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Bikash Debnath · Shovanlal Gayen · Anindya Basu · Kolluru Srikanth · Tarun Jha

Quantitative structure–activity relationship study on some benzodiazepine derivatives as anti-Alzheimer agents

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Abstract A QSAR study was performed in an attempt to explore the pharmacophore of some benzodiazepine derivatives as anti-Alzheimer agents for the inhibition of γ-secretase. The study, which used the electrotopological state atom (ETSA) index, which encodes electronic and topological information, reveals the importance of two phenyl rings—one substituted and another unsubstituted, for the inhibition of the enzyme. Fluorine substitution on the substituted phenyl ring has an important contribution to the activity. R-configurations of the aliphatic chain substituents provide the exact conformation of the molecules to enter into the binding pockets of the receptor(s).

Keywords Benzodiazepine · Alzheimer's disease · γ-Secretase · QSAR · ETSA index

Abbreviations *QSAR:* Quantitative structure–activity relationships · *ETSA:* Electrotopological state atom

Introduction

Formation of neurofibrillary tangles and amyloid plaques in the regions of central nervous system involved in learning and memory are believed to play a key role in the pathogenesis of Alzheimer's disease. [1, 2] β and γ-secretases produce amyloid β-protein (Aβ) and accumulation of Aβ in plaques or as soluble aggregates leads to synaptic dysfunction and neuronal toxicity. [3] Therefore, strategies to inhibit these enzymes are considered an important therapeutic approach likely to have benefit in the treatment of Alzheimer's disease.

In contrast to the activity of other known proteases, γ-secretase activity stems from a part of a membrane-bound multi-component complex of high molecular weight transmembrane proteins. The detailed picture of the catalytic site and mechanism of action of this enzyme are not clearly known. [3] However, it has been demonstrated that four proteins, presenilin, nicastrin, aph-1 and pen-2, exist in the multi-component system and co-expression of these proteins might be critical for γ-secretase activity. [3, 4]

The present communication is an attempt to consider quantitatively the structural variations required or responsible for γ-secretase inhibition by benzodiazepine derivatives reported by Churcher et al. [5] as a part of our composite program of rational drug design. [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18] The electrotopological state atom (ETSA) index of some common atoms and indicator parameters are used in the quantitative structure–activity relationship (QSAR) study. Increasing use of this topological index has demonstrated its importance in specifying essential fragments of molecules in QSAR studies. [13, 14, 16, 17, 18, 19, 20, 21] The information generated by this index is focused at the atomic level or on the submolecular fragments of the molecular skeleton. Thus, it is possible to exploit pharmacophoric atoms for a particular activity in a particular series of molecules by using ETSA indices in the QSAR studies. [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]

Materials and methods

Biological activity

γ-Secretase inhibitory activity of some benzodiazepine derivatives reported by Churcher et al. [5] was considered as the biological activity parameter for this QSAR study. The general structure of these benzodiazepine derivatives is shown in Fig. 1 and their γ-secretase inhibitory activities are listed in Table 1.

B. Debnath · S. Gayen · A. Basu · T. Jha (✉)
Division of Medicinal and Pharmaceutical Chemistry,
Department of Pharmaceutical Technology,
Jadavpur University,
PO Box No 17020, 700 032 Kolkata, India
e-mail: tjjupharm@yahoo.com
Tel.: +91(33)24146677

K. Srikanth
Department of Medicinal Chemistry, College of Pharmacy,
University of Minnesota,
8-125 Weaver Densford Hall, 308 Harvard St SE, Minneapolis,
MN 55455, USA

