VinaLigGen: A method to generate Ligplots and retrieval of hydrogen and hydrophobic interactions from protein-ligand complexes

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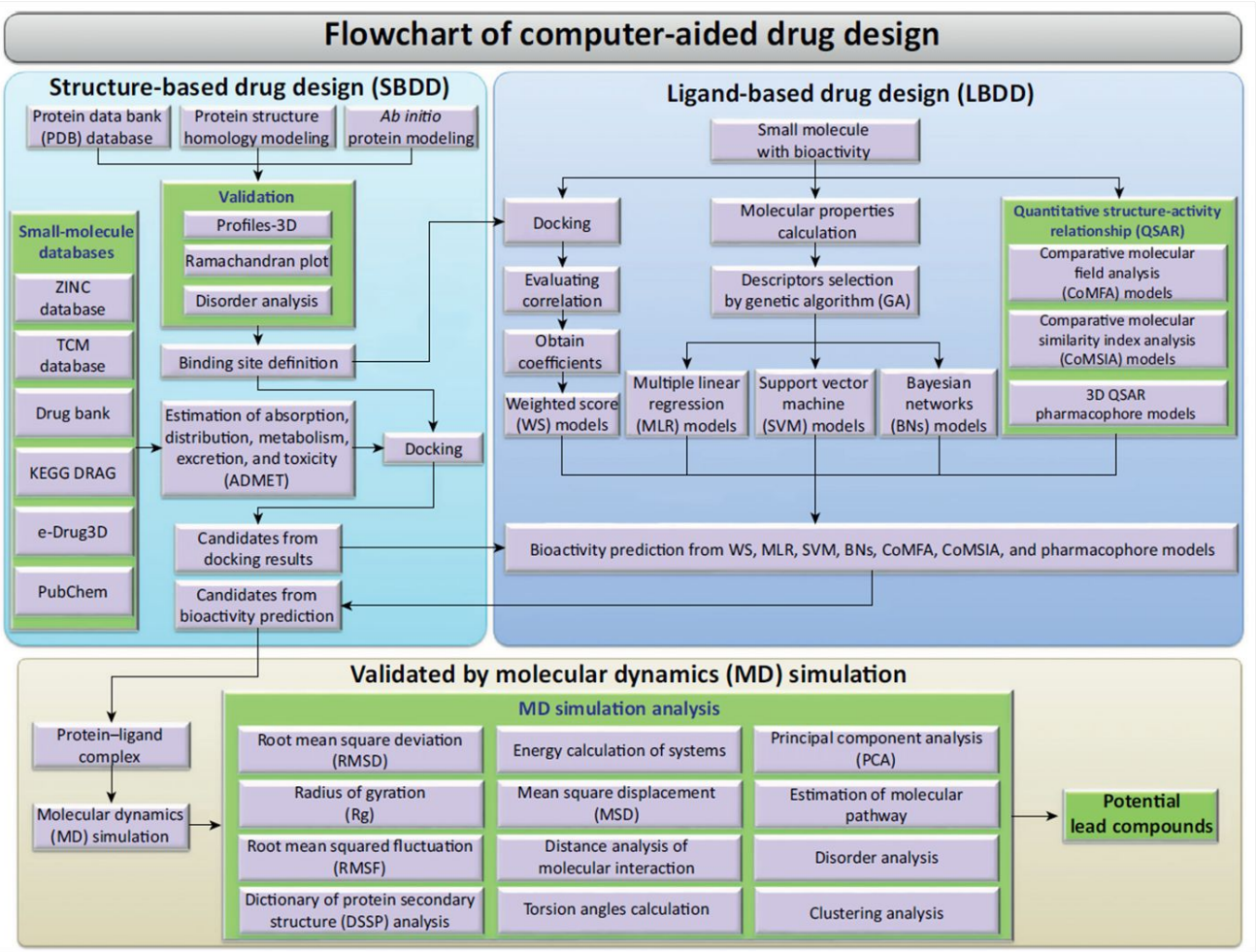
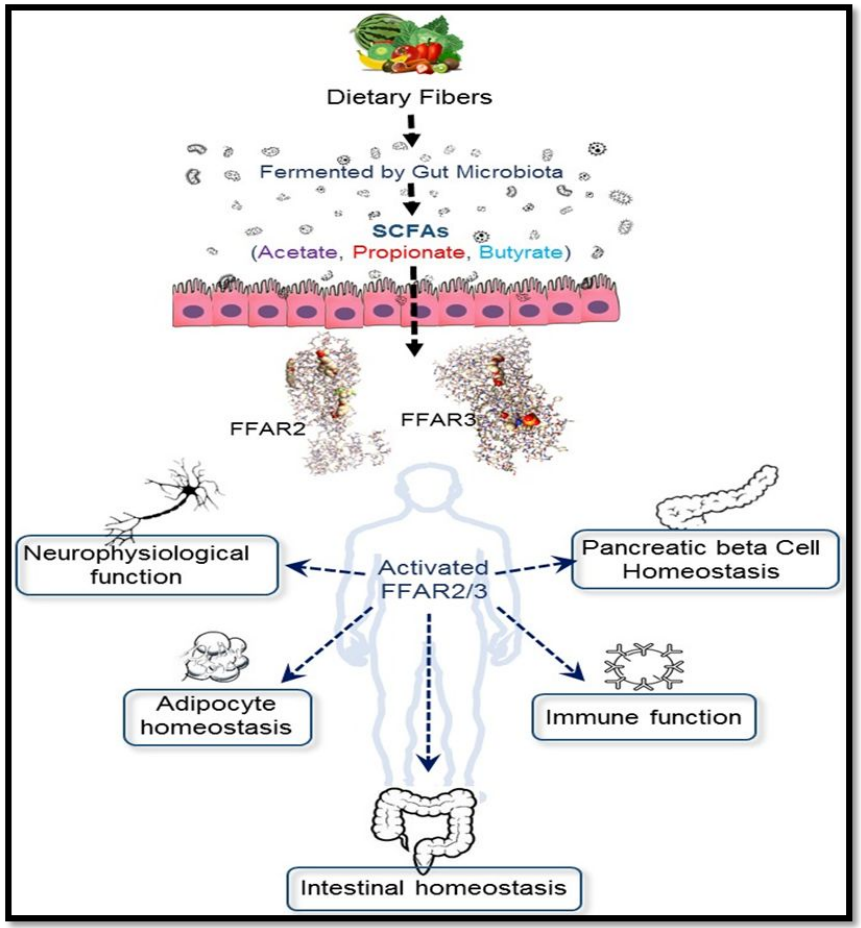


