CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.18303007

Available online at: http://www.iajps.com *Review Article*

QSAR ANALYSIS OF 5-N-SUBSTITUTED-2-(SUBSTITUTED BENZENESULPHONYL) - GLUTAMAMINES AS ANTITUMOR AGENT

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Abstract:
A data set of five was subjected to a quantitative structure–activity relationship (QSAR) analysis.The antitumor properties of N-substituted-2-(substituted Benzenesulphonyl)-glutamamine derivatives activity. Several kinds of descriptors, such as WHIM, 3DMorse, and 2D autocorrelationDescriptors were employed to establish a numerical correlation between antitumor activity andstructural characteristics. Six parametric models were discovered, according to a multiple linear regression analysisto be optimal for simulating the current set of compounds' log (TWI) activity. For optimal QSARThe model's R2 statisticsFor the current set of compounds, =0.9103; Q=30.385; N=32. ThisRidge and the leave-one-out (LOO) cross-validation method were used to further validate the model regression.

Keywords: *QSAR, 2D autocorrelation, (LOO) cross-validation, Ridge regression analysis, Model.*

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Please cite this article in ***press*** *Swapnil R. Patil* ***et al., QSAR Analysis Of 5-N-Substituted-2-(Substituted Benzenesulphonyl) - Glutamamines As Antitumor Agent,*** *Indo Am. J. P. Sci, 2026; 13(01).*

INTRODUCTION:

Studies reveal that tumor is a "nitrogen trap" as well as "glutamine trap". It is also evident that tumor cells are avid GLN consumer. After glucose, GLN is assumed to be the main energy source in tumor cells. In fact GLN plays a key role in tumor cell growth by supplying its amide nitrogen in the biosynthesis of other amino acids. A glutamine derivative was approved as a sedative-hypnotic by the U.S. FDA and is found to be very effective. Some reported iso glutamine derivatives are also found to be potent anticancer agents.Glutamine and iso glutamine derivatives have been act as anticancer agents. In this study we have tried to present QSAR on some Glutamines in which log of percentage tumour weight inhibition has been taken as dependent parameter and 2D-autocorelation, 3DMorse, and WHIM descriptors have been using as independent parameters. A six-parametric model has been obtained to model the antitumor activity of present set of compounds.

MATERIALS AND METHODS:

The methodology used in modeling the anti-tumor activities of 5- N, –substituted-2-(substituted Benzene sulphonyl) glutamines is based on QSAR, using 2D-autocorelation, 3DMorse, and WHIM descriptors. In the present study we took 32 glutamine derivatives with Log (TWI) activities as reported in the literature. The structural details of 5-N, –substituted-2-(substituted Benzene sulphonyl) a glutamine derivative which shows antitumoral activities are given in Table 1. Structures of all the compounds were sketched using ACD-lab software Chem Sketch. This Table also records the antitumor activity of these compounds in the form of log (TWI). We have used E-DRAGON software to calculate the topological descriptors.

These descriptors are reported in Table 2. From the descriptors calculated useful descriptors were generated by variable selection of descriptors in multiple regression analysis using NCSS software. These descriptors are reported in Table 2. They include: GATS2i, GATS4i, G3e, Gm, Mor21i, and Mor29p. Finallythe proposed models obtained were subjected to cross validation by leave-one-out procedure.

RESULTS AND DISCUSSION:

A close look at Table 3 gave following information:

a) Number of mono-parametric model is possible to model the antitumor activity of resent set of compounds.

b) GATS2i is the most suitable parameter in multi parametric model.

c) None of the parameters show auto correlation hence possibility of chance is not there.

The data discussed above were subjected to regression analysis using NCSS Software14 The data gave a correlation matrix which is reported in Table 3. The regression analysis gave many statistically significant regression models but only those which have more than 0.52 values in terms of R^2 have been presented in Table 4. A close look at this table clearly indicates that for modeling Log (TWI), GATS2i play a dominant role. On the basis of R^2 following models have been found useful in modeling the antitumor activity of these compounds:

3.1 One- Variable Model

Log (TWI) = 1.1557(±0.2013) GATS2i+ 0.2305 N=32, R^2=0.5236, R2A=0.5077, Se=0.0661, F=32.971,Q=10.947

Here, and here after N is the number of compound, Se is the standard error of estimation, R 2 is the square of correlation coefficient, R^2_{Adj} is the adjusted R^2, F is the Fisher's ratio, and Q is the Pogliani's quality factor which is the ratio of R/Se.

3.2 Two -variable model

When GATS4i is added to the above model a two-variable model with R^2 = 0.6697is obtained. The model is as under: Log (TWI) = 1.1601(±0.1705) GATS2i -0.6532(±0.01824) GATS4i+0.9066 N=32, R^2=0.6697, R^2_A=0.6469, Se=0.0559, F=29.394, Q=14.640

The R^2_A value shows improvement. This clearly indicates that the added parameter has a fair share.

