Qsar Studies on Gallic Acid Derivatives and Molecular Docking Studies of Bace1 Enzyme – A Potent Target of Alzheimer Disease.

KrishnaKant Gupta[1]
[1] PhD Research Scholar, Center for Bioinformatics, Pondicherry University, Pondicherry, India,

Abstract

It is reported that Alzheimer disease is linked with hypertension, diabetes type 2 and high cholesterolemia. The underlying genetic cause relating these diseases are not well studied clinically. But it has been widely accepted that beta secretase (BACE1) is the main culprit of causing Alzheimer disease. This enzyme comes under peptidase A1 family. In the present work, ligand based and structure based drug designing have been reported. QSAR studies were done using 21 gallic acid derivatives dataset to develop good predictive model in order to predict biological activity and certain descriptors was reported to further enhance the analgesic activity of gallic acid derivatives. Molecular docking studies were performed in order to find structure based drug design. Two natural gallic acid derivative have been repoted as a potent inhibitor to beta secretase enzyme.

Keywords: *Alzheimer Disease, beta secretase, QSAR, Molecular docking, Ligands, inhibitor.*

1. Introduction

Millions of peoples worldwide are affected by this devastating disease i.e., Alzheimer Disease (AD). The hallmark of AD brain includes the presence of amyloid plaques, neurofibrillary tangles, loss of neurons and synapses, and oxidative damage. Amyloid precursor protein (APP) is embedded in cell membrane, the barrier that encloses the cell. There are number of APP snipping enzymes. Alpha secretase, beta-secretase, and gamma-secretase are main APP snipping peptidase. These enzymes were discovered in 1999 and 2000. **[1]**

APP processing can follow one of two pathways that have very different consequences for the cell. In the non-harmful pathway, alpha-secretase snip the APP molecule and releases from the neuron a fragment called sAPPα, which has been reported for promoting neuronal growth and survival. The remaining APP fragment is then cleaved by gamma-secretase at the end of the beta-amyloid segment. The smaller of the resulting fragments also is released into the space outside the neuron, while the larger fragment remains within the neuron and interacts with factors in the nucleus. **[2]**

It is experimentally reported that oxidative stress results in increase in the activity of Beta Secretase (BACE1) through activation of the PKR-eIF2α pathway. In the harmful pathway, beta-secretase first snip the APP molecule, releasing sAPPβ from the cell. sAPPβ act as a ligand for DR6 (Death protein) – as is a fragment of its close relative, APLP2 - that triggers degeneration of cell bodies via caspase-3 and axons via caspase-6 **[3]**. Similarly as in case of alpha secretase

pathway, gamma-secretase then cuts the resulting APP fragment, the beta amyloid peptide is released into the space outside the neuron and begins to stick to other beta-amyloid peptides. These small, soluble aggregates of two, three, four, or even up to a dozen beta-amyloid peptides are called oligomers. Size dependent oligomers may be responsible for reacting with receptors on neighboring cells and synapses, affecting their ability to function. It is likely that some oligomers are cleared from the brain. Those that cannot be cleared clump together with more beta-amyloid peptides. As the process continues, oligomers grow larger, becoming entities called protofibrils and fibrils.

What is QSAR?

QSAR is a study of empirical relationships between structure and property. When considerable biological information is not available then QSAR study shed light on it . Quantitative structure-activity relationships (QSAR) are methods which correlate molecular structure (descriptors) to some kind of in vitro or in vivo biological property. When this approach is applied to modelling of toxicological data, it is termed quantitative structure —toxicity relationships (QSTR).When applied to modelling of physicochemical properties it is called quantitative structure — property relationships (QSPR).**[4]**

QSAR in particular, first developed by Hansch and Fujita 40 years ago, has been invaluable for understanding drug structure —activity relationships for lead discovery and optimisation.

What is Molecular docking?

Docking is a method which finds the preferred orientation of one molecule to a second when bound to each other to form a stable complex. **[5]** Algorithm of the search space and scoring function is the basis of predicting any binding affinity between two molecules.

In the present work, ligand based and structure based drug designing have been reported. QSAR studies were done using 21 gallic acid derivatives dataset to develop good predictive model in order to predict biological activity and certain descriptors was reported to further enhance the analgesic activity of gallic acid derivatives. Molecular docking studies were performed in order to find structure based drug design. Two natural gallic acid derivative have been repoted as a potent inhibitor to beta secretase enzyme.

2. Material and Methodology

2.1 Dataset retrieval for QSAR model building:

49 compounds with their biological activity dataset were taken from the paper entitled "**Structure–activity relationships for the analgesic activity of gallicacid derivatives.**" **[6]**

2.2 QSAR model building:

QSAR model were build using Sarchitect software. **[7]** The Multiple linear regressions were used to build QSAR model. The brief steps considered for model building are following:

Optimization of structure

Structure optimization is an important step as descriptors calculation and their accuracy is largely affected by the structure of molecules. Geometrical and conformational descriptors depend on structural features such as bond length, bond angle and position of atoms in space to provide confirmation.