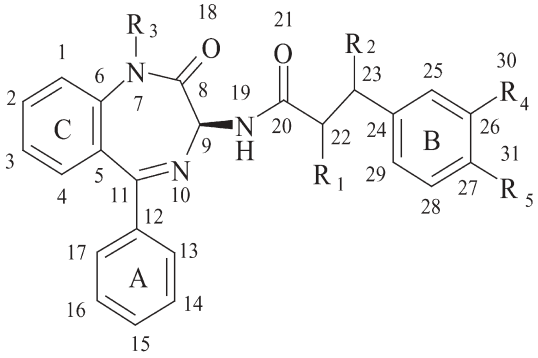


Fig. 1 General structure of benzodiazepine containing γ-secretase inhibitors

ETSA indices

For the development of QSAR model, ETSA indices of different common atoms were used. ETSA indices were calculated by Mouse, [27] a computer program developed in our laboratory. Before the calculation, the atoms of the molecule were numbered consecutively keeping the serial number of atoms the same in all molecules (Fig. 1). In the E-state formalism an every atom in a molecule is different from other atoms except where atoms map onto each other through a symmetry operation. The E-state index (S_i) of an atom (i) in a molecule is composed of an intrinsic state (I_i) and the perturbation effect (Δ_{ij}). [19, 20, 21, 22, 23] The general expression of the intrinsic state value of atom (i) in row N of the periodic table is given as

$$I_i = \left[\left((2/N)^2\delta^v + 1\right)/\delta\right] \quad (1)$$

δ^v=number of valence electrons–number of hydrogen atoms attached, δ=number of sigma electrons–number of hydrogen atoms attached.

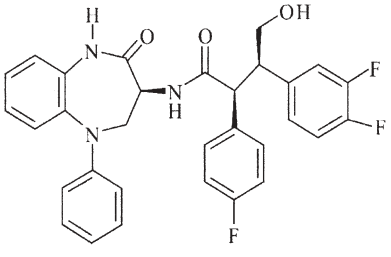
The information encoded into the intrinsic value of the atom (I_i) is both electronic and topological in nature. The count of π- and lone pair electrons (δ^v) gives important electronic information because electrons occupying these orbitals are more reactive and closely associated with long-range non-covalent intermolecular interactions such as drug–receptor encounters. The important topological attribution is the relative degree of mantle atom or buried atom status, encoded by the number of skeletal neighbors (δ). The general expression for the perturbation effect is as follows:

$$\Delta_{ij} = \Sigma\left(I_i - I_j\right)/r_{ij}^2 \quad (2)$$

in which r_{ij} is the topological distance in the shortest path between the atoms, given as the numbers i and j. Thus, the ETSA index is calculated as

$$S_i = I_i + \Delta_{ij} \quad (3)$$

Table 1 γ-Secretase inhibitory activity of benzodiazepine derivatives

Cpd.[a]	R_1	R_2	R_3	R_4	R_5	IC_{50}[b]	pIC_{50}[c]
1	Me (S)	H	Me	Cl	Cl	320	-2.505
2	4-F-(C_6H_4) (S)	H	Me	Cl	Cl	15	-1.176
3	Me (R)	OH (R)	Me	Cl	Cl	19	-1.279
4	Me (S)	OH (R)	Me	Cl	Cl	1340	-3.127
5	Me (S)	OH (S)	Me	Cl	Cl	880	-2.944
6	Me (R)	OH (S)	Me	Cl	Cl	380	-2.580
7	Me (R)	OMe (R)	Me	Cl	Cl	59	-1.771
8	Me (R)	$OCONH_2$ (R)	Me	Cl	Cl	2450	-3.389
9	Me (R)	OSO_2NH_2 (R)	Me	Cl	Cl	450	-2.653
10	Me (R)	OCH_2CONH_2 (R)	Me	Cl	Cl	4750	-3.677
11	Me	=O	Me	Cl	Cl	930	-2.968
12	Me	=NOH	Me	Cl	Cl	35	-1.544
13	Me	=NOMe	Me	Cl	Cl	>10000	-4.000
14	4-F-(C_6H_4) (R)	OH (R)	Me	Cl	Cl	1.2	-0.079
15	4-F-(C_6H_4) (R)	OH (R)	Me	F	F	0.8	0.097
16	4-F-(C_6H_4) (S)	OH (S)	Me	Cl	Cl	67	-1.826
17	4-F-(C_6H_4) (S)	OH (S)	Me	F	F	9.6	-0.982
18	4-F-(C_6H_4) (R)	C_2H_5 (R)	Me	F	F	212	-2.326
19	4-F-(C_6H_4) (R)	$CH{=}CH_2$ (R)	Me	F	F	100	-2.000
20	4-F-(C_6H_4) (R)	CH_2OH (R)	Me	F	F	0.07	1.155
21	4-F-(C_6H_4) (R)	CH_2-Br (R)	Me	F	F	6.7	-0.826
22	4-F-(C_6H_4) (R)	Me (R)	Me	F	F	1.5	-0.176
23	4-F-(C_6H_4) (R)	CH_2OH (R)	H	F	F	0.6	1.222
24						0.7	1.155