3.3 Three-variable model

Further improvement in statistical parameters has been observed when a third parameter G3e is added to bi-parametric model. The R^2 value changes from 0.6697 to 0.7571. The model is as under:

Log(TWI) = 2.4891(±0.7843)G3e +1.1073(±0.1497)GATS2i-0.7295(±0.1610)GATS4i + 0.5886 N=32, R^2=0.7571, R2A=0.7310, Se=0.0488, F=29.084, Q=17.830

3.4 Four -Variable Model

Addition of Mor29p gave even better model than the three –parametric model. Log(TWI) = 2.0467(±0.7621)G3e+1.2660(±0.1577)GATS2i-0.7076(±0.1513)GATS4i+0.3200(±0.1452)Mor29p + 0.4926 N=32, R^2=0.7941, R^2_A=0.7636, Se=0.0458, F=26.035, Q=19.457

This model has R^2 value equals 0'7941. Also Adj. R^2 value shows a significant change.

3.5 Five -Variable model

When Mor21i is added to four-parametric model a five-parametric with R^2= 0.8451 is obtained. The R^2_A value also changes from 0.7636 to 0.8153. The model is given below:

Log(TWI)=1.6223(±0.6892)G3e+1.3860(±0.1453) GATS2i-0.7124(±0.1337)GATS4i0.0637(±0.0218)Mor21i+ 0.4923(±0.1412) Mor29p+ 0.3297 N=32, R^2=0.8451, R^2_A=0.8153, Se=0.0405, F=28.363, Q=22.699

3.6 Six-Variable Model

To obtained still better model Gm is added to the above model, which yielded a six-parametric model. The R^2 value change from 0.8451 to 0.9103. The R^2_A value also showed a drastic change (0.8153 to 0.8887).Log(TWI)=1.7462(±0.5357)G3e+1.5997(±0.1235)GATS2i-0.7733(±0.1048)GATS4i 5.5553(±1.3036)Gm-0.1145(±0.0207)Mor21i+0.5968(±0.1123) Mor29p-0.9067 N=32, R2=0.9103, R2A=0.8887, Se=0.0314, F=42.263, Q=30.385

On the basis of Pogliani's quality factor we infer that the six- parametric model is the best for modeling Log (TWI) activity of present set of compounds. Further confirmation is obtainedby estimating the activity using model 21 which is reported in Table 5. The estimated values areingood agreement with observed values. A comparison of observed activity verses estimatedvalues is shown in Fig. 2. The predictive power of the model comes out to be 0.905. Further confirmation is obtained by calculating cross-validated parameters. Such values are given in Table 6. The PSE value close to0.4 for model suggests that this model is the best. Also cross validation R2 value for model 21 comes out to be 0.9103 which is the highest among all the discussed models. For any kind of possible defect we have calculated variance inflation factor, tolerance and condition number for various parameters using VIF plot which is given in Table 7. All the parameters show the value within the permissible limit. Therefore the model is free from any kind of defect. Ridge trace suggests that there is no co-linearity in the model.

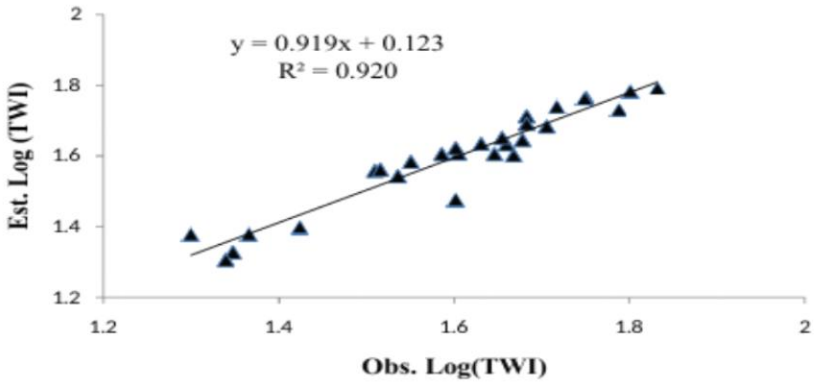


Fig. 1. Correlation between Observed and estimated Log (TWI) using model (Table 4)

