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# QSAR STUDIES OF SUBSTITUTED PHENYL SULPHONAMIDE DERIVATIVES AS γ-SECRETASE INHIBITOR

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**Abstract:**

The series of 23 compounds based on substituted phenyl sulphonamide derivatives were used to identify the requirement for the essential features by 2D QSAR. The individual, estate contribution and alignment independent were found to be important descriptors for the building the model. The best model has the coefficient of correlation ($r^2$) of 0.8 with the error of 0.2611.

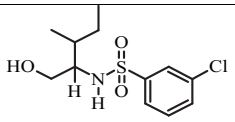
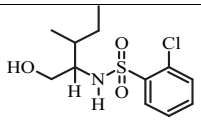
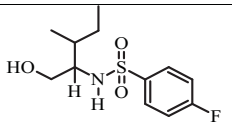
**Key Words:** *QSAR, γ-secretase inhibitor, partial least square, Alzheimer disease*

## 1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is the biggest unmet medical need in neurology due to the lack of disease-modifying anti-Alzheimer's drugs (DMAADs)[1, 2]. γ-secretase is the key enzyme responsible for the pathogenesis of Alzheimer disease [3, 4]. This enzyme forms the Aβ40 and Aβ42 which gets aggregated to form plaques, resulting into decrease cholinergic transmission [5-7]. The rate of formation of plaques increases in the mutated enzyme which generally occurs on the presellin gene located on the chromosome 14 and 1 making it vulnerable for the genetic defect [8, 9]. Inhibition of γ-secretase decreases the level of Aβ40 and Aβ42 which will decrease the plaque formation leading to decrease in the symptoms of Alzheimer disease [10]. Many leads have been identified for the inhibition of γ-secretase, among them simplest leads is substituted pheny sulphonamide derivatives [11].

## 2. Material and Methods

The series of 23 compounds based on substituted phenyl sulphonamide was selected for the QSAR studies [12]. The 2D and 3D structure of the series were sketched by using VLife MDS (Molecular Design Suite) ™ 3.5 software supplied by VLife Sciences Technologies Pvt. Ltd., Pune, India 2006 on workstations that are running on a 3.00 GHz Intel Pentium® IV processor running on Microsoft window XP professional version 2002.

| Code | Structure | Activity EC50(Nm) | PEC50 |
|---|---|---|---|
| AA001 |  | 18,304 | -4.2625 |
| AA002 |  | 56,619 | -4.7529 |
| AA003 |  | 4,243 | -3.6276 |

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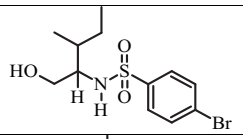
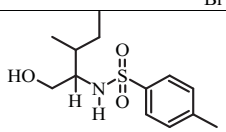
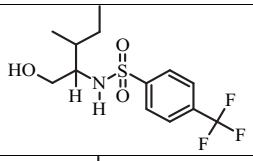
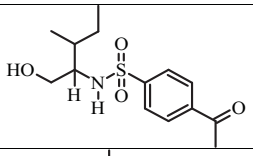
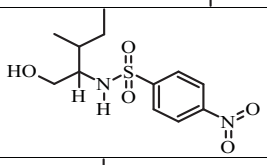
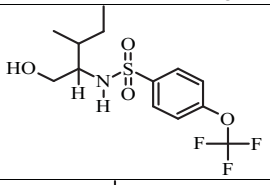
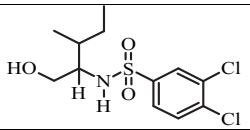
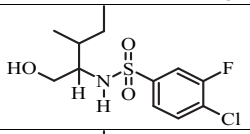
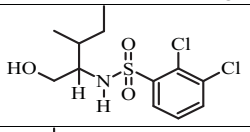
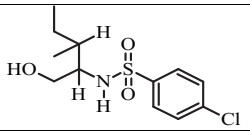
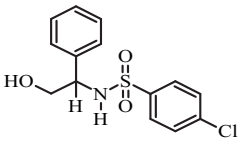
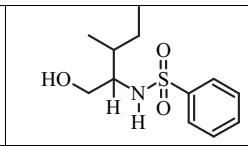
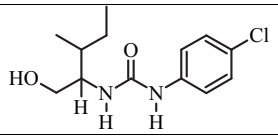
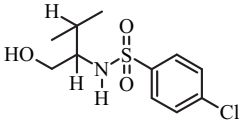
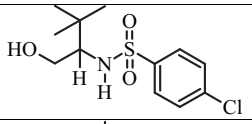
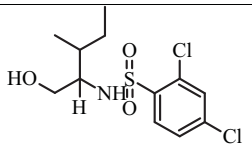
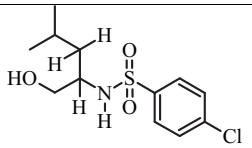
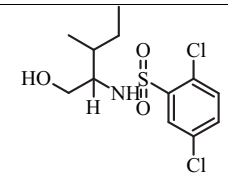
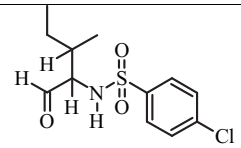
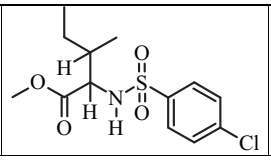
Mail ID: anupampathak@yahoo.com

