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QSAR STUDIES & DESIGNING OF POTENT HETEROCYCLIC COMPOUNDS AS γ-*SECRETASE* INHIBITORS

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ABSTRACT

Quantitative structure activity relationship (QSAR) studies ware performed on series of structurally similar heterocyclic sulfonamide with enzyme gamma secretase inhibitor activity. The compounds were divided into training and test set and generated different QSAR models using V-Life MDS 3.5 software multiple linear regression (MLR) method. Best QSAR models were selected on the basis of various statistical parameters like square correlation coefficient (r2), cross validated square correlation coefficient (q2), pred_r2, standard error of estimation (SE) and sequential Failure test (F). 2D QSAR study reveals that gamma secretase inhibitor activity is governed by physicochemical Alignment Independent (AI) descriptors and design new compounds, with more potent activity. The best models were found to be Model–I model-II and model-III. Model-I having 5 descriptors, r^2 = 0.8582, q^2 = 0.5701, Failure test = 22.9812 and predicted r^2 = 0.7513. Model-II having 4 descriptors, r^2 = 0.8170, q^2 = 0.6780, Failure test = 18.9765 and predicted r^2 = 0.6193. Model-III having 4 descriptors, r^2 = 0.8248, q^2 = 0.7006, Failure test = 20.0027 and predicted r^2 = 0.7791. On the basis of 2D descriptors we designed many compounds in which compound J49 have the highest potency (EC_{50} = 0.010 nM) in the design molecules as well as reported series.

INTRODUCTION: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized pathologically neuronal loss, synaptic damage, loss of cholinergic activity in susceptible brain regions and abnormal deposits of insoluble extracellular plaques composed of β-amyloid peptides and intracellular neurofibrillary tangles composed of hyper-phosphorylated tau protein in the brain [1-11].

Aβ peptides are released by sequential cleavage of the amyloid precursor protein (APP) in the amyloidogenic pathway by the action of two proteolytic membrane associated aspartic proteases. Firstly, β-*secretase* (BACE; β-amyloid precursor protein converting enzyme) cleaves amyloid precursor protein (APP) to form β-C-terminal fragment (β-CTF) and then γ-*secretase* cleaves β-CTF to form Aβ ($Aβ_{40}$ and $Aβ_{42}$) peptides and the cytosolic amyloid precursor protein intracellular domain (AICD) [12-17].

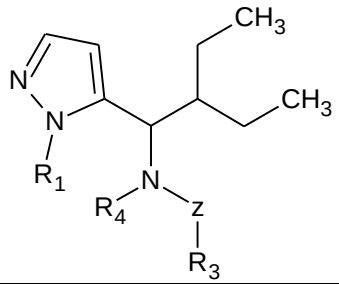
γ-*secretase* is a membrane-embedded multiprotein complex consisting of at least four components; the Presenilin (PS) heterodimer, Nicastrin, Anterior Pharynx Defective (APH-1) and Presenilin Enhancer-2 (PEN-2) [18]. Another reasons for Alzheimer disease includes destruction of cholinergic neuron due to oxidative stress and or decrease in level of choline acetyl transferase [19], genetic mutations.

APP is cleaved by α or β-*secretase* followed by γ-*secretase* to release P3 or Aβ peptides, respectively. Since β-*secretase* and γ-*secretase* are responsible for the production of amyloid peptide (Aβ), which is believed to play a central role in the neuropathology of Alzheimer's disease [20, 21]. There is an urgent need to design γ-*secretase* inhibitors with higher bioactivities and also need to analyze the correlation between gamma secretase inhibitors activity and physico-chemical parameters of each category of compounds using the Quantitative Structure Activity Relationship (QSAR) methods because the quantitative analysis of such molecules can be utilized for increasing the potency and minimizing the side effects.

MATERIALS AND METHODS: QSAR studies and designing were performed on a computer using the software VLifeMDS 3.5 (V-life sciences technology Pvt. Ltd. Pune, India). For the QSAR studies a series of 47 compounds based heterocyclic sulfonamide was selected in which 36 compounds having definite γ-*secretase* inhibitory activity [1]. The biological activity log ($1/EC_{50}$ or $-\log EC_{50}$) was calculated, subsequently used as dependent variable for the QSAR studies. The structure of the compounds with new code and biological activity was shown in **table 1** (**1a, 1b and 1c**).

TABLE 1: LIST OF COMPOUNDS USED FOR THE QSAR STUDIES OF γ-*SECRETASE* INHIBITOR ACTIVITY

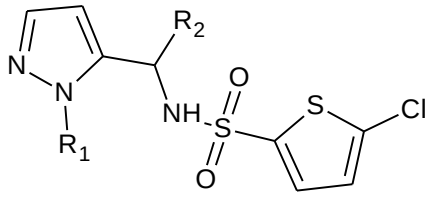
TABLE 1a



Code	R_1	R_3	R_4	Z	$A\beta_{40}$ EC_{50} (μM)	-log EC_{50}
J01	H	5-Cl-Thiophene	H	SO_2	19.49	-1.2898
J02*	4-OMe-benzyl	5-Cl-Thiophene	H	SO_2	0.13	0.8860
J03	Butyl	5-Cl-Thiophene	H	SO_2	1.0	0
J04	4-Me-$PhSO_2$	5-Cl-Thiophene	H	SO_2	1.68	-0.2253
J05	Phenyl	5-Cl-Thiophene	H	SO_2	1.62	-0.2095
J06	4-OMe-benzyl	4-Cl-Benzene	H	SO_2	1.98	-0.2966
J07	4-OMe-benzyl	4-Br-Benzene	H	SO_2	2.27	-0.3560
J08	Phenyl	4-Cl-Benzene	H	SO_2	22.97	-1.3611
J09**	Phenyl	4-CN-Benzene	H	SO_2	85.24	-1.9306
J10	Phenyl	3,4-Di-Cl-Benzene	H	SO_2	25.51	-1.4067
J11	4-OMe-benzyl	4-Cl-Benzene	H	CO	42.36	-1.6269
J12	Phenyl	5-Br-Thiophene	H	SO_2	1.53	-0.1846
J13	Phenyl	4,5-Di-Cl-Thiophene	H	SO_2	13.36	-1.1258
J14	Phenyl	5-Cl-Thiophene	CH_3	SO_2	70.15	-1.8460
J15	Phenyl	5-Br-Thiophene	CH_3	SO_2	65.12	-1.8137

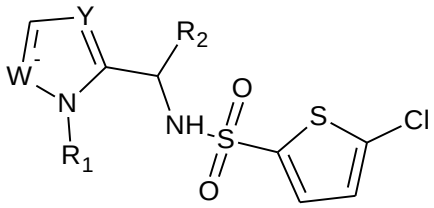
The * compound code indicate the potent where as ****** on the compound code indicates the worst activity.