[a]Compound no.
[b]50% inhibitory concentration in nM
[c]Negative logarithm of IC_{50}

Indicator parameter

Indicator parameters were used to obtain structural information, i.e., substitution pattern, specific substituent at a specific position for the inhibition of γ-secretase. R-configurations at R_1 and R_2 positions were used as an indicator parameter (*I*), which has a value of 1 for the presence of R-configured substitutions at both R_1 and R_2 positions, otherwise it is zero.

Statistical analysis

All the statistical analyses were carried out by the computer program Multi Regress [28] developed in our laboratory.

Correlation analysis

Correlation analysis [29] of ETSA indices, indicator parameters and biological activity was performed. The auto-correlated parameters were eliminated depending on their individual correlation with the biological activity. All possible combinations of parameters were considered for the QSAR study.

Multiple linear regression analysis

Multiple regression analysis [30, 31] was carried out using γ-secretase inhibitory activity as the dependent variable and ETSA indices as well as indicator parameters as independent variables in all possible combinations. The statistical quality of the regression equations were justified by parameters such as correlation coefficient (*R*), percentage of explained variance (%EV), adjusted R^2 (R^2_A), variance ratio (*F*), standard error of estimate (SEE). All the final equations have regression coefficients, intercepts and variance ratio (*F*) significant to more than 95% confidence level. Use of more than one variable in the multivariate equation was justified by an autocorrelation study.

Validation of the QSAR model

The predictive powers of the equations were validated by the leave-one-out (LOO-) cross validation method. [32] Predicted residual sum of square (PRESS), total sum of squares (SSY) and cross-validated R^2 (R^2_{CV}) were considered for the validation of the models.

Results and discussion

The values of ETSA indices of different common atoms are listed in Table 2. The correlation matrix of independent parameters and biological activity is shown in Table 3. Autocorrelation of ETSA indices of atoms 12–17 (S_{12}–S_{17}) restrict their use in combination in a single QSAR model. Thus, an average of these ($S_{av(12–17)}$) was considered to be the best single variable in a QSAR model. Same consideration was made for the ETSA indices of atoms 24–31 (S_{24}–S_{31}) and another composite ETSA index ($S_{av(24–31)}$) was formulated to obtain statistically robust QSAR models. Predictor variables with higher *p* values were removed in developing QSAR equations.

Depending on the auto-correlation of various independent parameters, the following mathematical equations were developed in a stepwise fashion to explore the γ-secretase inhibitory activity:

$$pIC_{50} = 25.284(\pm 12.220) - 16.180(\pm 7.181)S_{av(12-17)} + 2.180(\pm 0.490)I \quad (4)$$

n=24; *R*=0.808; %EV=65.30; R^2_A= 0.620; $F_{(2,21)}$=19.755; *p*<0.000; SEE=0.950; PRESS=24.168; SSY=54.569; R^2_{CV}= 0.557 where *n* is the number of data points, *R* is correlation coefficient. %EV, R^2_A, *F*, *p*, SEE, PRESS, SSY, R^2_{CV} are percentage of explained variance, adjusted R^2, ratio between the variances of observed and calculated activities, probability factor related to *F*-ratio, standard error of estimate, predicted residual sum of squares, total sum of squares and cross validated R^2, respectively. *I* is the indicator parameter for R-configurations of the substituents at R_1 and R_2 positions. The value within the parentheses are the confidence intervals of the corresponding parameters.