| | | | |
|---|---|---|---|
| AA004 |  | 2,214 | -3.3451 |
| AA005 |  | 14,292 | -4.1550 |
| AA006 |  | 13,053 | -4.1157 |
| AA007 |  | 6,021 | -3.7796 |
| AA008 |  | 20,903 | -4.3202 |
| AA009 |  | 23,532 | -4.3716 |
| AA010 |  | 37,002 | -4.5682 |
| AA011 |  | 7,840 | -3.8943 |
| AA012 |  | 4,274 | -3.6308 |
| AA013 |  | 758 | -2.8796 |
| AA014 |  | 68,843 | -4.8378 |

| | | | |
|---|---|---|---|
| AA015 |  | 4,145 | -3.6175 |
| AA016 |  | 47,313 | -4.6749 |
| AA017 |  | 4,575 | -3.6603 |
| AA018 |  | 29,108 | -4.4640 |
| AA019 |  | 23,496 | -4.3709 |
| AA020 |  | 15,279 | -4.1840 |
| AA021 |  | 54,808 | -4.7388 |
| AA022 |  | 7,859 | -3.8953 |
| AA023 |  | 64,947 | -4.8125 |

The batch optimization of 3D structure was done by using MMFF. To achieve global minimization 10000 cycles was input with the converse criteria (rms gradient) of 0.01. The distance dependent function was kept at 1.0.

**1. QSAR study:**

All the 2D descriptors (thermodynamic, spatial, electronic and topological parameters) were calculated for QSAR analysis using Vlife MDS software. Thermodynamic parameters describe free energy change during drug enzyme complex formation. Spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with enzyme. Electronic parameters describe weak non-covalent bonding between drug molecules and enzyme.

Partial least square regression method is used to generate QSAR equation. For variable selection, stepwise forward-backward method was used.

Criteria for Selection of Model:

n = number of molecules (> 20 molecules)

K = number of descriptors in a model (statistically n/5 descriptors in a model)

df = degree of freedom (n-k-1) (higher is better)

$r^2$ = coefficient of determination (> 0.7)

$q^2$ = cross-validated r (>0.5)

pred_$r^2$ = r for external test set (>0.5)

SEE = standard error of estimate (smaller is better)

F-test = F-test for statistical significance of the model (higher is better, for same set of descriptors and compounds).

**Selected Models:**

In search of newer and potent γ-secretase inhibitor, QSAR investigation of substituted phenyl sulphonamide derivatives was performed by using VLife MDS 3.5 software. Several QSAR models were generated by using partial least square regression method coupled with stepwise forward-backward method. Among the various models, two significant QSAR models were finally selected. Model summary of two best models are given below.

**2. Result and discussion:**

The 407 two dimensional descriptors were calculated and the activity was inserted in negative log of EC50. The structure and activity correlation was studied by using variable selection method and the regression was done by partial least square. From the number of models that has been generated two models were found to be most predictive.

For QSAR analysis regression was performed using PEC50 values as dependent variables and calculated 407 parameters as independent variables. In any thorough investigation of the effects of molecular properties, it is essential to prove that the results are both statistically valid and make chemical sense. It would be appropriate to obtain insight into the physical meaning of the correlation obtained as an output of the regression analysis. The magnitude of a descriptor could be used as a guideline to improve the γ-secretase activity of molecules.

Among the generated QSAR models; two models were selected on the basis of various statistical parameters such as squared correlation co-efficient ($r^2$) which is relative measure of quality of fit. Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity, standard error ($r^2$ _se) representing absolute measure of quality of fit, and cross-validated square correlation co-efficient ($q^2$), standard error of cross-validated square correlation co-efficient ($q^2$_se), predicted squared regression (pred_$r^2$) and standard error of predicted squared regression (pred_$r^2$ se) to estimate the predictive potential of the models respectively.