Table 1b



Code	R_1	R_2	$A\beta_{40}$ EC_{50}(μM)	-log EC_{50}
J16	4-OMe-benzyl	CH_3	1.2	-0.0791
J17	4-OMe-benzyl	$CH_2CH_2CH_3$	0.93	0.0315
J18	4-OMe-benzyl	$CH(CH_3)_2$	0.41	0.3872
J19	Phenyl	$CH(CH_3)_2$	1.12	-0.0492
J20	4-Me-phenyl	$CH(CH_3)_2$	0.42	0.3767
J21	3-Me-phenyl	$CH(CH_3)_2$	2.53	-0.4031
J22	4-F-phenyl	$CH(CH_3)_2$	2.76	-0.4409
J23	4-CF_3-phenyl	$CH(CH_2CH_3)_2$	2.19	-0.3404
J24	4-OMe-phenyl	$CH(CH_2CH_3)_2$	1.56	-0.1931
J25	4-OH-benzyl	$CH(CH_2CH_3)_2$	0.14	0.8538
J26	4-OH-phenyl	$CH(CH_2CH_3)_2$	0.63	0.2006

Table 1c



Code	W	Y	R_1	R_2	$A\beta_{40}$ EC_{50} (μM)	-log EC_{50}
J27	CH	N	4-OMe-benzyl	$CH(CH_2CH_3)_2$	50.63	-1.7044
J28	CH	N	Benzyl	$CH(CH_2CH_3)_2$	19.4	-1.2878
J29	CH	CH	4-OMe-benzyl	$CH(CH_3)_2$	13.32	-1.1245
J30	N	N	4-OMe-benzyl	$CH(CH_2CH_3)_2$	0.94	0.0268
J31	N	N	Benzyl	$CH(CH_2CH_3)_2$	1.01	-0.0043
J32	N	N	4-Me-benzyl	$CH(CH_2CH_3)_2$	0.88	0.0555
J33	N	N	4-OCF_3-benzyl	$CH(CH_2CH_3)_2$	0.99	0.0043
J34	N	N	4-F-benzyl	$CH(CH_2CH_3)_2$	0.48	0.3187
J35	N	N	Benzyl	$CH(CH_3)_2$	3.36	-0.5263
J36	N	N	4-Me-benzyl	$CH(CH_3)_2$	2.89	-0.4608

Draw the 2D and 3D structure: The structure of molecule was drawn in 2D orientation with the help of software ACDLABS chemsketch 12.0 version and save in .mol2 file format. All 2D structures were converted into 3D orientation with the help of software VLifeMDS 3.5 version and save in .mol2 file format.

Energy minimization: Energy minimization [22] is the process of changing the geometry of a structure to reduce its energy. Lower the energy states are of interest because molecules preferentially adopt them. Consequently, they are more indicative of molecular behavior than their high energy neighbors. In many situations it is necessary to know about the thermodynamic properties like enthalpies, entropy, free energy and forces between atoms. The energies and optimized geometries of a molecule can calculate by using different force field and quantum mechanical methods. The force field method is to provide information about molecular structure, interaction between atoms in a molecule. The mathematical formulation of a typical molecular mechanics force field which also called the Potential Energy Function (PEF)[23], the potential energy function is a sum of many

individual contributions (energy). It can be divided into bonded (Bond stretching, Angle bending, Torsions, Inversion (out of plane bending)) and non-bonded (Electrostatics, Van der waals forces, Hydrogen bonding) contribution, responsible for intramolecular and intermolecular interaction between atoms. There are many force field methods to calculate the energies and optimized geometries of molecule like universal force field (UFF) [24, 25], Merck molecular force field (MMFF) [26-29].

Selection of Training and Test: The biological data were divided in training and test set. Selection of molecules in the training set and test is a key and important feature of QSAR model. Therefore the care was taken in such a way that biological activities of all compounds in test set lie within the maximum and minimum value range of biological activities of training set of compounds. Generally Manual data selection method used for the selection of training and test.

Variable Selection Method:

Stepwise Forward Backward Method: In stepwise procedure a variable that entered the model in the earlier stages of selection may be deleted at the later stages. The calculations made for inclusion and elimination of variables are the same as forward selection and backward procedures. That is the stepwise method is essentially a forward selection procedure, but at each stage the possibility of deleting a variable, as in backward elimination, is considered. The number of variables retained in the model is based on the levels of significance assumed for inclusion and exclusion of variables from the model [30].

Statistical Method: Regression methods are used to build a QSAR model in the form of a mathematical equation. This equation explains variation of one or more dependent variables (usually activity) in terms of independent variables (descriptors). The regression method (MLR) is the QSAR molecular models that were used to predict and design a compound with best possible inhibitory property.

(i) **Multiple Linear Regressions:** Multiple linear regressions (MLR) are the standard method for multivariate data analysis. This method of regression estimates the values of the regression coefficients by applying least squares curve fitting method. For getting reliable results, dataset having typically 5 times as many data points (molecules) as independent variables (descriptors) is required. The regression equation takes the form-

$$Y = B_1X_1 + B_2X_2 + B_3X_3 + C$$

Where 'Y' is the dependent variable, the 'B' is regression coefficients for corresponding 'X' (independent variable), 'C' is a regression constant or intercept.