Yu-Chian Chen, Trends in Pharmacological Sciences (2015) 36:2, 78-95

Introduction to the problem



S.No.	Name of Libraries	No. of Compounds
1	AfroDb Natural Products	1008
2	AnalytiCon Discovery NP	20000
3	Herbal Ingredients In-Vivo Metabolism	1465
4	Herbal Ingredients Targets	9862
5	IBScreen NP	68000
6	Indofine Natural Products	20000
7	Nubbe Natural Products	2147
8	Specs Natural Products	800
9	TCM Database @ Taiwan	20000
10	NPACT Database	1574
Total		**144356**

S. P. Mishra, 2020

Vina score and LigPlot generation

Manual procedure

Number of ligands 16
Number of conformations/ligand is

= 16 * 9 (docked vina conformations)

= 144 conformations

To generate LigPlot of 144 conformations

= 144 * 2 minutes/conformation

= 288 minutes

= ~5 Hours

Our solution:

20 - 30 minutes

ZINC ID	Compound Name	Human FFAR2
ZINC00968029	Darwinol	-6.6
ZINC02040990	Beta-terpineol	-6.5
ZINC95099135	7-hydroxycamphene	-6.1
ZINC01597139	(±)-Carvomenthol	-6.1
ZINC00157548	Norpseudoephedrine hydrochloride	-6
ZINC00403588	Synephrine	-6
ZINC00388198	Octopamine hydrochloride	-5.8
ZINC02034811	3-Pinanone	-5.8
ZINC00968099	Borneol	-5.8
ZINC00074836	Ephedrine	-5.7
ZINC00967571	(+)-Fenchone	-5.7
ZINC01081099	FENCHOL	-5.5
ZINC03581377	L-Leucinamide hydrochloride	-5.4
ZINC00895132	Butyrate	-4.3
PubChem CID:175	Acetate	-3
ZINC118616157	CATPB	-9.8

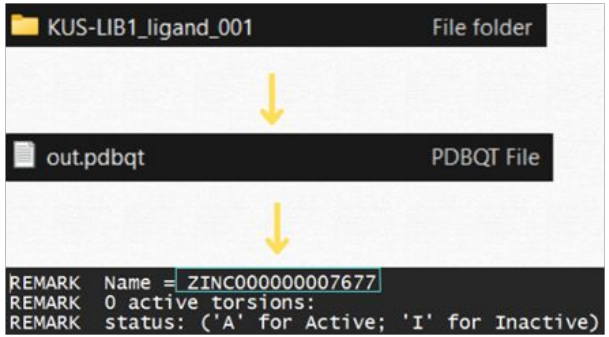
VinaLigGen - AutoDock **Vina** results to **Lig**Plot **Gen**eration

- A program that extracts hydrogen, hydrophobic interactions and generates postscripts/png of these interactions for better analysis.
- The tool takes the docked protein-ligand complex (_out.pdbqt files) along with the macromolecule (.pdb) file.
- Before extracting interaction data, It shortlists docked complexes based on the given molecule IDs.
- This tool does not require any pre-processing of the complexes.
- The output of this tool is a .zip file which consists of,
  - An excel sheet which has the hydrogen and hydrophobic bond data.
  - A folder ‘Target Files’, Which has the files that were considered for generating the above.
  - Another folder ‘LigPlot’, Which has the postscript, and bond interactions data files.

VinaLigGen - AutoDock **Vina** results to **Lig**Plot **Gen**eration

- The docked complexes used as input files can be of the following 3 types,
  - Type 1: The Molecule ID is in the file name itself.
  - Type 2: The Molecule ID is inside the file.
  - Type 3: This one is very similar to Type 2, But the only difference is that the molecule
  - file is inside a folder and the molecule ID is inside the file. As per this example, the molecule i.e 'out.pdbqt' is placed inside. Example: 'KUS-LIB1_ligand_001' and the molecule ID is inside out.pdbqt

