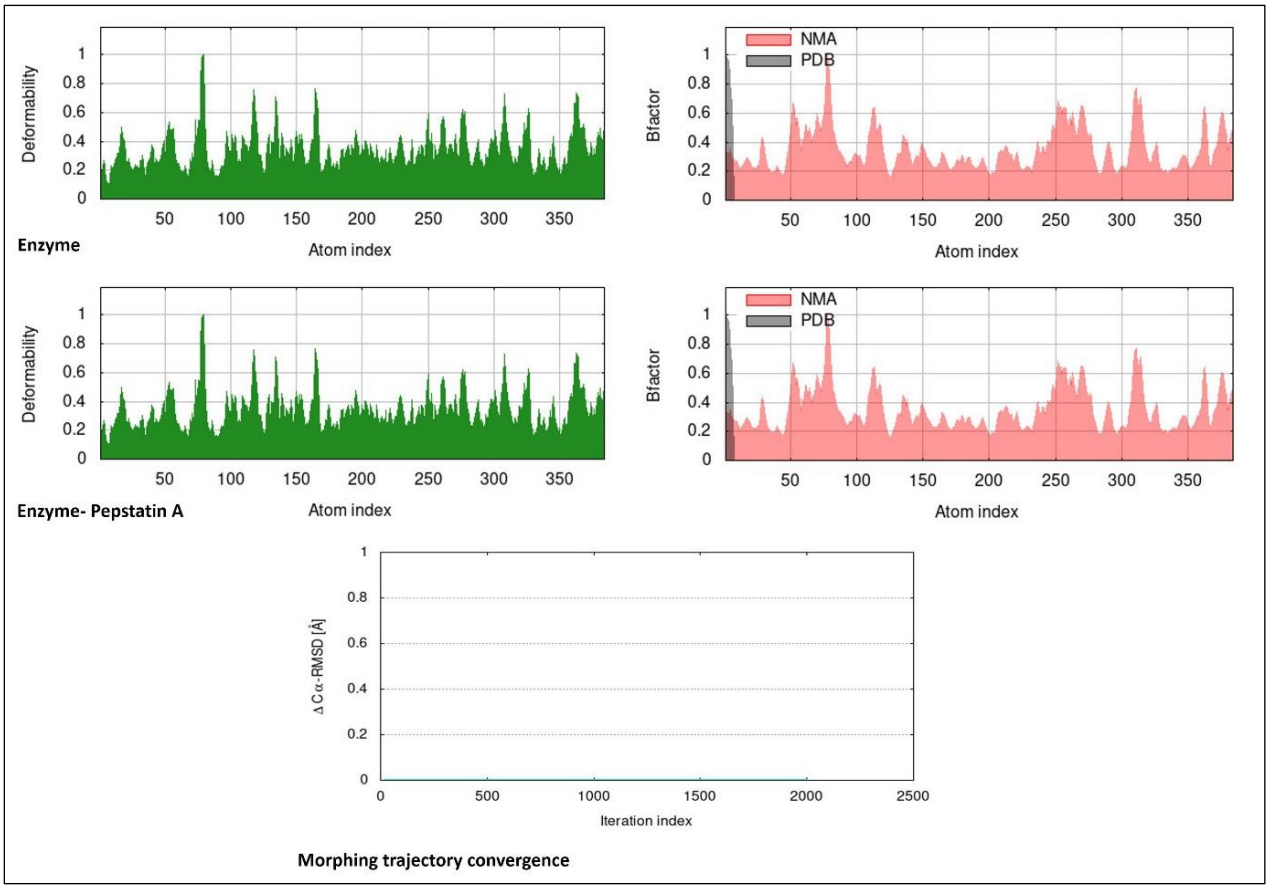

Figure 3. Comparison of alpha-carbon atom motion during molecular dynamics simulation for each amino acid of the enzyme compared to the enzyme-ligand complex. Deformability models of enzyme model ("iMode results" ID 0600064232716) and enzyme-peptatain model (iMode results" ID 0600070348259) are very Mach, Morphing trajectory convergence model note no difference in alpha carbons movement between tow trajectories.

They often have high absorption in the digestive tract but have limited ability to cross the blood-brain barrier and often have molecular weights greater than 400 Da (7, 8, and 13). Some of the compounds we studied in the molecular affinity docking study had higher binding affinity for the beta-secretase enzyme model than some of these known compounds. However, they also had a higher molecular weight. The compounds with CID numbers: 10532731, 16084771, 122177562, 155209842, 155228360, 155228472, 155228476, 162667790, 163186155, 164960792 that their molecular weight is between 400 and 700 Daltons.

Other compounds with molecular weight between 300 and 400 Da, which have lower affinity, were also investigated in this study. Among the compounds with molecular weight less than or about 400 daltons, the pseudo-peptide compound Ac-Ser-Sta(3R,4R)-Val-OH (CID number: 101039397) with a molecular weight of 402.4 daltons and a docking score of -143.6 and the compound with CID numbers: 58057434 with a molecular weight of 386.4 daltons and a docking score of -141.1 have the highest affinity.

CONCLUSION

Numerous studies have been conducted in the field of beta-secretase inhibition. Many compounds have been proposed, and many of them have been used in clinical trials. Following previous studies, in the present study, we attempted to apply the molecular docking method by investigating the binding affinity of the molecular model of some compounds similar to pepstatin (A) with the molecular model of beta-secretase enzyme to search for compounds with similar inhibitory properties. Among the compounds studied, compounds with size greater than 400 daltons and low hydrophobicity cannot cross the blood-brain barrier, while compounds with high hydrophobicity in the 400-dalton weight range have good digestive absorption and can cross the blood-brain barrier. In the current study, the pseudo-peptide compound Ac-Ser-Sta(3R,4R)-Val- OH (CID:101039397) and the compound with CID number: 58057434 showed the highest binding affinity for the active site of human BACE1 enzyme (6EQM) in the weight range of about 400 daltons and can be further investigated as beta-secretase enzyme inhibitors.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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