The resulted MLR equations could describe the structure activity relationships well. However, due to the co-linearity problem in MLR analysis, we removed the collinear descriptors before MLR model development. Therefore, some information was discarded in MLR analysis [31-37].

(ii) **k-Nearest Neighbor Molecular Field Analysis**: 3D QSAR methods, k-nearest neighbor Molecular Field Analysis (k-NN MFA) [38-41] requires suitable alignment of set of molecules. This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic energies are computed at the lattice points of the grid using methyl probe of charge +1. These interaction energy values at the grid points are considered for relationship generation using k-NN method and utilized as descriptors for obtaining distances within this method. An optimal training and test set can be generated for k-NN method using sphere exclusion method. This algorithm allows constructing training sets covering all descriptor space areas occupied by representative points. It is expected that the predictive ability of QSAR models generally decreases when the dissimilarity level increases. Once the training and test sets are generated, kNN methodology is applied to descriptors generated over grid.

(iii) **k-NN MFA with Stepwise Variable Selection Method:** This method employs the k-NN classification principle combined with the stepwise variable selection procedure for optimization of (i) The number of nearest neighbors (k) used to estimate the activity of each compound (ii) Selection of variables from the original pool of all molecular descriptors (steric and electrostatic field at the lattice points) that are used to calculate

similarities between compounds (i.e. distances in number of variable-dimensional descriptor space).

2D qsar:

Unicolumn Statistic:

RESULT AND DISCUSSION:

TABLE 2: UNICOLUMN STATISTICS OF DIFFERENT MODELS OF γ-SECRETASE INHIBITOR

Model no.	Column name	Average	Max	Min	Std. dev	Sum
1	PEC_{50} training	-0.5247	0.8860	-1.9306	0.8346	-13.1187
	PEC_{50} test	-0.3661	0.3872	-1.8460	0.6236	-4.0267
2	PEC_{50} training	-0.4502	0.8860	-1.8460	0.7984	-9.9055
	PEC_{50} test	-0.0328	0.3872	-0.4608	0.3140	-0.2620
3	PEC_{50} training	-0.3254	0.8860	-1.8460	0.7452	-7.1593
	PEC_{50} test	-0.3760	0.8538	-1.2878	0.6992	-3.0082

In all model the max of training is higher than the test set where as in case of min. the test have high value than the training set. In all models the std. deviation lies in between 0.31 to 0.83.

TABLE 3: CORRELATION MATRIX OF DIFFERENT STRUCTURAL DESCRIPTORS ARISES IN DIFFERENT MODELS

	A	B	C	D	E	F	G	H
A	1.0							
B	-0.0198	1.0						
C	0.1057	-0.1329	1.0					
D	-0.2185	0.5401	-0.2084	1.0				
E	0.3320	0.2262	0.2673	0.3314	1.0			
F	-0.1104	-0.2919	0.6839	-0.3354	-0.3112	1.0		
G	-0.1104	-0.2919	0.6839	-0.3354	-0.3112	1.0	1.0	
H	0.3560	0.0849	0.2087	0.0171	0.3331	-0.2325	-0.2325	1.0

A: SssNHE-index **B:** SaasN(Noxide)E-index **C:** T_2_N_8, **D:** T_C_C_6 **E:** T_C_O_10 **F:** T_N_S_5 **G:** T_N_S_7, **H**:T_N_Cl_8

From the observation table it was seen that few descriptors has strong correlation with each other which has been given in the shaded portion of the table. Descriptor present in the individual model does not show correlation more than 0.5 with each other.

Equations of the various models:

Model-1: PEC50 = 1.0360(± 0.1767) T_N_S_7 + 0.2370(± 0.0247) T_C_O_10 + 0.4611(± 0.1172) SssNHE-index + 1.0235(± 0.2572) T_N_S_5 + 0.4888(± 0.1865) SaasN(Noxide)E-index - 4.8224

Model-2: PEC50 = 0.7344(± 0.1186) T_2_N_8 + 0.6448(± 0.0955) SssNHE-index - 0.6067(± 0.1696) T_N_Cl_8 + 0.0461(± 0.0093) T_C_C_6 - 4.2055

Model-3: PEC50 = 0.5697(± 0.0861) SssNHE-index + 0.7168(± 0.1340) T_2_N_8 - 0.4370 (± 0.1400) T_N_Cl_8 + 0.5140(± 0.1773) SaasN(Noxide)E-index - 4.0313

Importance of Descriptor:

SssNHE-index: - Electrotopological state indices for number of –NH group connected with two single bonds.

SaasN(Noxide)E-index:- Electrotopological state indices for number of nitro-oxide group connected with two aromatic and one single bond.

T_N_S_7:- This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any sulphur atom (single double or triple bonded) by 7 bonds in a molecule.

T_N_S_5:- This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any sulphur atom (single double or triple bonded) by 5 bonds in a molecule.

T_N_Cl_8:- This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any chlorine atom (single double or triple bonded) by 8 bonds in a molecule.

T_2_N_8:- This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from Nitrogen atom by 8 bonds.

T_C_O_10:- This is the count of number of Carbon atoms (single double or triple bonded) separated from

any Oxygen atom (single or double bonded) by 10 bonds distance in a molecule.

T_C_C_6:- This is the count of number of Carbon atoms (single double or triple bonded) separated from any Carbon atom (single or double bonded) by 6 bonds distance in a molecule.