Type 2



Type 3

Type 1

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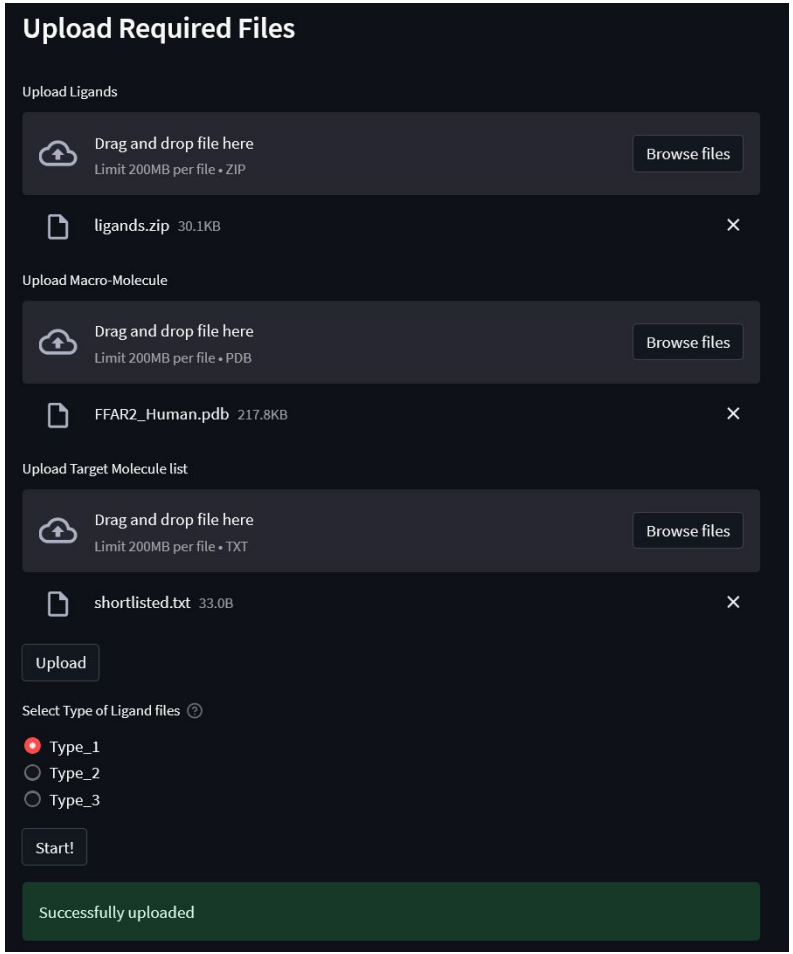
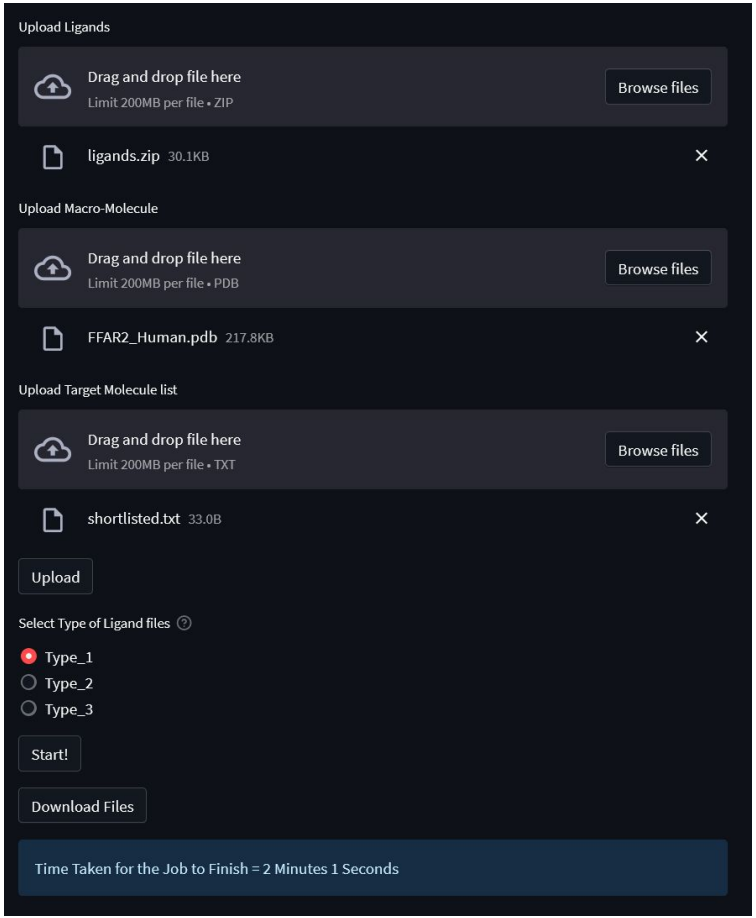
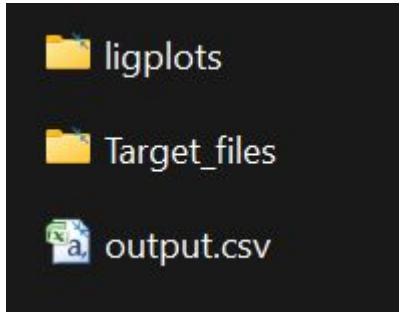
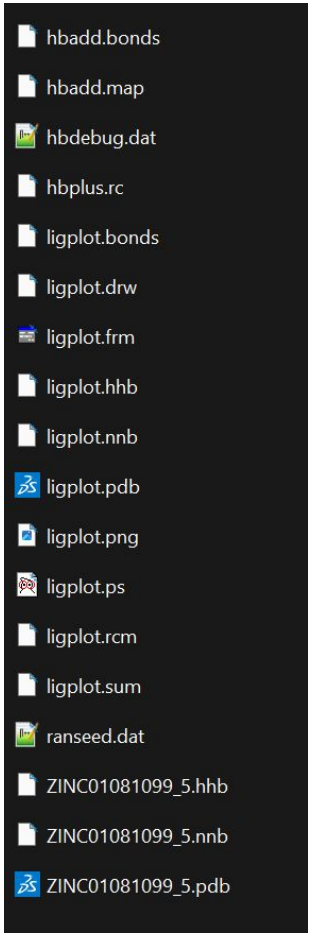



```
Zip files :  ligands.zip
PDB File :  macromolecule.pdb
Text File :  shortlist.txt

Getting short listed files - using File name...

       - Fetching short listed files...!
       - SUCCESS: Fetched all the 3 short listed files!!


Starting Splitting of Files

       - Fetched 3 files which are going to be split
Spliting Files...:  67%|                                                  | 2/3 [00:07<00:03,  3.91s/it]
       - SUCCESS: All the 3 files have been split to 27 files!!

Generating of ligplot Generator File!
       - The files required are,
       - ligplot_generator.bat
       - hbadd.exe
       - hbplus.exe
       - ligplot.exe
       - ligplot.prm

       - Checking if all dependencies are satisfied...

       - All dependencies satisfied!

       - Please run the D:\Technical\VinaLigGen-main\Master_folder\\top_40_files /ligplot_generator.bat file

Program has started
Processing ligand 175_1 |# [1/27]
Processing ligand 175_2 |### [2/27]
Processing ligand 175_3 |##### [3/27]
Processing ligand 175_4 |####### [4/27]
Processing ligand 175_5 |######### [5/27]
Processing ligand 175_6 |########### [6/27]
Processing ligand 175_7 |############ [7/27]
Processing ligand 175_8 |############## [8/27]
Processing ligand 175_9 |################ [9/27]
```