The best two QSAR equations are discussed below:

**Unicolumn statistics:**

| Model | Set | Colum Name | Average | Max | Min | StdDev | Sum |
|---|---|---|---|---|---|---|---|
| 01 | Training | pEC50 | -4.0799 | -2.8796 | -4.7529 | 0.5465 | -65.2785 |
| | Test | pEC50 | -4.2401 | -3.6308 | -4.8378 | 0.4643 | -29.6806 |
| 02 | Training | pEC50 | -4.1544 | -3.3451 | -4.8378 | 0.4573 | -66.4712 |
| | Test | pEC50 | -4.0697 | -2.8796 | -4.8125 | 0.6741 | -28.4879 |

**Statistic of models**:

| Parameters | Model 1 | Model 2 |
|---|---|---|
| $r^2$ | 0.7547 | 0.8022 |
| $q^2$ | 0.5875 | 0.6120 |
| Pred_$r^2$ | 0.4998 | 0.5023 |
| R2_Se | 0.2344 | 0.2611 |
| Q2_Se | 0.3799 | 0.3656 |
| Pred_$r^2$_Se | 0.3378 | 0.3328 |
| OC | 01 | 02 |
| DOF | 14 | 13 |
| Ftest | 43.0760 | 26.3643 |
| n | 16 | 16 |

Where n = number of molecules, $r^2$ = coefficient of determination, $q^2$ = cross-validated $r^2$, pred_$r^2$ = $r^2$ for external test set, O.C. = optimum components, DOF= degree of freedom, F-test = F-test for statistical significance of the model (higher is better). $r^2$_Se, $q^2$_se, pred_$r^2$_se are the error for $r^2$, $q^2$, pred_$r^2$ respectively.

**Equations:**

Model 1: PEC50 = - 0.2761 T_C_Cl_9 - 0.3118 T_2_N_3 - 0.6516 T_Cl_Cl_5 -3.0820

Model 2: PEC50=-0.2216 T_T_T_7+0.2002 T_T_O_6-0.5836 SsCH3count-0.6103 T_Cl_Cl_3 -1.1131

**Correlation Matrix**: **Model 1:**

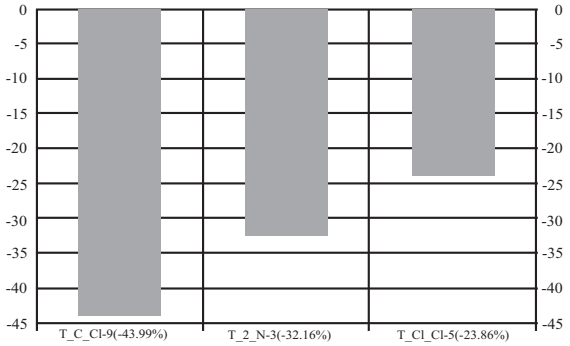
| | T_Cl_Cl_5 | T_C_Cl_9 | T_2_N_3 |
|---|---|---|---|
| T_Cl_Cl_5 | 1.0 | | |
| T_C_Cl_9 | -0.030643 | 1.0 | |
| T_2_N_3 | -0.118345 | 0.032638 | 1.0 |

**Model 2:**

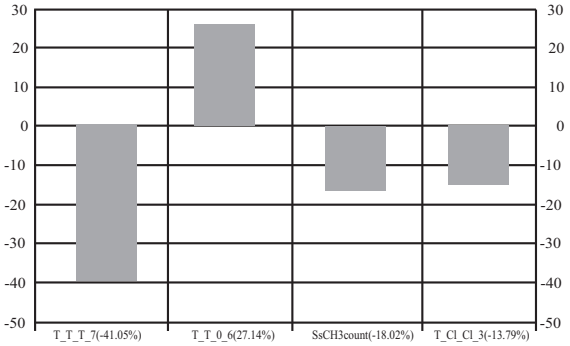
| | SsCH3Count | T_T_T_7 | T_T_O_6T_Cl_Cl_3 |
|---|---|---|---|
| SsCH3Count | 1.0 | | |
| T_T_T_7 | -0.238095 | 1.0 | |
| T_T_O_6 | -0.032530 | 0.271083 | 1.0 |
| T_Cl_Cl_3 | -0.097590 | 0.097590 | 0.1555561.0 |