TABLE 4: VALUES OF DIFFERENT PARAMETERS GENERATED IN MODEL DURING 2D QSAR

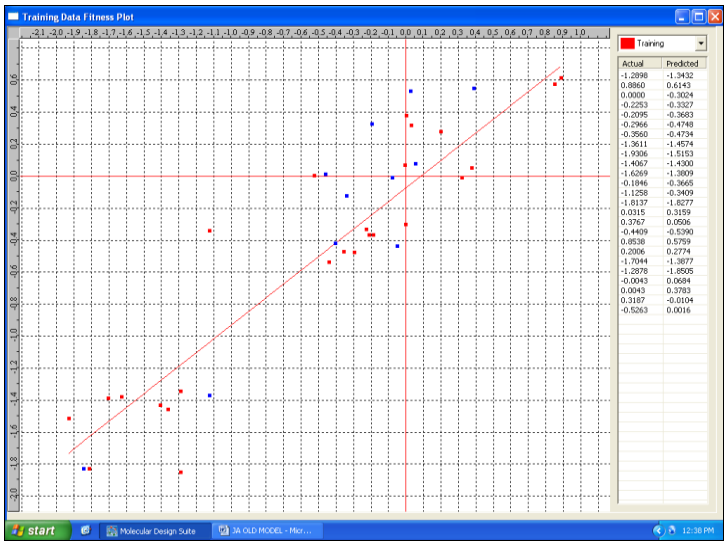
Parameters	MODEL-1	MODEL-2	MODEL-3
N	25	22	22
Degree of freedom	19	17	17
No. of descriptor	5	4	4
r^2	0.8582	0.8170	0.8248
q^2	0.5701	0.6780	0.7006
F test	22.9892	18.9765	20.0027
r2 se	0.3533	0.3796	0.3467
q2 se	0.6151	0.5035	0.4532
pred_r2	0.7513	0.6193	0.7791
pred_r2se	0.3219	0.3367	0.3296

TABLE 5: PREDICATED ACTIVITY OF MODEL-1, 2 AND 3 GENERATED DURING 2D QSAR OF γ-*SECRETASE* INHIBITORS

Code	Actual	Model-1		Model-2		Model-3	
		P	R	P	R	P	R
J01	-1.2898	-1.3431	0.0533	-0.8042	-0.4856	-1.2804	-0.0094
J02	0.886	0.6143	0.2717	0.7090	0.177	0.5092	0.3768
J03	0	-0.3024	0.3024	-0.3070	0.307	-0.1753	0.1753
J04	-0.2253	-0.3327	0.1074	0.4006	-0.6259	-0.0044	-0.2209
J05	-0.2095	-0.3683	0.1588	-0.1729	-0.0366	-0.2451	0.0356
J06	-0.2966	-0.4748	0.1782	-	-	-	-
J07	-0.356	-0.4734	0.1174	-	-	-	-
J08	-1.3611	-1.4574	0.0963	-	-	-	-
J09	-1.9306	-1.5153	-0.4153	-	-	-	-
J10	-1.4067	-1.43	0.0233	-	-	-	-
J11	-1.6269	-1.3809	-0.246	-	-	-	-
J12	-0.1846	-0.3665	0.1819	0.4354	-0.62	0.1939	-0.3785
J13	-1.1258	-0.3408	-0.785	-0.7503	-0.3755	-0.6494	-0.4764
J14	-1.846	-1.8282	-0.0178	-2.144	0.298	-2.0520	0.206
J15	-1.8137	-1.8277	0.014	-1.5372	-0.2765	-1.6144	-0.1993
J16	-0.0791	-0.0098	-0.0693	0.0936	-0.1727	0.3310	-0.4101
J17	0.0315	0.31586	-0.28436	0.4132	-0.3817	0.4360	-0.4045
J18	0.3872	0.5474	-0.1602	0.3661	0.0211	0.4302	-0.043
J19	-0.0492	-0.4351	0.3859	-0.5158	0.4666	-0.3241	0.2749
J20	0.3767	0.0506	0.3261	-0.4623	0.839	-0.3107	0.6874
J21	-0.4031	-0.4182	0.0151	-0.368	-0.0351	-0.3050	-0.0981
J22	-0.4409	-0.5389	0.098	-0.5562	0.1153	-0.4386	-0.0023
J23	-0.3404	-0.1237	-0.2167	-0.2199	-0.1205	-0.4986	0.1582
J24	-0.1931	0.3278	-0.5209	-0.1743	-0.0188	-0.2609	0.0678
J25	0.8538	0.5759	0.2779	0.6441	0.2097	0.4664	0.3874
J26	0.2006	0.2773	-0.0767	-0.1974	0.398	-0.3170	0.5176
J27	-1.7044	-1.3877	-0.3167	-1.3348	-0.3696	-1.3027	-0.4017
J28	-1.2878	-1.8504	0.5626	-1.3798	0.092	-1.2907	0.0029
J29	-1.1245	-1.3713	0.2468	-0.9845	-0.14	-0.8519	-0.2726
J30	0.0268	0.5311	-0.5043	-0.0763	0.1031	-0.0204	0.0472
J31	-0.0043	0.0684	-0.0727	-0.1213	0.117	-0.0084	0.0041
J32	0.0555	0.0771	-0.0216	-0.1154	0.1709	0.0014	0.0541
J33	0.0043	0.3783	-0.374	-0.1462	0.1505	-0.1904	0.1947
J34	0.3187	-0.0103	0.329	-0.1541	0.4728	-0.0956	0.4143
J35	-0.5263	0.0016	-0.5279	-0.4642	-0.0621	-0.0874	-0.4389
J36	-0.4608	0.0103	-0.4711	-0.4583	-0.0025	-0.0775	-0.3833

P: Predicted activity, **R:** Residual. Structure code in bold indicates test set.