Calculation of Descriptors

Molecular descriptors are numerical values obtained by the quantification of various structural and physicochemical characteristics of the molecule. It is envisaged that molecular descriptors quantify these attributes so as to determine the behavior of the molecule and the way the molecule interacts with a physiological system. Since the exact mechanism of drug activity is unknown in many cases, it is desirable to start with descriptors spanning as many attributes of the molecules as possible and then assess their ability to predict the desired activity/property. Some programs compute over a thousand descriptors covering constitutional, topological and conformational spaces of compounds. Descriptors for present dataset were calculated using E-Dragon **[8]** which an online tool is provided by Virtual Chemistry Laboratories. Parameter Client is the interface for the E-Dragon. This program makes all classes of descriptors available according to their categories. Topological, geometrical, Constitutional, Conformational, Connectivity based etc. can be easily calculated using this program. Its offline version DRAGON can also be used to calculate descriptors but only for the molecules having atoms less than 50 and number of descriptors are also less as compare to E-Dragon.

Pruning of Descriptors

The Prune Descriptors Wizard drops descriptors with low variance and handles missing values. This step was used to removes all descriptors for which either Standard Deviation or Coefficient of variance were less than the specified cutoff.

Statistical Tests/Correlation

This step ranks the descriptors in the order of their relevance to the endpoint (Biological activity) value. Ensure that the appropriate dataset is chosen in the Navigator. If the endpoint is Categorical, ranking is done using Kruskal-Wallis (uses H-statistic) and if the endpoint value is Continuous, ranking is based on Correlation (uses Pearson Correlation Coefficient.

Forward/Backward Selection

The most straightforward search strategies are based on stepwise addition or elimination of descriptors. A sequential selection wrapper proceeds by adding or removing features from the current set to form a new candidate. This was then evaluated using some validation metric (n-fold or leave-one-out accuracy) and if it is superior then it replaces the current optimal set and the algorithm continues. The process terminates when no more valid operations (addition/removal) can be performed or if no candidate feature exceeds the performance of its predecessor. Forward Selection and Backward Elimination select the most relevant descriptors based on stepwise addition or elimination of features. In forward selection, variables are progressively incorporated into larger and larger subsets, whereas in backward elimination one starts with the set of all

variables and progressively eliminates the least promising ones. Both methods yield nested subsets of variables.

Generation of Models for Dataset.

The best models out of all available models can be chosen after study of their statistical parameters like regression coefficient r^2, adjusted r^2 standard error and F-state t- test etc. a model with r^2 values higher than 0.499 can be selected for prediction of activity in QSAR.

2.3 Docking studies

Downloading crystal structure of Beta secretase and active site residues analysis:

The crystal structure of beta secretase (2HIZ) was downloaded from Protein data bank (PDB) **[9]**. This structure was subjected to active site residues analysis. Both Prediction based and literature based proof was considered to find the most potent domain of this A1 peptidase. Molegro virtual docker **[10]** was used to predict active sites in beta secretase and an article entitled "Crystallization and structure determination of glycosylated human beta secretase, an enzyme implicated in alzheimer's disease." [ref] was used to verify the predicted active site cavity.

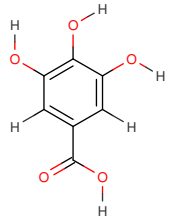
Molecular docking studies and interaction analysis:

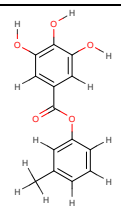
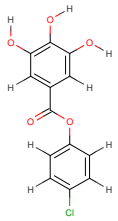
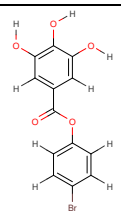
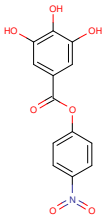
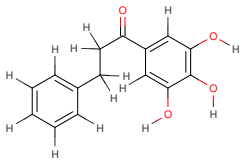
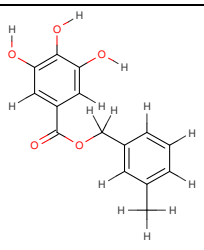
Molegro Virtual docker was used for molecular docking studies. All the ligands from gallic acid deivatives that were used for QSAR studies, were used to screen the selected active site of beta secretase. Based on RMSD, Moldock score and three types of interaction analysis i.e., Hydrogen bond, electrostatic interaction and hydrophobic interaction, the affinity of proposed ligands were ranked and top two ligands were proposed as a potent and natural inhibitor for beta secretase enzyme.

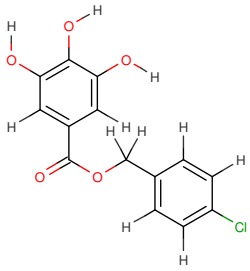
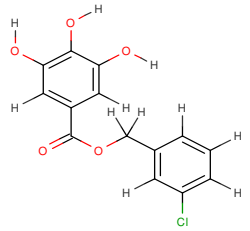
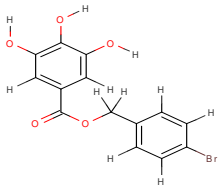
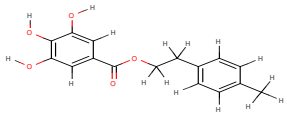
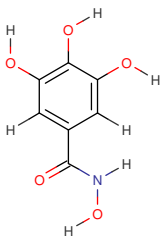
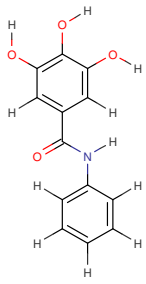
3. Result