**Contribution Chart**:

**Model 1:**




**Model 2 :**



**Actual predicted activity table: Model 1:**

| Code | PEC50 | Prediction | Residual | Extrapolation |
|---|---|---|---|---|
| AA001 | -4.2625 | -4.13793 | -0.12457 | 0 |
| AA002 | -4.7529 | -4.56549 | -0.18741 | 0 |
| AA003 | -3.6276 | -3.71036 | 0.08276 | 0 |
| AA004 | -3.3451 | -3.71036 | 0.36526 | 0 |
| AA005 | -4.155 | -4.25607 | 0.10107 | 0 |
| AA006 | -4.1157 | -4.25607 | 0.14037 | 0 |
| AA007 | -3.7796 | -4.32892 | 0.54932 | -0.00027 |
| AA008 | -4.3202 | -3.71036 | -0.60984 | 0 |
| AA009 | -4.3716 | -3.98322 | -0.38838 | 0 |
| AA010 | -4.5682 | -4.13793 | -0.43027 | 0 |
| AA011 | -3.8943 | -3.71036 | -0.18394 | 0 |
| AA012 | -3.6308 | -3.99305 | 0.36225 | 0 |
| AA013 | -2.8796 | -3.41036 | 0.43076 | 0 |
| AA014 | -4.8378 | -4.80177 | -0.03603 | -0.00055 |
| AA015 | -3.6175 | -3.71036 | 0.09286 | 0 |
| AA016 | -4.6749 | -4.68363 | 0.00873 | 0 |
| AA017 | -3.6603 | -3.43751 | -0.22279 | 0 |
| AA018 | -4.464 | -4.25607 | -0.20793 | 0 |
| AA019 | -4.3709 | -4.56549 | 0.19459 | 0 |
| AA020 | -4.184 | -3.71036 | -0.47364 | 0 |
| AA021 | -4.7388 | -4.99305 | 0.25425 | 0 |
| AA022 | -3.8953 | -3.71036 | -0.18494 | 0 |
| AA023 | -4.8125 | -3.98322 | -0.82928 | 0 |

**Actual predicted activity table: Model 1:**

| Code | PEC50 | Prediction | Residual | Extrapolation |
|---|---|---|---|---|
| AA001 | -4.2625 | -4.13859 | -0.12391 | 0 |
| AA002 | -4.7529 | -4.36017 | -0.39273 | 0 |
| AA003 | -3.6276 | -3.51671 | -0.11089 | 0 |
| AA004 | -3.3451 | -3.51671 | 0.17161 | 0 |
| AA005 | -4.155 | -4.10028 | -0.05472 | 0 |
| AA006 | -4.1157 | -4.5109 | 0.3952 | -0.00006 |
| AA007 | -3.7796 | -4.22959 | 0.44999 | 0 |
| AA008 | -4.3202 | -4.44587 | 0.12567 | 0 |
| AA009 | -4.3716 | -4.24571 | -0.12589 | 0 |
| AA010 | -4.5682 | -4.57019 | 0.00199 | 0 |
| AA011 | -3.8943 | -3.95986 | 0.06556 | 0 |
| AA012 | -3.6308 | -4.11365 | 0.48285 | 0 |
| AA013 | -2.8796 | -3.11671 | 0.23711 | 0 |
| AA014 | -4.8378 | -4.25698 | -0.58082 | -0.00016 |
| AA015 | -3.6175 | -3.69543 | 0.07793 | 0 |
| AA016 | -4.6749 | -4.78189 | 0.10699 | 0 |
| AA017 | -3.6603 | -3.47386 | -0.18644 | 0 |
| AA018 | -4.464 | -4.50059 | 0.03659 | 0 |
| AA019 | -4.3709 | -4.58174 | 0.21084 | 0 |
| AA020 | -4.184 | -3.164 | -0.3676 | 0 |
| AA021 | -4.7388 | -4.80332 | 0.06452 | 0 |
| AA022 | -3.8953 | -3.51671 | -0.37859 | 0 |
| AA023 | -4.8125 | -4.18598 | -0.62652 | 0.003 |

**Descriptor:**

SsCH3count: This descriptor defines the total number of -CH3 group connected with single bond.

T_T_T_7: This is the count of any atom or bond (T) separated from any atom (T) by 7 bonds.

T_T_O_6: This is the count of any atom or bond (T) separated from oxygen atom by 6 bonds.

T_Cl_Cl_3: This is the count of chlorine atom separated from another chlorine atom by 3 bonds.

T_C_Cl_9: This is the count of carbon atom separated from chlorine atom by 9 bonds.

T_Cl_Cl_5: This is the count of chlorine atom separated from another chlorine atom by 5 bonds.

T_2_N_3: This is the count of number of double bonded atoms separated from nitrogen atom by 3 bonds.

**Conclusion:**

From the QSAR studies it was found that the -secretase inhibitor activity only T_T_O_6 was found to have positive correlation with the activity. Hence increase in this descriptor will help to increase the binding affinity of the molecule towards γ-secretase which eventually helps to increase the inhibitory activity where as decrease in SsCH3Count, T_T_T_7, T_Cl_Cl_3, T_C_Cl_9, T_Cl_Cl_5 and T_2_N_3 in this descriptors will increase the γ-secreatse binding affinity.

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