VinaLigGen - AutoDock **Vina** results to **Lig**Plot **Gen**eration







VinaLigGen - AutoDock **Vina** results to **Lig**Plot **Gen**eration

Significance of hydrogen bonding and hydrophobic interactions

Molecular Recognition: Hydrogen bonds enable specific interactions between ligands and receptors.

Binding Affinity: They contribute to strong non-covalent bonding and higher binding affinities.

Binding Orientation: Hydrogen bonds guide ligands into the correct binding position.

Binding Specificity: They help discriminate between similar ligands based on bonding patterns.

Scoring Functions: Docking algorithms use hydrogen bond data in scoring ligand-receptor complexes.

Drug Design: Hydrogen bonds inform the optimization of ligand structures for binding.

Biological Function: Hydrogen bonds are crucial in various biological processes.

Virtual Screening: Hydrogen bond predictions aid in screening potential drug candidates.

Complementarity: Hydrophobic interactions contribute to the complementarity between ligands and receptors.

Binding Affinity: They play a crucial role in stabilizing ligand-receptor complexes.

Nonpolar Regions: Hydrophobic groups on ligands and receptors interact favorably in nonpolar environments.

Core Binding: Hydrophobic interactions often form the core of protein-ligand complexes.

Specificity: They aid in discriminating between ligands with different hydrophobic properties.

Binding Strength: Hydrophobic interactions can significantly enhance the overall binding strength.

Structural Stability: They contribute to the structural stability of ligand-receptor complexes.