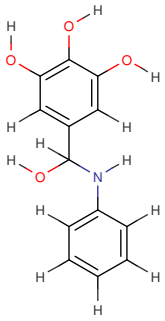
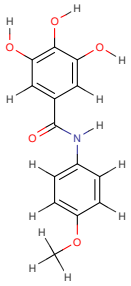
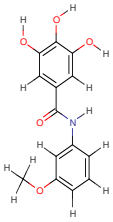
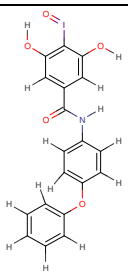
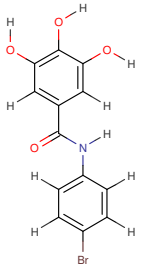
Out of 49 derivatives, only 21 compounds were considered for QSAR model building. **(Table 1)** All compounds were considered as training set. No test set were assigned.

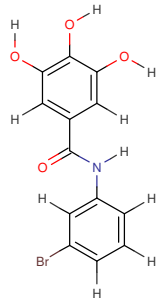
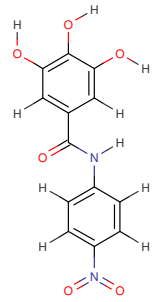
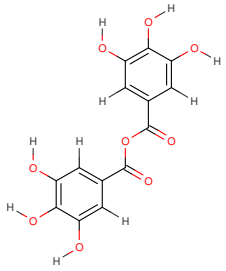
Table1: Structure-Activity of 21 gallic acid derivatives

Compound	**Structure** (gallic acid derivatives)	**Analgesic Activity**(MICROMOL/KG)
A(1)		30.4

B(2)		39.48
C(3)		39.26
D(4)		17.51
E(5)		17.96
F(6)		31.16
G(7)		20.15

H(8)		21.05
I(9)		17.62
J(10)		12.62
K(11)		37.87
L(12)		23.6
M(13)		27.79

N(14)		15.2
O(15)		29.17
P(16)		17.16
Q(17)		11.66
R(18)		11.46

S(19)		11.24
T(20)		14.28
U(21)		14.23

The following descriptors were best correlating with biological activity:

[H1e] - H autocorrelation of lag 1 weighted by atomic Sanderson electronegativities.
[RDF080m] -Radial Distribution Function - 8 weighted by atomic masses.
[H6m] -H autocorrelation of lag 6 weighted by atomic masses.
[GGI7] - topological charge index of order 7.
All these descriptors are 3D descriptors (such as, for example, 3D-MoRSE descriptors, WHIM descriptors, GETAWAY descriptors, quantum-chemical descriptors, size, steric, surface and volume descriptors)

On considering all these four descriptors, QSAR model with combination of H1e, RDF080m and H6m were giving best model to predict biological activity of other gallic acid derivatives. On the other side, the combination of addition of GG17 was adding to the predictive ability of QSAR model, Therefore Two model were built with 3 and 4 descriptors combination.

QSAR Model with three best correlated descriptors (Third model):

ID50 (MICROMOL/KG) =138.228 -56.266(±7.811)(H1e)
+4.932(±0.570) (RDF080m) +9.174(±2.264) (H6m)
N=21 R^2=0.822 R^2A=0.799 S.E. =4.29 F=26.25
Cross Validated R^2=0.678

Table 2: Regression table for third model

Identifier	Actual ID50(micromole/kg)	Predicted ID50(micromole/kg))	Standard Error
Molecule 0	30.4	31.242846	2.808154
Molecule 1	39.48	37.243	3.136649
Molecule 2	39.26	40.263668	2.471943
Molecule 3	17.51	11.131079	2.167675
Molecule 4	17.96	20.306305	0.991691
Molecule 5	31.16	24.911776	1.127495
Molecule 6	20.15	24.503511	1.074339
Molecule 7	21.05	19.300695	1.038736
Molecule 8	17.62	18.44808	1.547177
Molecule 9	12.62	20.168905	0.975231
Molecule 10	37.87	35.263847	3.812829
Molecule 11	23.6	22.031733	0.996928
Molecule 12	27.79	26.798569	1.264356
Molecule 13	15.2	14.387059	2.321131
Molecule 14	29.17	25.130392	1.354378
Molecule 15	17.16	17.517506	1.177181
Molecule 16	11.66	19.106829	1.361958
Molecule 17	11.46	13.954358	1.642515
Molecule 18	11.24	13.429987	1.427232
Molecule 19	14.28	8.167043	1.835055
Molecule 20	14.23	17.562872	1.343545

The graph (Figure 1) is linear and not scattered; it implied the power of prediction is good.

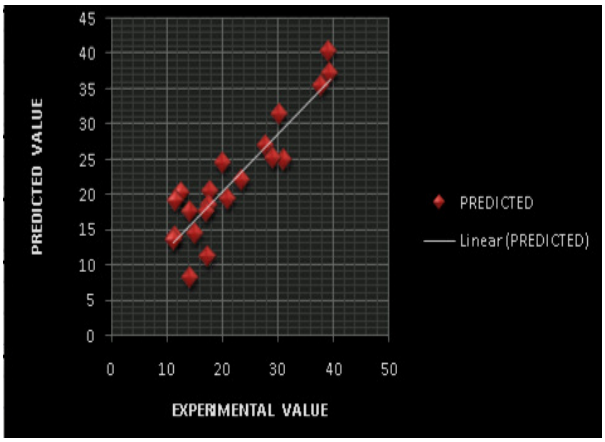


Figure 1: Graph showing third model predictive ability.