Fitness plots (Actual vs. Predicted activity) and contribution chart of different models:



GRAPH 1: FITNESS PLOT OF MODEL-1

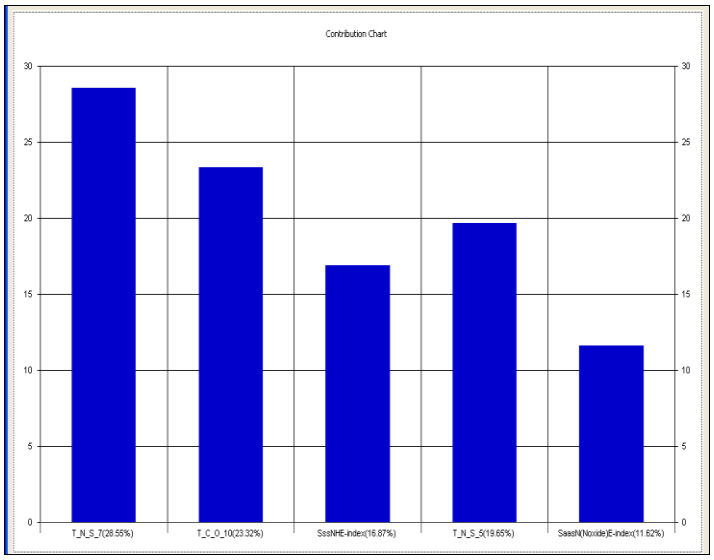
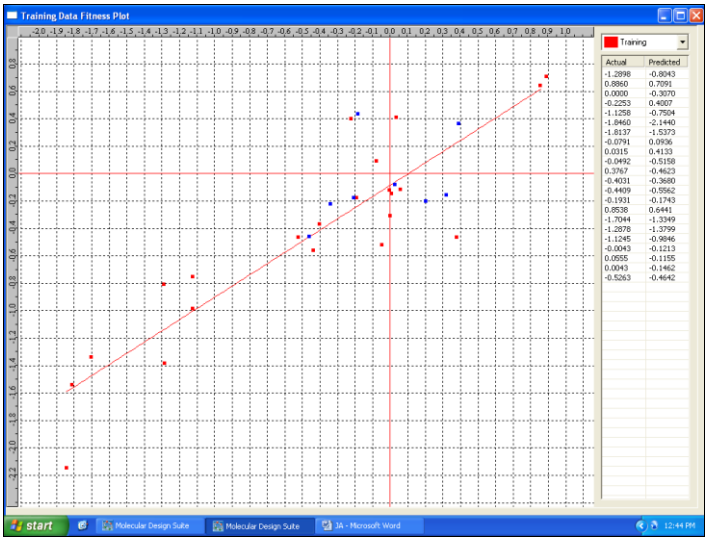


CHART 2: CONTRIBUTION CHART OF MODEL-1



GRAPH 2: FITNESS PLOT OF MODEL-2

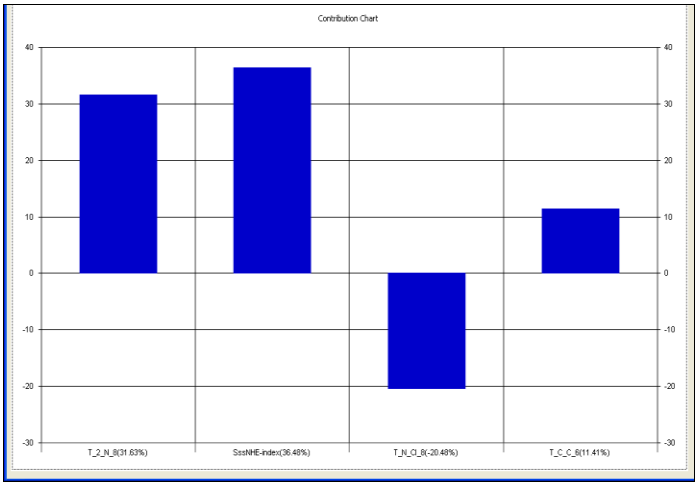
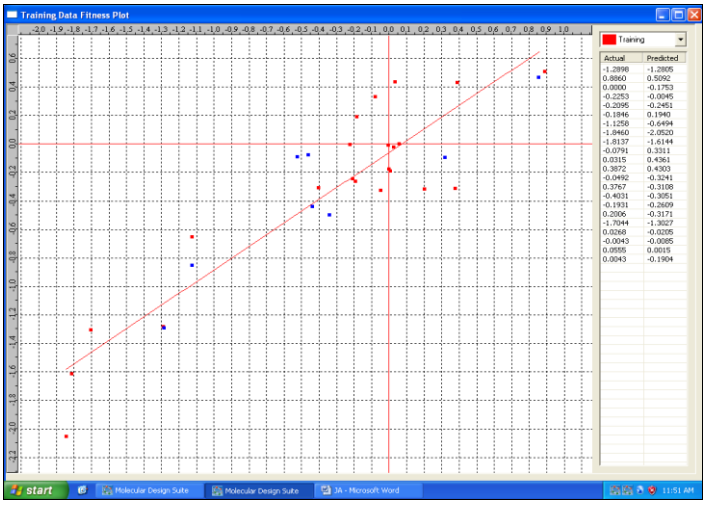


CHART 2: CONTRIBUTION CHART OF MODEL-2



GRAPH 3: FITNESS PLOT OF MODEL-3

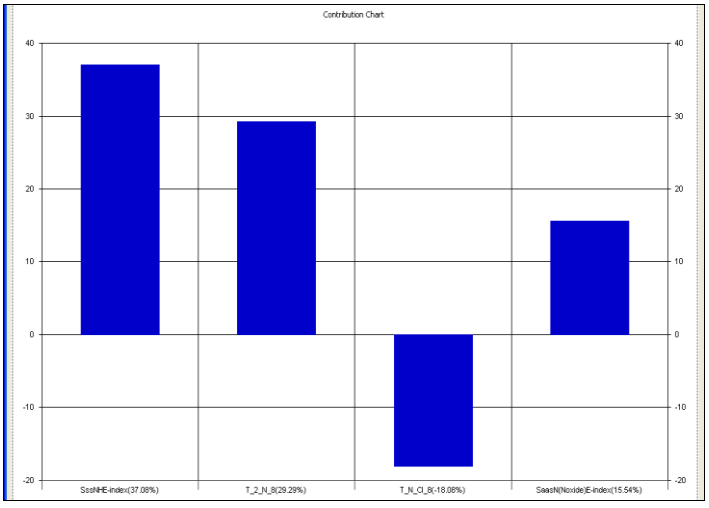


CHART 3: CONTRIBUTION CHART OF MODEL-3

Interpretation of 2D equations: There are many type of descriptor that are found in 2D QSAR but only 4 descriptors are found to be strongly correlated with the biological activity. The common descriptors in 2D QSAR models of heterocyclic sulfonamide are **SssNHE-index**, **T_N_S_7**, **T_N_Cl_8** and **T_2_N_8.**

The remaining descriptors that arise in the equation are SaasN(Noxide)E-index, T_C_O_10, T_N_S_5 and T_C_C_6. It is clear from contribution chart of different 2D models that SssNHE-index, T_N_S_7, T_2_N_8 and T_N_Cl_8 has strong correlation than other descriptors.