Equation (4) explains up to 65.30% of the variation of the activities. The presence of composite ETSA index $S_{av(12–17)}$ in the equation implies that the phenyl ring A has an important electronic effect in the biological activity. A negative coefficient of $S_{av(12–17)}$ reveals that lower value of this index corresponds to higher activity of these compounds. A positive coefficient of the indicator parameter I signifies the importance of R-conformation of substituents at R_1 and R_2 positions for better activity. Stepwise deletion of the outliers (**2, 7, 23**), which had a standard residual more than three times larger than the standard error of the estimate, from the data set yielded Eqs. (5), (6) and (7) respectively.

$$pIC_{50} = 28.319(\pm 11.936) - 18.014(\pm 7.018)S_{av(12-17)} + 2.214(\pm 0.473)I \quad (5)$$

DC=**2**; *n*=23; *R*=0.832; %EV=65.16; R^2_A=0.661; $F_{(2,20)}$=22.425; *p*<0.000; SEE=0.916; PRESS=21.904; SSY=54.389; R^2_{CV}=0.597

$$pIC_{50} = 34.170(\pm 12.145) - 21.507(\pm 7.152)S_{av(12-17)} + 2.209(\pm 0.457)I \quad (6)$$

DC=**2, 7**; *n*=22; *R*=0.852; %EV=72.59; R^2_A=0.697; $F_{(2,19)}$=25.165; *p*<0.000; SEE=0.886; PRESS=19.840; SSY=54.362; R^2_{CV}=0.635

$$pIC_{50} = 30.874(\pm 10.872) - 19.639(\pm 6.399)S_{av(12-17)} + 2.380(\pm 0.412)I \quad (7)$$

DC=**2, 7, 22;** *n*=21; *R*=0.887; %EV=78.67; R^2_A= 0.763; $F_{(2,18)}$=33.198; *p*<0.000; SEE=0.787; PRESS= 15.685; SSY=52.231; R^2_{CV}=0.700 where DC is the deleted compound. These compounds might act through a different mechanism of action that the model did not capture. The statistical quality of these equations [Eqs. (4), (5), (6) and (7)] gradually improves in a stepwise fashion as shown by their statistical parameters given after each equation. Equation (7) explains up to 78.67% of the variance in the biological activity. The *F*-ratio of Eq. (7) increases by 14 units (approximately)

Table 2 Useful ETSA indices and indicator parameter of benzodiazepine containing γ-secretase inhibitors