Leverage status is OK for most of the predictions. (Table 3)

\

Table3: Validation: MLR Diagnostics of third model

Id	ID50(micromole/kg)	Predicted	S.E.	Ordinary Residuals	Jack-Knifed Residuals	Leverage	Leverage Status
Molecule 0	30.4	31.24285	2.808154	-0.84285	-0.25228	0.427025	HIGH
Molecule 1	39.48	37.243	3.136649	2.237	0.752329	0.532774	HIGH
Molecule 2	39.26	40.26367	2.471943	-1.00367	-0.27811	0.330893	OK
Molecule 3	17.51	11.13108	2.167675	6.378922	1.827465	0.254448	OK
Molecule 4	17.96	20.30631	0.991691	-2.34631	-0.55017	0.053255	OK
Molecule 5	31.16	24.91178	1.127495	6.248224	1.566446	0.06884	OK
Molecule 6	20.15	24.50351	1.074339	-4.35351	-1.04924	0.062502	OK
Molecule 7	21.05	19.3007	1.038736	1.749304	0.4097	0.058428	OK
Molecule 8	17.62	18.44808	1.547177	-0.82808	-0.20097	0.129626	OK
Molecule 9	12.62	20.16891	0.975231	-7.54891	-1.93665	0.051502	OK
Molecule 10	37.87	35.26385	3.812829	2.606152	1.34391	0.787237	HIGH
Molecule 11	23.6	22.03173	0.996928	1.568268	0.366043	0.053819	OK
Molecule 12	27.79	26.79857	1.264356	0.991432	0.234975	0.086566	OK
Molecule 13	15.2	14.38706	2.321131	0.812941	0.218761	0.291749	OK
Molecule 14	29.17	25.13059	1.354378	4.039608	0.989969	0.099332	OK
Molecule 15	17.16	17.51751	1.177181	-0.35751	-0.08408	0.075041	OK
Molecule 16	11.66	19.10683	1.361958	-7.44683	-1.96742	0.100447	OK
Molecule 17	11.46	13.95436	1.642515	-2.49436	-0.61725	0.146093	OK
Molecule 18	11.24	13.42999	1.427232	-2.18999	-0.52938	0.110306	OK
Molecule 19	14.28	8.167043	1.835055	6.112957	1.64619	0.182351	OK
Molecule 20	14.23	17.56287	1.343545	-3.33287	-0.80862	0.09775	OK

QSAR Model with four best correlated descriptors (fourth model):

ID50 (MICROMOL/KG) =101.544 -35.452(±8.940)(H1e)
+5.609(±0.570) (RDF080m) +11.366(±1.931) (H6m)-48.907(±15.029) (GGI7)
N=21 R^2=0.893 R^2A=0.866 S.E. =3.436 F=33.450
Cross Validated R^2=0.826

Table 4: Regression table for third model

Identifier	Actual ID50(micromole/kg)	Predicted-ID50(micromole/kg))	Standard Error
Molecule 0	30.4	31.522116	2.246998
Molecule 1	39.48	40.811497	2.737265
Molecule 2	39.26	38.65903	2.037107
Molecule 3	17.51	17.087208	2.520715
Molecule 4	17.96	20.21786	0.793407
Molecule 5	31.16	27.765854	1.257754
Molecule 6	20.15	19.096748	1.870386
Molecule 7	21.05	18.839857	0.842543
Molecule 8	17.62	17.169989	1.297946
Molecule 9	12.62	17.210522	1.197702
Molecule 10	37.87	38.687008	3.225053
Molecule 11	23.6	21.386591	0.82141
Molecule 12	27.79	24.010975	1.325069
Molecule 13	15.2	15.365001	1.880115
Molecule 14	29.17	25.172848	1.083019
Molecule 15	17.16	15.83926	1.073275
Molecule 16	11.66	18.166601	1.126677
Molecule 17	11.46	13.283099	1.32943
Molecule 18	11.24	13.518935	1.141521
Molecule 19	14.28	8.458354	1.470011
Molecule 20	14.23	18.600592	1.120608

The graph (Figure 2) is linear and not scattered; it implied the power of prediction is good as compared to figure 1.