The contribution of SssNHE-index in all models is positive means it has positive contribution with the activity. The values of SssNHE-index are 16.87%, 36.48% and 37.08% in model-1, 2 and 3 respectively. This descriptor provides importance of NH groups that are connected with two single bonds. The compound J14 and J15 was not possessing SssNHE-index in the structure and has most poor the biological activity. So increase the NH group or addition of NH group in the molecule will lead to increase in activity.

The contribution of T_N_S_7 descriptor was found to be 28.55% in model-1. The importance of this descriptor was found be presence of nitrogen atom that was separated from sulphur by 7 bonds. In complete series sulphur is present in the thiophene ring and nitrogen present on pyrazole ring. So these nitrogen and sulphur are separated by 7 bonds and contribution is positive that indicates the 7 bonds difference between nitrogen and sulphur is required for the biological activity. Hence, this descriptor (SssNHE-index and T_N_S_7) is used for the designing of the molecule.

3d QSAR:

Alignment of molecule: 30 molecules have been selected for the 3D QSAR studies since structure code J06 to J11 contains phenyl moiety instead of thiophene. Since for 3D QSAR common core is essential. Hence to perform the 3D QSAR 30 molecules has been selected.

From the **figure 1 and 2**, the alignment of thiophene core has been achieved this leads to calculation of descriptors (Electrostatic and steric) from the non-align area of the molecule. The data that was obtained after the alignment of 30 molecules was shown in **table 6.**

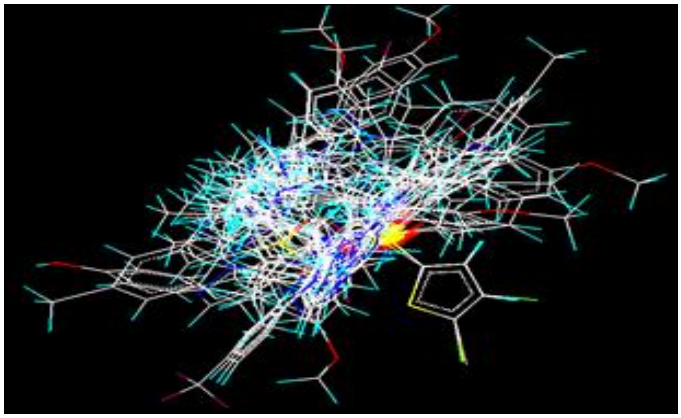


FIG. 1: ALIGNMENT OF THIOPHENE

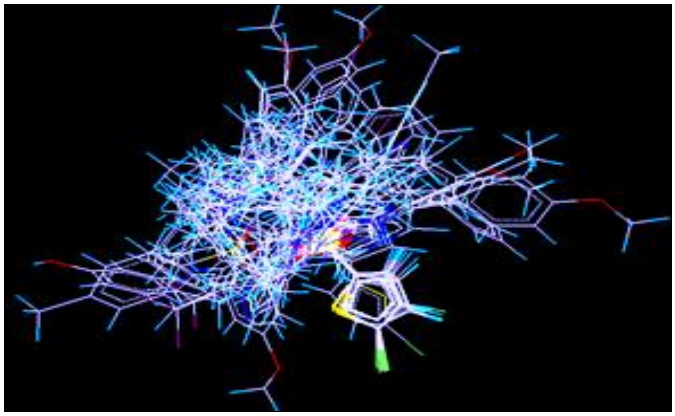


FIG. 2: ALIGNMENT OF THIOPHENE-2-SULPHONAMIDE

TABLE 6: ALIGNMENT RESULTS OF 30 COMPOUNDS BY USING THIOPHENE AND THIOPHENE-2-SULPHONAMIDE AS Γ-*SECRETASE* INHIBITOR

Code	Thiophene-2-sulfonamide	Thiophene	Code	Thiophene-2-sulfonamide	Thiophene
J01	1.200528	0.00818	J22	0.005488	0.00578
J02	0.000000	0.00000	J23	0.177992	0.00364
J03	0.011347	0.00066	J24	0.017762	0.00320
J04	0.007442	0.00398	J25	0.002568	0.00697
J05	0.182285	0.00146	J26	0.006990	0.01044
J12	0.177885	0.00263	J27	1.202394	0.01126
J13	0.200149	0.00176	J28	1.200331	0.01131
J14	1.211016	0.00384	J29	1.198534	0.00221
J15	0.223218	0.00178	J30	1.202672	0.01128
J16	0.003527	0.00685	J31	0.014290	0.01127
J17	0.009706	0.00067	J32	1.203119	0.01136
J18	0.005654	0.00945	J33	0.008491	0.01070
J19	1.197676	0.00280	J34	0.013758	0.03356
J20	1.198508	0.00283	J35	0.010099	0.00141
J21	1.198339	0.00852	J36	0.010206	0.00703

3D model: From hundreds of models that have been the best model that observed is given above. The different descriptors that has arises are: **S_1322** (-0.0565, -0.0192), **S_1871** (-0.3631, -0.1947), **S_1482** (-0.1567, -0.0463) and **S_1704** (-0.0994, -0.0291)