Cpd[a]	S_{12}	S_{13}	S_{14}	S_{15}	S_{16}	S_{17}	$S_{av(12-17)}$	S_{24}	S_{25}
1	0.872	1.942	1.920	1.924	1.920	1.942	1.753	0.887	1.750
2	0.819	1.912	1.895	1.902	1.895	1.912	1.723	0.764	1.695
3	0.821	1.904	1.889	1.898	1.889	1.904	1.718	0.447	1.519
4	0.821	1.904	1.889	1.898	1.889	1.904	1.718	0.447	1.519
5	0.821	1.904	1.889	1.898	1.889	1.904	1.718	0.447	1.519
6	0.821	1.904	1.889	1.898	1.889	1.904	1.718	0.447	1.519
7	0.849	1.929	1.910	1.915	1.910	1.929	1.740	0.704	1.675
8	0.789	1.883	1.871	1.882	1.871	1.883	1.697	0.419	1.494
9	0.752	1.854	1.846	1.861	1.846	1.854	1.669	0.252	1.385
10	0.801	1.894	1.879	1.889	1.879	1.894	1.706	0.523	1.562
11	0.804	1.889	1.877	1.888	1.877	1.889	1.704	0.253	1.419
12	0.810	1.896	1.883	1.892	1.883	1.896	1.710	0.426	1.509
13	0.832	1.917	1.900	1.907	1.900	1.917	1.729	0.569	1.609
14	0.768	1.874	1.864	1.876	1.864	1.874	1.687	0.324	1.463
15	0.718	1.832	1.827	1.843	1.827	1.832	1.647	–0.074	0.788
16	0.768	1.874	1.864	1.876	1.864	1.874	1.687	0.324	1.463
17	0.718	1.832	1.827	1.843	1.827	1.832	1.647	–0.074	0.788
18	0.758	1.872	1.860	1.872	1.860	1.872	1.682	0.403	1.069
19	0.742	1.859	1.849	1.862	1.849	1.859	1.670	0.285	0.998
20	0.718	1.839	1.832	1.848	1.832	1.839	1.651	0.153	0.909
21	0.751	1.866	1.855	1.867	1.855	1.866	1.677	0.356	1.039
22	0.767	1.872	1.860	1.871	1.860	1.872	1.684	0.370	1.038
23	0.719	1.830	1.826	1.843	1.826	1.830	1.646	0.151	0.903
24	0.803	1.886	1.865	1.871	1.865	1.886	1.696	0.176	0.923

Cpd[a]	S_{26}	S_{27}	S_{28}	S_{29}	S_{30}	S_{31}	$S_{av(24-31)}$	I
1	0.443	0.466	1.709	1.838	6.103	5.988	2.398	0.000
2	0.365	0.401	1.663	1.782	6.221	6.081	2.372	0.000
3	0.280	0.352	1.560	1.607	6.058	5.954	2.222	1.000
4	0.280	0.352	1.560	1.607	6.058	5.954	2.222	0.000
5	0.280	0.352	1.560	1.607	6.058	5.954	2.222	0.000
6	0.280	0.352	1.560	1.607	6.058	5.954	2.222	0.000
7	0.370	0.414	1.660	1.763	6.170	6.038	2.349	0.000
8	0.223	0.301	1.526	1.582	6.134	6.009	2.211	0.000
9	0.135	0.233	1.445	1.473	6.104	5.985	2.127	0.000
10	0.265	0.330	1.571	1.649	6.184	6.048	2.267	0.000
11	0.219	0.311	1.499	1.507	6.107	5.924	2.155	0.000
12	0.258	0.333	1.548	1.597	6.089	5.976	2.217	0.000
13	0.321	0.379	1.617	1.697	6.173	6.041	2.301	0.000
14	0.202	0.288	1.513	1.551	6.175	6.047	2.195	1.000
15	–1.203	–1.117	0.838	1.152	14.001	13.571	3.495	1.000
16	0.202	0.288	1.513	1.551	6.175	6.047	2.195	0.000
17	–1.203	–1.117	0.838	1.152	14.001	13.571	3.495	0.000
18	–1.034	–1.005	1.020	1.434	14.331	13.919	3.767	0.000
19	–1.081	–1.039	0.972	1.362	14.297	13.894	3.711	0.000
20	–1.145	–1.086	0.909	1.274	14.249	13.857	3.640	1.000
21	–1.054	–1.020	0.999	1.404	14.316	13.908	3.744	0.000
22	–1.043	–1.006	0.998	1.402	14.113	13.653	3.691	0.000
23	–1.145	–1.082	0.902	1.467	14.121	13.655	3.622	1.000
24	–1.130	–1.070	0.917	1.287	14.134	13.665	3.613	1.000

[a] Compound number

compared to Eq. (4). The predictive power of this QSAR model has been increased to a significant level in Eq. (7) as suggested by its R^2_{CV} value (0.700).Another QSAR model (Model 2) was developed by using another average ETSA index $S_{av(24-31)}$ instead of $S_{av(12-17)}$ in Model 1 as shown in Eq. (8).