VinaLigGen - AutoDock **Vina** results to **Lig**Plot **Gen**eration

LIGAND_NAME	Hydrogen_bonds	d_distance	Hydrophobic_bonds	Hydrophobic_bond_distance
175_1	HIS242	2.88	ARG180 | PHE168 | HIS242 | VAL176 | PHE168	3.78 | 3.83 | 3.87 | 3.78 | 3.78
175_2			PHE231 | SER262 | PHE235 | PHE231 | ILE93	3.69 | 3.87 | 3.81 | 3.85 | 3.79
175_3			LYS65 | ILE10	3.77 | 3.74
175_4			| ILE17 | TYR14 | TYR14	3.85 | 3.62
175_5	HIS242	3.24	TYR90 | TYR90 | TYR90 | TYR90 | TYR90	3.83 | 3.87 | 3.85 | 3.79
175_6			PHE235	3.46 | 3.56 | 3.60 | 3.78 | 3.80 | 3.78
175_7			VAL260 | LEU62	3.64 | 3.69
175_8			SER86 | THR85 | THR85 | THR85 | LYS65	3.80 | 3.62 | 3.77 | 3.61 | 3.67
175_9			THR85 | THR85 | THR85	3.89 | 3.76 | 3.73
ZINC00388198_1	TYR238	2.71 | 3.07	TYR90 | TYR90 | TYR90 | TYR90 | LEU187 | LEU183 |	3.78 | 3.66 | 3.84 | 3.81 | 3.48 | 3.65 | 3.52 |
ZINC00388198_2	ASN239	2.95	TYR238 | PHE235 | HIS242 | PHE235 | PHE235 |	3.76 | 3.51 | 3.57 | 3.73 | 3.63 | 3.75 | 3.41 |
ZINC00388198_3	GLU166	3.03 | 2.98	TRP75 | TRP75	3.74
ZINC00388198_4	GLU166	3.04 | 3.00	PHE89 | SER86	3.68
ZINC00388198_5	TYR238 | GLN148	2.93 | 2.90	PHE89 | PHE89 | PHE89 | PHE89	3.84 | 3.83 | 3.80
ZINC00388198_6	GLN148 | SER86 | GLU166	3.04	SER86 | THR85 | PHE89	3.64 | 3.86 | 3.56
ZINC00388198_7	TYR238 | THR85	2.70 | 3.06	PHE89 | PHE89 | LYS65	3.66 | 3.62
ZINC00388198_8	GLU166	2.94	SER86 | SER86	3.70
ZINC00388198_9	TYR238 | CYS164	2.88 | 3.33	PHE89 | PHE89	3.64
ZINC01081099_1			ILE10 | ILE10 | ILE10 | VAL260 | VAL259 | VAL260 |	3.83 | 3.78 | 3.48 | 3.73 | 3.83 | 3.75 | 3.86 |
ZINC01081099_2			PHE89 | PHE89 | CYS164	3.84 | 3.78
ZINC01081099_3			TYR90 | TYR90 | PHE89	3.52 | 3.44
ZINC01081099_4	HIS242	3.1	TYR90 | TYR90 | TYR90 | TYR90 | TYR90 | LEU183 |	3.85 | 3.86 | 3.54 | 3.84 | 3.54 | 3.49 | 3.49 |
ZINC01081099_5	GLU166 | GLN148 | SER86	3.01	PHE89 | PHE89 | PHE89 | PHE89 | SER86	3.83 | 3.45 | 3.72 | 3.65 | 3.56
ZINC01081099_6			PHE89 | PHE89 | PHE89 | PHE89 | LYS65	3.78 | 3.90 | 3.66 | 3.72
ZINC01081099_7			PHE89 | PHE89	3.84
ZINC01081099_8			VAL259 | PHE89 | PHE89 | PHE89 | PHE89 | VAL259 |	3.82 | 3.60 | 3.61 | 3.85 | 3.68 | 3.86 | 3.83 |
ZINC01081099_9			SER86 | SER86 | PHE89 | PHE89 | PHE89 | PHE89 |	3.67 | 3.49 | 3.68 | 3.72 | 3.72 | 3.60 | 3.73