TABLE 7: VALUES OF DIFFERENT PARAMETERS GENERATED IN 3D MODEL

Statistical parameter	Value
k Nearest Neighbor	3
n	22
Degree of freedom	17
q2	0.7958
q2_se	0.3167
Predr2	-0.7822
pred_r2se	1.1252

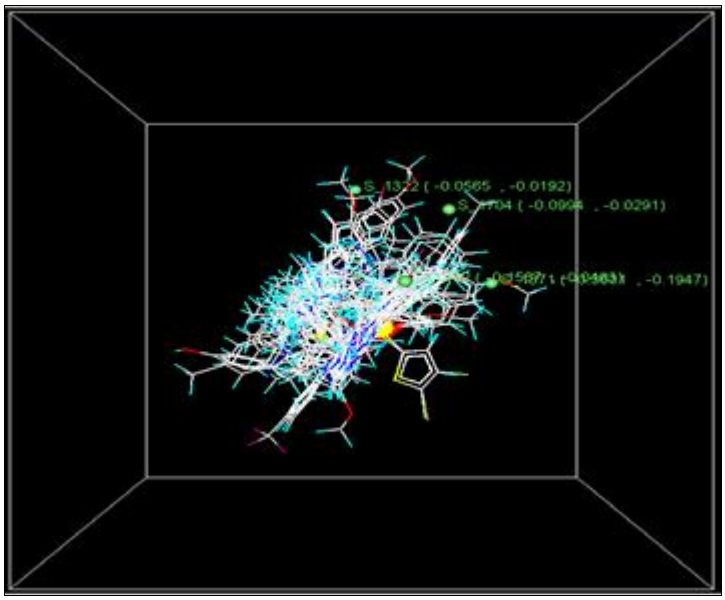
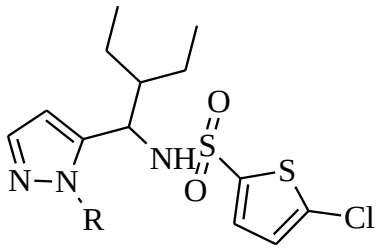


FIG. 3: SHOW POINTS IN A MODEL (3D QSAR)

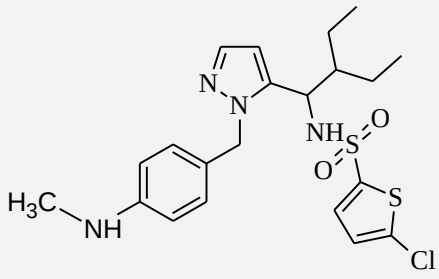
Designing of potent γ-*secretase* inhibitor: On the basis of 2D descriptor SssNHE-index the –NH group is required for the activity in new design compound (**Table 8**). According to positive contribution value of T_C_C_6 is required for activity; means addition of chain length is helpful for activity of new design compound. Other descriptors like T_N_S_7 and SaasN(Noxide)E-index are also responsible for the activity.

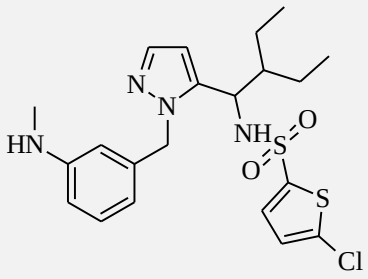
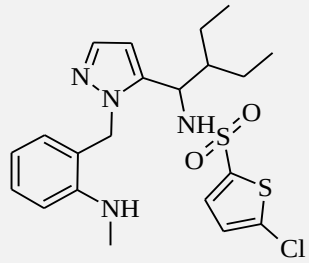
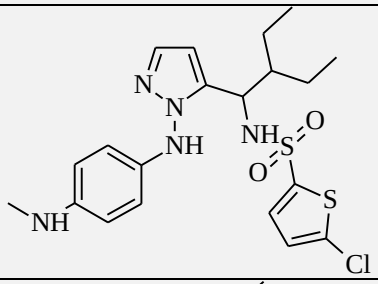
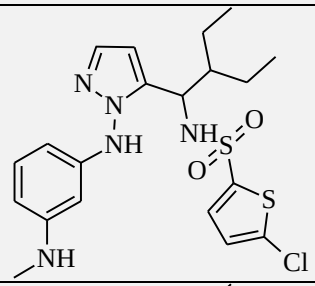
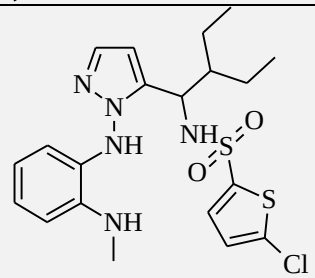
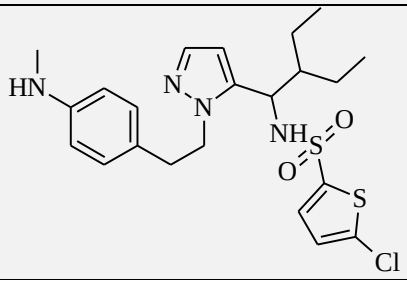
Activity of all designed compound was predicted and compared with respected to the predicted activity of the reported compounds. γ-*secretase* inhibitor of all designed compound was predicted using the best 2D model. The entire new designed compound shows the good to potent activity. Compound J49 show the most potent activity. All the data that was obtained after designing is shown in table 8.