$$pIC_{50} = -4.911(\pm 0.690) + 1.006(\pm 0.251)S_{av(24-31)} + 2.141(\pm 0.394)I \quad (8)$$

n=24; R=0.869; %EV=75.59; R^2_A=0.733; $F_{(2,21)}$= 32.520; p<0.000; SEE=0.796; PRESS=17.127; SSY= 54.569; R^2_{CV}=0.686

Equation (8) explains up to 75.59% of the variance in the activity data. Model 2 shows the importance of the substituted phenyl ring B in the γ-secretase inhibition of the benzodiazepine derivatives. Positive coefficients of the index $S_{av(24-31)}$ imply that higher value of this index corresponds to better inhibition of the enzyme. After deletion of the outliers (**2**, **12**), Eqs. (9) and (10) were evolved as

$$pIC_{50} = -5.096(\pm 0.661) + 1.045(\pm 0.238)S_{av(24-31)} + 2.202(\pm 0.375)I \quad (9)$$

Table 3 Correlation matrix of the ETSA indices, indicator parameter and the biological activity

	S_{12}	S_{13}	S_{14}	S_{15}	S_{16}	S_{17}	S_{24}	S_{25}	S_{26}
S_{12}	1.00								
S_{13}	0.99	1.00							
S_{14}	0.98	0.99	1.00						
S_{15}	0.98	0.99	0.99	1.00					
S_{16}	0.98	0.99	1.00	0.99	1.00				
S_{17}	0.99	1.00	0.99	0.99	0.99	1.00			
S_{24}	0.84	0.90	0.90	0.90	0.90	0.89	1.00		
S_{25}	0.85	0.86	0.89	0.90	0.89	0.86	0.84	1.00	
S_{26}	0.79	0.78	0.81	0.83	0.81	0.77	0.70	0.97	1.00
S_{27}	0.78	0.76	0.79	0.81	0.79	0.76	0.68	0.97	0.99
S_{28}	0.83	0.83	0.85	0.87	0.85	0.83	0.77	0.99	0.99
S_{29}	0.84	0.87	0.89	0.90	0.89	0.86	0.93	0.94	0.87
S_{30}	–0.73	–0.71	–0.74	–0.76	–0.74	–0.71	–0.62	–0.94	–0.99
S_{31}	–0.73	–0.71	–0.74	–0.76	–0.74	–0.71	–0.61	–0.94	–0.99
$S_{av(12–17)}$	0.99	1.00	0.99	0.99	0.99	0.99	0.89	0.88	0.80
$S_{av(24–31)}$	–0.68	–0.64	–0.68	–0.70	–0.67	–0.64	–0.53	–0.90	–0.98
I	–0.36	–0.40	–0.42	–0.43	–0.42	–0.41	–0.46	–0.43	–0.38
PIC_{50}	–0.54	–0.56	–0.58	–0.61	–0.58	–0.56	–0.50	–0.67	–0.67

	S_{27}	S_{28}	S_{29}	S_{30}	S_{31}	$S_{av(12–17)}$	$S_{av(24–31)}$	I	pIC_{50}
S_{27}	1.00								
S_{28}	0.99	1.00							
S_{29}	0.85	0.91	1.00						
S_{30}	–0.99	–0.97	–0.81	1.00					
S_{31}	–0.99	–0.97	–0.81	0.99	1.00				
$S_{av(12–17)}$	0.78	0.84	0.87	–0.73	–0.73	1.00			
$S_{av(24–31)}$	–0.98	–0.94	–0.74	0.99	0.99	–0.67	1.00		
I	–0.37	–0.41	–0.40	0.34	0.34	–0.40	0.31	1.00	
PIC_{50}	–0.67	–0.68	–0.56	0.66	0.66	–0.57	0.64	0.75	1.00

Table 4 t and p values of QSAR Eqs. (<equationcite>4</equationcite>) to (<equationcite>10</equationcite>)