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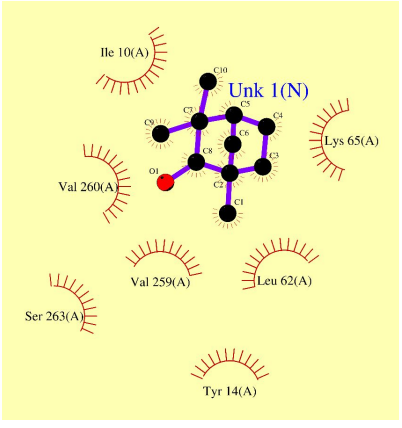

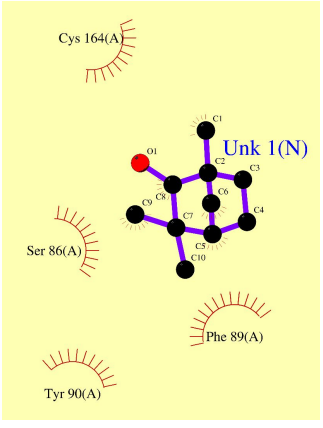

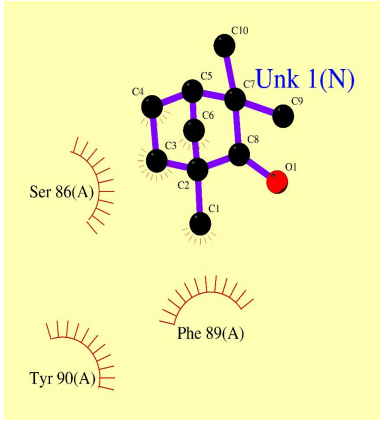

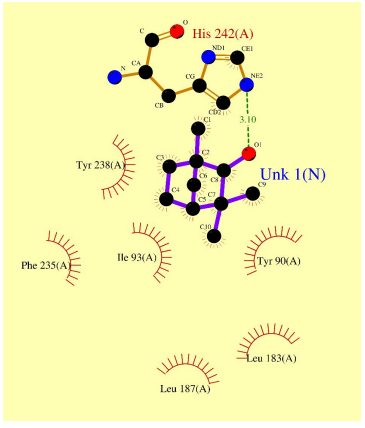

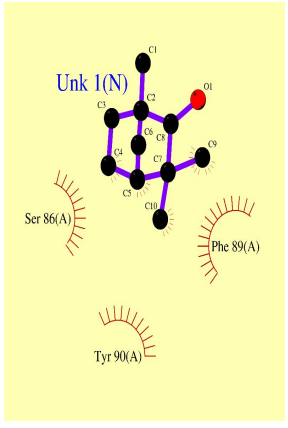

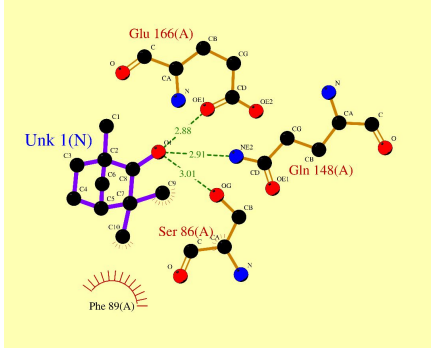

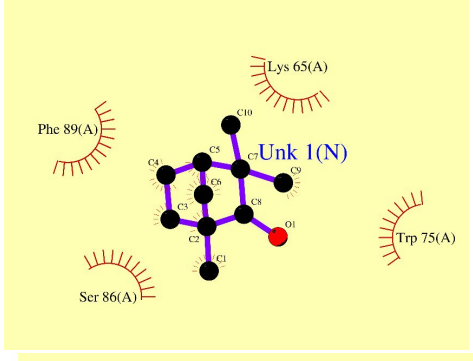

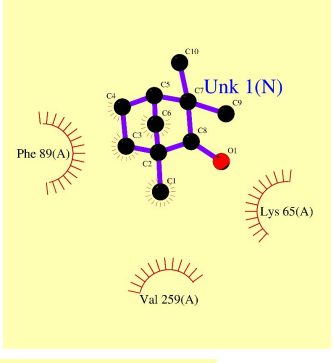

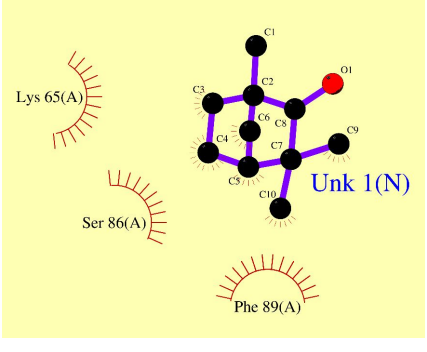

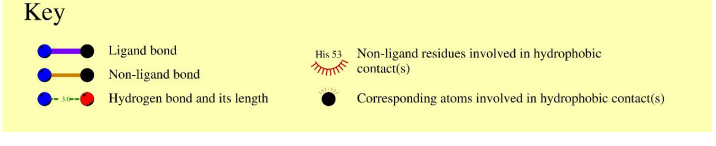

VinaLigGen - AutoDock **Vina** results to **Lig**Plot **Gen**eration

Sl. No.	Compounds	H-Bonding Residues Human_FFAR2	Probability as Agonist Ser86, Tyr90, His140, Ile145, Val179, Arg180, Leu183, Tyr238, His242, Arg255
1	175 (Acetate)	**His242**, Tyr238	Potential Agonist
2	ZINC003881988 (Octopamine hydrocholride)	Leu183, **Tyr238**, His242, Asn239, Gln148, Cys164, Glu166, **Ser86**, Glu68, Thr85,	70%
3	ZINC010810909 (Fenchol)	Glu166, **Ser86**, **His242**, Gln148, **Tyr238**	50%

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Activation of Microbiota Sensing – Free Fatty Acid Receptor 2 Signaling Ameliorates Amyloid-β Induced Neurotoxicity by Modulating Proteolysis-Senescence Axis

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Multiple emerging evidence indicates that the gut microbiota contributes to the pathology of Alzheimer's disease (AD)—a debilitating public health problem in older adults. However, strategies to beneficially modulate gut microbiota and its sensing signaling pathways remain largely unknown. Here, we screened, validated, and