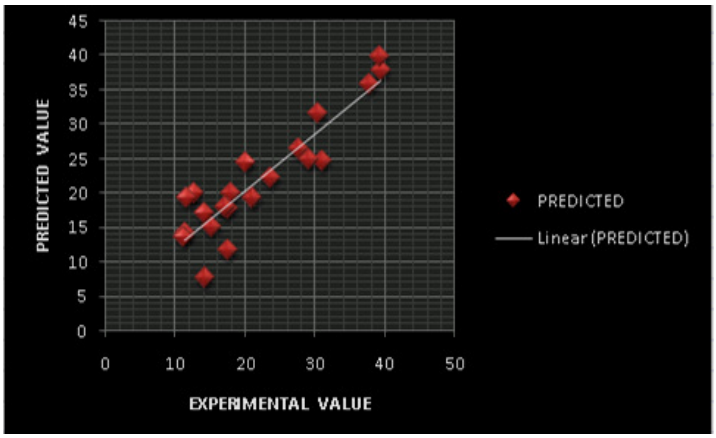


Figure 2: Graph showing fourth model predictive ability.
In fourth model also Leverage status is OK for most of the predictions. (Table 5)

Table5: Validation: MLR Diagnostics of fourth model

Id	ID50(micromole/kg)	Predicted	S.E.	Ordinary Residuals	Jack-Knifed Residuals	Leverage	Leverage Status
Molecule 0	30.4	31.52212	2.246998	-1.12212	-0.42109	0.427648	OK
Molecule 1	39.48	40.8115	2.737265	-1.3315	-0.62959	0.634622	HIGH
Molecule 2	39.26	38.65903	2.037107	0.600967	0.210995	0.351487	OK
Molecule 3	17.51	17.08721	2.520715	0.422792	0.175828	0.538182	HIGH
Molecule 4	17.96	20.21786	0.793407	-2.25786	-0.66417	0.053318	OK
Molecule 5	31.16	27.76585	1.257754	3.394146	1.065704	0.13399	OK
Molecule 6	20.15	19.09675	1.870386	1.053251	0.355901	0.296309	OK
Molecule 7	21.05	18.83986	0.842543	2.210142	0.652167	0.060126	OK
Molecule 8	17.62	17.16999	1.297946	0.450012	0.137305	0.14269	OK
Molecule 9	12.62	17.21052	1.197702	-4.59052	-1.47369	0.121501	OK
Molecule 10	37.87	38.68701	3.225053	-0.81701	-0.67812	0.880958	HIGH
Molecule 11	23.6	21.38659	0.82141	2.213409	0.652097	0.057148	OK
Molecule 12	27.79	24.01098	1.325069	3.779026	1.208015	0.148716	OK
Molecule 13	15.2	15.365	1.880115	-0.165	-0.05566	0.299399	OK
Molecule 14	29.17	25.17285	1.083019	3.997152	1.245496	0.099347	OK
Molecule 15	17.16	15.83926	1.073275	1.32074	0.394446	0.097567	OK
Molecule 16	11.66	18.1666	1.126677	-6.5066	-2.22526	0.107518	OK
Molecule 17	11.46	13.2831	1.32943	-1.8231	-0.56373	0.149697	OK
Molecule 18	11.24	13.51894	1.141521	-2.27894	-0.69233	0.11037	OK
Molecule 19	14.28	8.458354	1.470011	5.821646	2.041726	0.18303	OK
Molecule 20	14.23	18.60059	1.120608	-4.37059	-1.38098	0.106363	OK

DOCKING RESULTS:

Active site Residues with 10 angstrom of inhibitor binding site from beta secretase (PDBID: 2HIZ) are following:

ARG 7 TYR 71 LEU 121 THR 232 GLY 8 THR 72 ALA 122 ASN 233 LYS 9 GLN 73 TYR 123 LEU 234 SER 10 GLY 74 ALA 124 ARG 235 GLY 11 LYS 75 GLU 125 ARG 307 GLN 12 TRP 76 ILE 126 PHE 322 GLY 13 GLU 77 ALA 127 ALA 323 TYR 14 ILE 102 ARG 128 ILE

324 TYR 15 SER 105 PRO 129 SER 325 ILE 29 ASP 106 LEU 154 GLN 326 LEU 30 LYS 107 TRP 197 SER 327 VAL 31 PHE 108 TYR 198 SER 328 ASP 32 PHE 109 TYR 199 THR 329 THR 33 ILE 110 ASP 223 GLY 330 GLY 34 ASN 111 LYS 224 THR 331 SER 35 SER 113 SER 225 VAL 332 SER 36 TRP 115 ILE 226 MET 333 ASN 37 GLU 116 VAL 227 GLY 334 ALA 39 GLY 117 ASP 228 ALA 335 TYR 68 ILE 118 SER 229 VAL 336 VAL 69 LEU 119 GLY 230 MET 338 PRO 70 GLY 120 THR 231 GLU 339

All the 21 ligands were checked for scoring function and space search in terms of MDS and RMSD respectively. Least MDS with less RMSD is supposed to be good for docking. Torsion represents the number of rotation a ligand can do. (Table 6)

Table6: RMSD, MDS and torsion of 21 ligands

S.No.	Ligand	MDS(Grid)	MDS	ReRank score	RMSD	TORSION
1	A	-93.08	-86.01	-64.77	0.01	1
2	B	-117.52	-112.43	-88.20	0.193	3
3	C	-112.62	-107.68	-77.42	0.382	3
4	D	-119.72	-110.29	-83.05	1.11	3
5	E	-104.027	-91.55	-83.51	0.95	4
6	F	-118.33	-114.16	-87.15	1.96	4
7	G	-127.46	-125.09	-99.11	1.01	4
8	H	-118.13	-116.78	-90.69	0.72	4
9	I	-123.08	-117.88	-91.39	0.58	4
10	J	-111.53	-109.71	-85.97	0.51	4
11	K	-124.12	-126.5	-97.3	0.08	5
12	L	-97.93	-87.77	-62.14	0.129	1
13	M	-99.22	-93.23	-74.14	0.122	2
14	N	-112.73	-107.11	-76.01	1.84	2
15	O	-107.96	-103.09	-76.5	0.74	3
16	P	-110.95	-107.3	-80.18	0.85	3
17	Q	-107.48	-99.75	-80.23	0.46	5
18	R	-92.49	-92.49	-57.51	0.22	2
19	S	--111.11	-105.14	--76.84	0.97	2
20	T	-124.23	-105.38	-82.06	0.97	3
21	U	-140.02	-129.32	-92.23	1.15	4