Equation	Intercept/ Parameters	t value	p value	Equation	Intercept/ Parameters	t value	p value
(<equationcite>	Intercept	2.0690	0.0511	(<equationcite>	Intercept	–7.1173	0.0000
4</equationcite>)	I	4.4506	0.0002	8</equationcite>)	I	5.4279	0.0000
	$S_{av(12–17)}$	–2.2533	0.0351		$S_{av(24–31)}$	4.0100	0.0006
(<equationcite>	Intercept	2.3727	0.0278	(<equationcite>	Intercept	–7.7099	0.0000
5</equationcite>)	I	4.6833	0.0001	9</equationcite>)	I	5.8729	0.0000
	$S_{av(12–17)}$	–2.5668	0.0184		$S_{av(24–31)}$	4.3837	0.0003
(<equationcite>	Intercept	2.8136	0.0111	(<equationcite>	Intercept	–8.3259	0.0000
6</equationcite>)	I	4.8331	0.0001	10</equationcite>)	I	6.3158	0.0000
	$S_{av(12–17)}$	–3.0072	0.0072		$S_{av(24–31)}$	4.8352	0.0001
(<equationcite>	Intercept	2.8397	0.0109				
7</equationcite>)	I	5.7771	0.0000				
	$S_{av(12–17)}$	–3.0692	0.0066				

DC=2; n=23; R=0.889; %EV=79.09; R^2_A=0.770; $F_{(2,20)}$=37.826; p<0.000; SEE=0.754; PRESS=14.973; SSY=54.389; R^2_{CV}=0.725

$$pIC_{50} = -5.334(\pm 0.641) + 1.105(\pm 0.229)S_{av(24-31)} + 2.253(\pm 0.357)I \quad (10)$$

DC=2, 12; n=22; R=0.906; %EV=82.13; R^2_A=0.803; $F_{(2,19)}$=43.670; p<0.000; SEE=0.715; PRESS=13.100; SSY=54.385; R^2_{CV}=0.759

Exclusion of these compounds from Model 2 might be due to the same reason as discussed earlier. Deletion of the outliers improves the statistical quality of Model 2, as shown from the statistical parameters given after each equation. Equation (10) explains up to 82.13% of the variance in the enzyme inhibitory activity. The F-ratio of the model has been improved significantly in Eq. (10). The significant value of R^2_{CV} (0.759) confirms the model's validity and good predictivity. Confidence intervals of the final Eqs. (7) and (10) are more than 95%, as suggested by the p and t values shown in Table 4. The observed, calculated, residual, LOO-predicted and predicted residual activities of the Eqs. (7) and (10) are listed in Table 5.

The QSAR study reveals the importance of two phenyl rings (A and B) of the benzodiazepine derivatives in the inhibition of γ-secretase for the prevention of Alzheimer's disease. The non-covalent attraction between the enzyme and phenyl rings (unsubstituted phenyl ring A and substituted phenyl ring B) may be responsible for the re-

Table 5 Observed (Obs), calculated (Calc), residual (Res) LOO-predicted (Pred) and predicted residual (Pres) activities of Eqs. (<equationcite>7</equationcite>) and (<equationcite>10</equationcite>)