established the agonists of free fatty acid receptor 2 (FFAR2) signaling, which senses beneficial signals from short chain fatty acids (SCFAs) produced by microbiota. The abundance of SCFAs, is often low in the gut of older adults with AD. We demonstrated that inhibition of FFAR2 signaling increases amyloid-beta (Aβ) stimulated neuronal toxicity. Thus, we screened FFAR2 agonists using an in-silico library of more than 144,000 natural compounds and selected 15 of them based on binding with FFAR2-agonist active sites. Fenchol (a natural compound commonly present in basil) was recognized as a potential FFAR2 stimulator in neuronal cells and demonstrated protective effects against Aβ-stimulated neurodegeneration in an FFAR2-dependent manner. In addition, Fenchol reduced AD-like phenotypes, such as Aβ-accumulation, and impaired chemotaxis behavior in *Caenorhabditis (C.) elegans* and mice models, by increasing Aβ-clearance *via* the promotion of proteolysis and reduced senescence in neuronal cells. These results suggest that the inhibition of FFAR2 signaling promotes Aβ-induced neurodegeneration, while the activation of FFAR2 by Fenchol ameliorates these abnormalities by promoting proteolytic Aβ-clearance and reducing cellular senescence. Thus, stimulation of FFAR2 signaling by Fenchol as a natural compound can be a therapeutic approach to ameliorate AD pathology.

Keywords: microbiota, free fatty acid, G-coupled protein receptor, FFAR2 (GPR43), fenchol, natural compounds, Alzheimer's

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