BEST MOLECULES:

Table7: RMSD, MDS and torsion of best 5 ligands

S.No.	Ligand	MDS(Grid)	MDS	ReRank score	RMSD	TORSION
1	B	-117.52	-112.43	-88.20	0.193	3
2	C	-112.62	-107.68	-77.42	0.382	3
3	L	-97.93	-87.77	-62.14	0.129	1
4	M	-99.22	-93.23	-74.14	0.122	2
5	R	-92.49	-92.49	-57.51	0.22	2

Based on Least energy and less RMSD, two molecules was proposed to be the most potent inhibitor of beta secretase enzyme. Molecule B and Molecule C must be checked preclinically and clinically to support this work. (Table 8)

Table8: RMSD, MDS and torsion of best two ligands

S.No.	Ligand	MDS(Grid)	MDS	ReRank score	RMSD	TORSION
1	B	-117.52	-112.43	-88.20	0.193	3
2	C	-112.62	-107.68	-77.42	0.382	3

POSES AND INTERACTIONS:

Hydrogen bond, Electrostatic and Hydrophobic interactions are shown in Fig3-fig8.

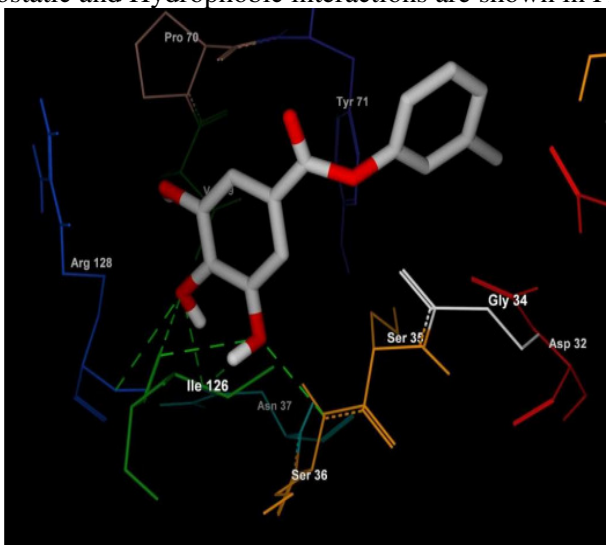


Figure3: H-bond (ligand B-2HIZ)

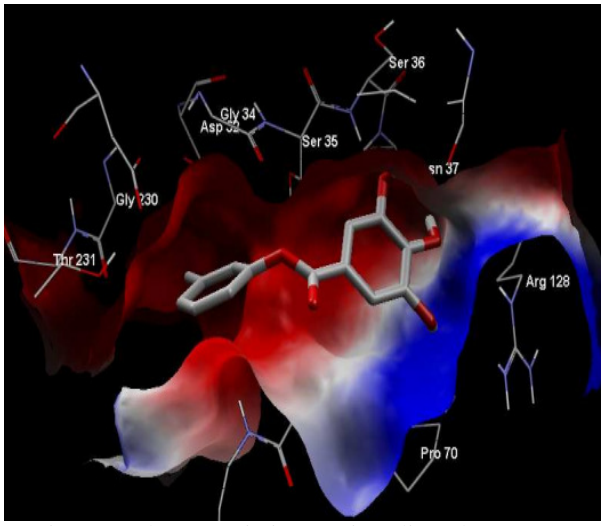


Figure4: Electrostatic interaction (ligand B-2HIZ)

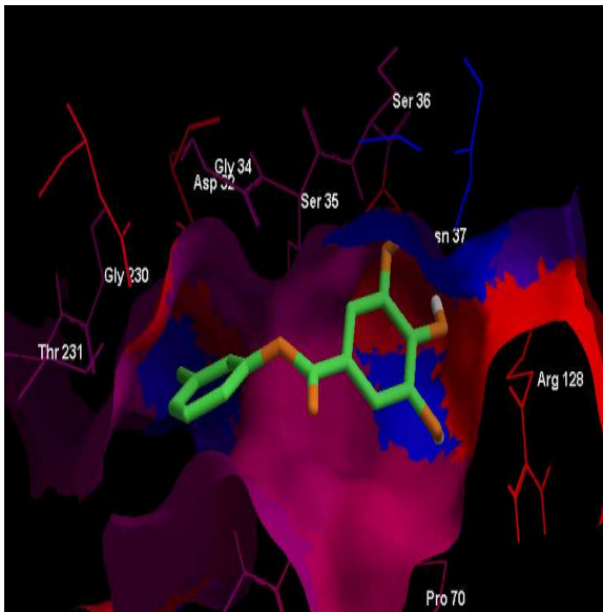


Figure5: Hydrophobic interaction (ligand B-2HIZ)