Cpd[a]	Obs	Eq. (<equationcite>7</equationcite>)				Eq. (<equationcite>10</equationcite>)			
		Calc	Res	Pred	Pres	Calc	Res	Pred	Pres
1	−2.505	−3.561	1.056	−3.938	1.433	−2.685	0.179	−2.698	0.193
2	−1.176	–	–	–	–	–	–	–	–
3	−1.279	−0.477	−0.802	−0.146	−1.133	−0.626	−0.653	−0.407	−0.872
4	−3.127	−2.857	−0.270	−2.830	−0.297	−2.879	−0.248	−2.856	−0.271
5	−2.944	−2.857	−0.088	−2.848	−0.096	−2.879	−0.066	−2.872	−0.072
6	−2.580	−2.857	0.277	−2.885	0.305	−2.879	0.299	−2.907	0.327
7	−1.771	–	–	–	–	−2.738	0.968	−2.816	1.045
8	−3.389	−2.445	−0.945	−2.377	−1.012	−2.891	−0.498	−2.844	−0.545
9	−2.653	−1.901	−0.752	−1.792	−0.861	−2.985	0.331	−3.019	0.366
10	−3.677	−2.631	−1.046	−2.553	−1.124	−2.830	−0.847	−2.756	−0.921
11	−2.968	−2.592	−0.377	−2.564	−0.404	−2.953	−0.015	−2.951	−0.017
12	−1.544	−2.710	1.166	−2.804	1.260	–	–	–	–
13	−4.000	−3.080	−0.920	−2.946	−1.054	−2.792	−1.208	−2.690	−1.310
14	−0.079	0.129	−0.208	0.174	−0.253	−0.655	0.576	−0.854	0.775
15	0.097	0.917	−0.821	1.144	−1.047	0.780	−0.683	0.930	−0.833
16	−1.826	−2.251	0.425	−2.287	0.461	−2.908	1.082	−3.012	1.186
17	−0.982	−1.463	0.480	−1.620	0.638	−1.473	0.491	−1.545	0.563
18	−2.326	−2.166	−0.160	−2.151	−0.175	−1.172	−1.155	−0.917	−1.409
19	−2.000	−1.924	−0.076	−1.914	−0.086	−1.234	−0.766	−1.079	−0.921
20	1.155	0.823	0.332	0.739	0.416	0.941	0.214	0.890	0.265
21	−0.826	−2.055	1.229	−2.190	1.364	−1.198	0.372	−1.277	0.451
22	−0.176	–	–	–	–	−1.256	1.080	−1.469	1.293
23	1.222	0.934	0.288	0.853	0.369	0.920	0.301	0.849	0.373
24	1.155	−0.055	1.210	−0.355	1.510	0.911	0.244	0.853	0.302

[a] Compound no.

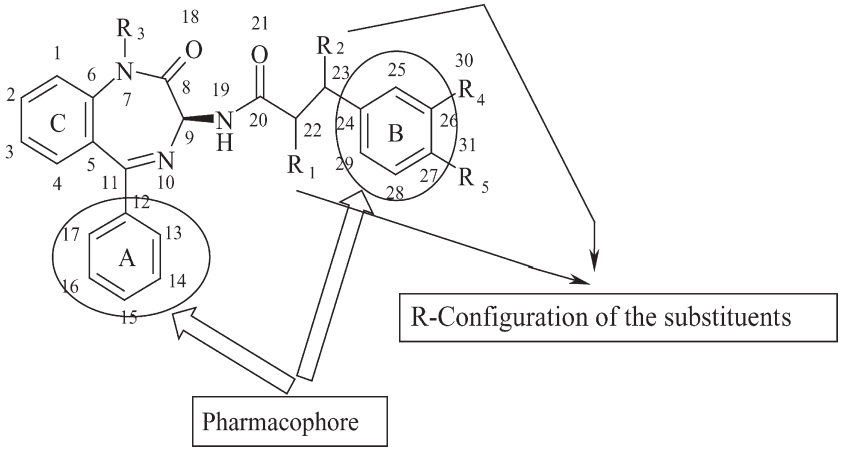


Fig. 2 Pharmacophoric requirements of γ-secretase inhibitors

ceptor binding of the benzodiazepine inhibitors. Substitutions at the R_4 and R_5 positions of the phenyl ring B have some important contributions to the activity. A fluorine atom rather than chlorine at these two positions (R_4 and R_5) is conducive to the activity as fluorine substitution increases the value of the average index $S_{av(24–31)}$. Configurations of the substituents at the R_1 and R_2 positions of the compounds also have a large contribution to the inhibitory activity. R-configurations may help the inhibitors to match with the binding pockets of the receptors. Pharmacophoric requirements of these compounds for the inhibition of γ-secretase are shown in the Fig. 2.

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