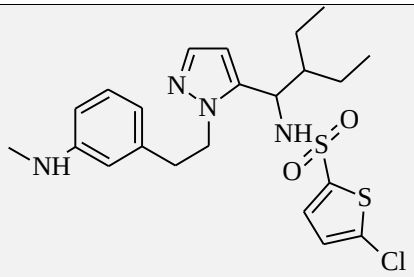
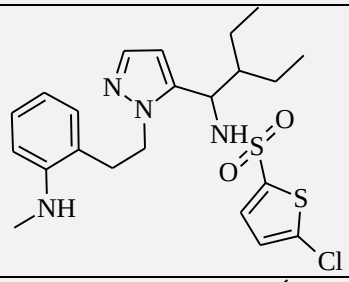
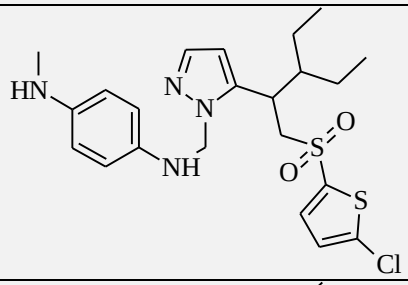
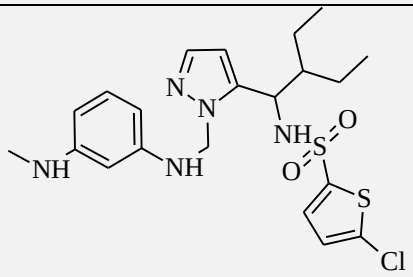
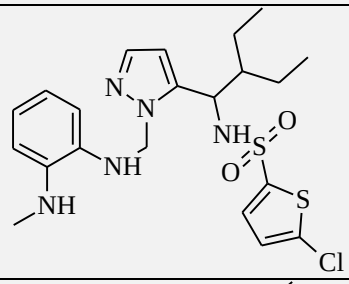
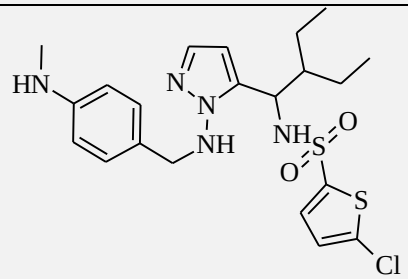


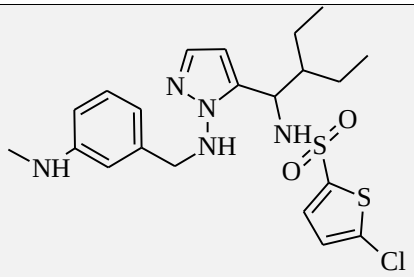
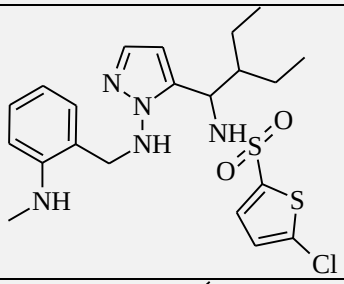
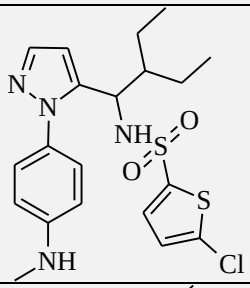
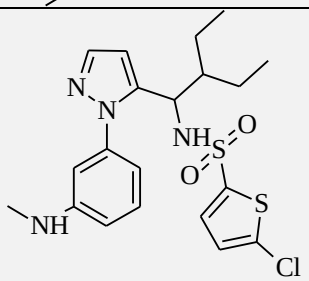
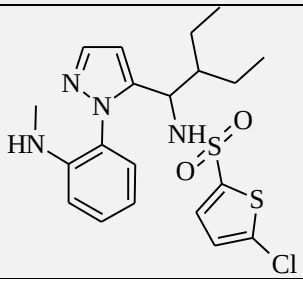
Lead moiety used for designing of potent γ-*secretase* inhibitor

Table 8: Structure of design molecule and predicted activity

Code	Design molecule	Model-1		Model-2	
		-logEC_{50}	EC_{50} (nM)	-logEC_{50}	EC_{50} (nM)
J37		0.144569	741.685	1.527322	29.694

J38		0.162519	687.829	0.007271	983.397
J39		0.674739	211.475	0.847739	141.991
J40		3.58869	0.257	4.928087	0.0118
J41		3.606171	0.247	3.457561	0.348
J42		4.118307	0.0761	4.29791	0.050
J43		0.647446	225.192	1.481278	33.015

J44		0.666031	215.759	1.507313	31.094
J45		0.698107	200.397	0.007085	983.818
J46		2.131273	7.391	4.235511	0.058
J47		2.149388	7.254	4.31107	0.048
J48		2.18138	6.585	2.810724	1.546
J49		4.117798	0.0762	4.969034	**0.010**

J50		4.135973	0.0731	4.944312	0.0113
J51		**4.167579**	**0.0679**	**3.493607**	**0.320**
J52		-0.37792	2387.371	-0.12327	1328.219
J53		0.120179	758.264	0.697376	200.735
J54		0.697602	200.630	2.331775	4.658

Compound in bold indicate most potent compound

CONCLUSIONS: γ-secretase is membrane-bound proteases that process amyloid precursor protein (APP). APP is cleaved by γ-secretase to release Aβ peptides. Since γ-secretase are responsible for the production of amyloid peptide (Aβ), which is believed to play a central role in the neuropathology of Alzheimer's disease (AD). QSAR is a branch of computational chemistry that provides the knowledge structure properties of the molecule and helps to correlate the structural properties and the biological activity via linear regression.

In 2D QSAR studies of heterocyclic sulfonamide different models has been generated. The best three models were found to be Model-1 model-2 and model-3. Model-1 having 5 descriptors, $r^2 = 0.8582$, $q^2 = 0.5701$, Failure test = 22.9892 and predicted $r^2 = 0.7513$. Another model-2 having 4 descriptors, $r^2 = 0.8248$, $q^2 = 0.7006$, Failure test = 20.0027 and predicted $r^2 = 0.7791$. The descriptor that was generated shows that the NH group connected with two single bonds, should as high for good activity.

For designing of potent molecule as γ-secretase inhibitor the suggestion provided are same i.e. increasing NH group (from 2D QSAR) and steric properties (from 3D QSAR). On this basis we have design 18 compounds. For validation of model-2 was found in J49. For validation of model-1 was found in J51. In both structure J49 and J51 we have increase the NH group connected with two single bonds. Structure J49 has the highest potency {EC_{50} = 0.000010 µM **(0.010nM)**} in the design molecule whereas reported series have **(EC_{50} = 0.13 µM)**.

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