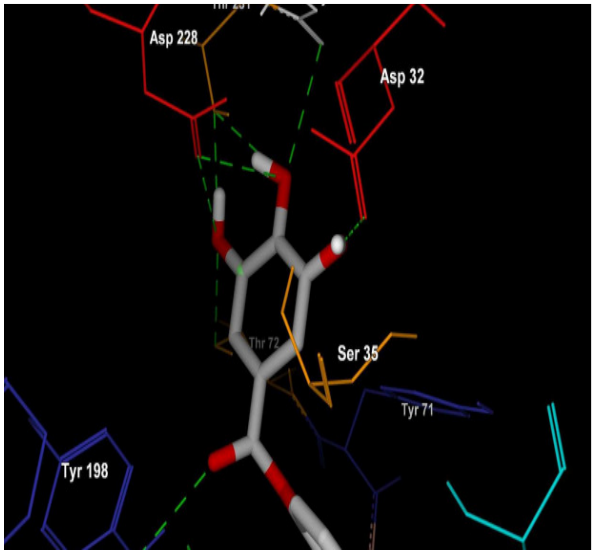


Figure6: H-bond (ligand C-2HIZ)

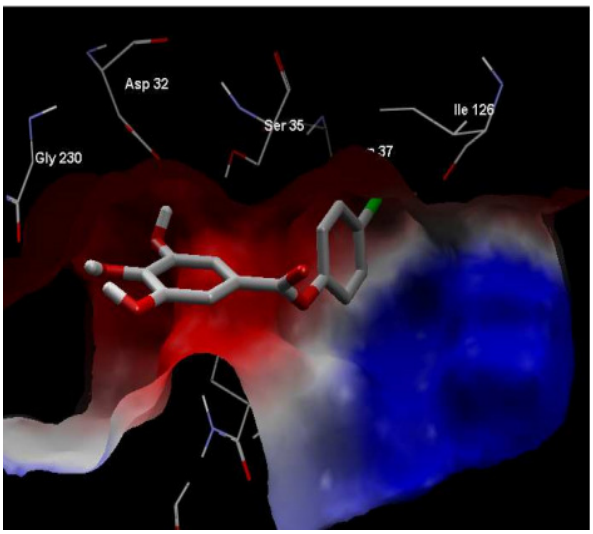


Figure7: Electrostatic interaction (ligand C-2HIZ)

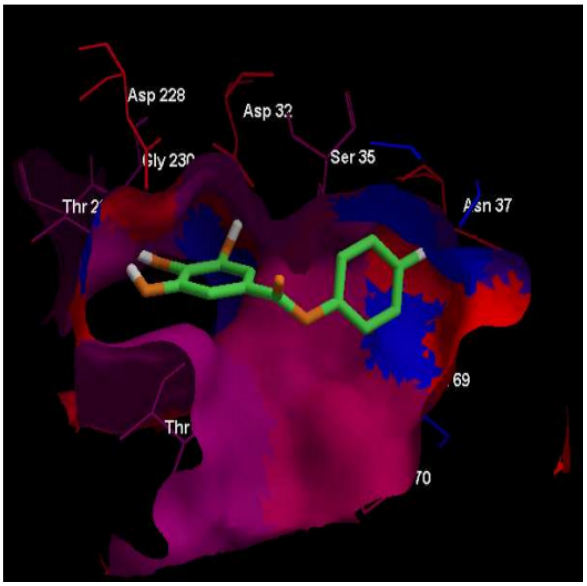


Figure8: Hydrophobic interaction (ligand C-2HIZ)

4. Discussion

All the models from univaraint to tetravariable descriptors with their corresponding regression coefficients r^2 and adjusted r^2, standard error along with their F values etc. are given in table. Results show progressive improvement in the r^2 and decrease in the standard error. This indicates addition of another descriptor to each model brings positive effect in the modeling criteria.

As the best two models of Gallic acid derivative's activity show high values of r^2 0.822, and 0.893 respectively. Thus both models should be used for prediction of activity in this QSAR studies. Each model is studied with taking account on their F value, t- test, and over most errors for each coefficient used in the model. Hence finally we have chosen both models with

descriptors 3 and 4 for the QSAR of Gallic acid derivatives to predict their biological activity as shown in table.

Statistically both models are accepted as they satisfy all the parametric requirements for approval. As described earlier these models have got highest r^2 and lowest standard error. F value represents the quality of whole model and it is highest when compared to all models. In both equations it is clear that each coefficient is larger enough to its error to avoid the chances of withdrawal of this model. Using this model the activity has been predicted and shown in tables above. Present QSAR work concludes important criteria for the Gallic acid derivatives as inhibitors with respect to the structure affecting their ID50 activity to inhibit the BACE-1 enzyme which is a prime target for Alzheimer. Lower activity of established drugs form market and higher side effect profile is considered the base of search of new candidates of desired activity with lower side effect profile. Thereafter search of lead molecule for BACE-1 Inhibition is in progress and many research groups have made it target of their work. Organic synthesis of molecules and their preclinical testing bears high cost on economy of pharmaceutical industries. QSAR studies have always been used by the organic synthesis groups to converge the search of lead molecules as it describes structural features required for increasing activity or decreasing it. Present work has explained the role of different groups and their contribution towards ID50 activity. Researchers synthesizing new derivatives of Gallic acid derivatives may use the information from this work and can work more efficiently and faster the rate of search inhibitors for BACE-1.

3D Structure of Beta Secretase Enzyme (PDB ID 2HIZ) was chosen for carrying out docking studies. A considerable part of population is suffering from Alzheimer and its associated disorders. Present work is an effort to find better BACE-1 Inhibitors, as established drugs for it show lower activity or higher side effects. We have selected a set of 21 molecules which were being used in QSAR studies as Gallic acid derivatives. Docking studies have been an important key step in screening of large data to an active molecule, it also enables us to calculate the interactions out of hydrogen bonding, electrostatics and hydrophobic interactions. Docking accuracy and output of result largely depends on input parameters and is finally decided by RMSD value for the particular candidate. To date there are many docking software present in chemoinformatics community, Such as FlexX, Glide, GOLD, Molegro Virtual Docker. Every Docking tool uses different algorithms for the calculation of interactions and Scoring. Present work output contains best 5 candidates out of 21 molecules; showing appreciable interactions which are listed above in table. Their hydrogen bond, electrostatic and hydrophobic interactions are also shown in diagrams separately. Best candidate obtained in present work is B with RMSD value of 0.195 and score of 117.957. This candidate also shows appreciable interaction as compared to others and amino acids residues present around it find reasonable interactions. The next molecule of favourable activity found is C with RMSD value 0.382 and score 112.62. Both the above molecules are newer than others and showing good possibilities of inhibition of the protein. Following to this molecule there are other 3 molecules showing good RMSD and SCORE they are given in table with their RMSD and corresponding SCORE. Thus these two molecules with structure B and C can be further analyzed using ADMET studies, as these two shows favourable docking capability to protein. This work confines to only docking studies and further studies might favour their ability to inhibit the protein to significance concentrations. Present work can be considered as the first steps towards efforts to find inhibitors for protein BACE-1. Finally this inhibition can provide better health to human being.

5. CONCLUSIONS

As per QSAR model, Researchers synthesizing new derivatives of Gallic acid derivatives may use the information from this work and can work more efficiently and faster the rate of search inhibitors for BACE-1.

Present work can be considered as the first steps towards efforts to find inhibitors for protein BACE-1. Finally this inhibition can provide better health to human being.

ACKNOWLEDGEMENT

This work has been done in Eminent Bioscience, Indore, Madhya Pradesh, INDIA; under the guidance of Dr. Mukesh yadav and Dr. Anuraj Nayarisseri. I am very thankful to both of them for their support and good guidance.

REFERENCES

1. Gosselet F, Saint-Pol J, Candela P, Fenart L.Amyloid-β Peptides, Alzheimer's Disease and the Blood-Brain Barrier.Curr Alzheimer Res. 2013 Oct 23.
2. Musardo S, Marcello E, Gardoni F, Di Luca M.ADAM10 in Synaptic Physiology and Pathology.Neurodegener Dis. 2013 Sep 4.
3. Zhang X, Song W. The role of APP and BACE1 trafficking in APP processing and amyloid-β generation.Alzheimers Res Ther. 2013 Oct 8;5(5):46.
4. Basak SC.Mathematical Descriptors in the Prediction of Property, Bioactivity, and Toxicity of Chemicals from their Structure: A Chemical-Cum-Biochemical Approach.Curr Comput Aided Drug Des. 2013 Oct 21.
5. Weill N, Therrien E, Campagna-Slater V, Moitessier N.Methods for Docking Small Molecules to Macromolecules: A User's Perspective. 1. The Theory.Curr Pharm Des. 2013 Aug 13.
6. Krogh R, Yunes RA, Andricopulo AD.Structure-activity relationships for the analgesic activity of gallic acid derivatives.Farmaco. 2000 Nov-Dec;55(11-12):730-5.
7. Availablefrom:http://www.strandls.com/sarchitect/index.html
8. R.Todeschini and V.Consonni: "Molecular Descriptors for Chemoinformatics", (2 volumes), WILEY-VCH,Weinheim (Germany) 2009, 1257 pp.
9. F.C.Bernstein, T.F.Koetzle, G.J.Williams, E.E.Meyer Jr., M.D.Brice, J.R.Rodgers, O.Kennard, T.Shimanouchi, M.Tasumi, "The Protein Data Bank: A Computer-based Archival File For Macromolecular Structures," J. of. Mol. Biol., 112 (1977): 535.
10. MolDock: A New Technique for High-Accuracy Molecular Docking René Thomsen and Mikael H. Christensen J. Med. Chem., 2006, 49(11), pp 3315 - 3321.

BIOGRAPHIES

Krishna Kant Gupta is pursuing PhD in Bioinformatics from Center for Bioinformatics, Pondicherry University. He received his M.Sc. in Bioinformatics at the Devi Ahilya University, Indore. He is a 2012 passout student at the School of Biotechnology and Bioinformatics subcenter. He is Research trainee at Nthrys Biotech Labs. His research interests include computer aided drug designing, molecular docking studies, protein-protein interaction, epitope design. He is author of a great deal of research studies published at national and international journals.