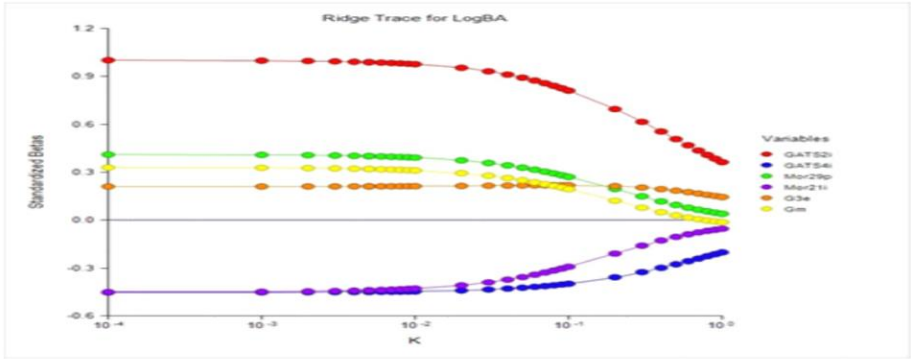
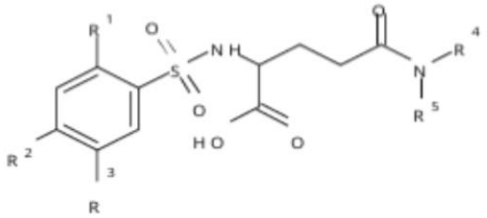


Fig: 2. Ridge trace for Six-parametric model

Table .1 Structural details and Log BA values for the compounds used in present study.



Comp. no.	R^1	R^2	R^3	R^4	R^5	Log (TWI)
1	H	Br	H	i-C_3H_7	H	1.668
2	H	Br	H	c-C_6H_{11}	H	1.801
3	H	Br	H	$C_6H_5CH_2$	H	1.536
4	H	Br	Cl	CH_3	CH_3	1.424
5	Cl	H	Cl	CH_3	H	1.605
6	Cl	H	Cl	n-C_3H_7	H	1.602
7	Cl	H	Cl	i-C_3H_7	H	1.717
8	Cl	H	Cl	n-C_4H_9	H	1.678
9	Cl	H	Cl	i-C_4H_9	H	1.683
10	Cl	H	Cl	n-C_6H_{13}	H	1.751
11	Cl	H	Cl	C_6H_5	H	1.683
12	Cl	H	Cl	$C_6H_5CH_2$	H	1.631
13	Cl	H	Cl	CH_3	CH_3	1.348
14	Cl	H	H	i-C_3H_7	i-C_3H_7	1.646
15	CH_3	CH_3	H	H	H	1.366
16	CH_3	CH_3	H	n-C_4H_9	H	1.551
17	CH_3	CH_3	H	C_2H_5	C_2H_5	1.340
18	H	t-C_4H_9	H	H	H	1.300
19	H	t-C_4H_9	H	CH_3	H	1.602
20	H	t-C_4H_9	H	C_2H_5	H	1.510
21	H	t-C_4H_9	H	n-C_3H_7	H	1.516
22	H	t-C_4H_9	H	i-C_3H_7	H	1.660
23	H	t-C_4H_9	H	n-C_4H_9	H	1.655
24	H	t-C_4H_9	H	i-C_4H_9	H	1.586
25	H	t-C_4H_9	H	n-C_6H_{13}	H	1.706
26	H	t-C_4H_9	H	c-C_6H_{11}	H	1.788
27	H	t-C_4H_9	H	C_6H_5	H	1.832
28	H	t-C_4H_9	H	$C_6H_5CH_2$	H	1.531
29	H	t-C_4H_9	H	CH_3	CH_3	1.372
30	H	t-C_4H_9	H	C_2H_5	C_2H_5	1.358
31	H	t-C_4H_9	H	i-C_3H_7	i-C_3H_7	1.458

Table 2. Calculated values of 2D autocorrelation, 3D MoRSE, and WHIM descriptors for compounds used in present study.

S.No.	GATS2i	GATS4i	Mor29p	Mor21i	G3e	Gm
1	1.251	1.004	-0.168	-0.922	0.198	0.168
2	1.302	1.000	-0.171	-1.914	0.211	0.161
3	1.171	1.091	0.071	-1.054	0.195	0.165
4	0.992	1.013	0.057	-1.209	0.173	0.185
5	1.148	1.096	-0.086	-1.091	0.191	0.201
6	1.263	1.021	-0.149	-1.213	0.180	0.168
7	1.283	1.008	-0.150	-1.510	0.169	0.179
8	1.276	1.066	-0.133	-1.685	0.165	0.168
9	1.228	0.881	-0.106	-1.302	0.181	0.168
10	1.299	1.054	-0.190	-2.482	0.168	0.170
11	1.330	1.005	-0.258	-2.061	0.190	0.163
12	1.269	1.066	0.081	-0.971	0.168	0.169
13	1.195	1.094	-0.023	-1.430	0.218	0.170
14	1.019	1.018	-0.138	-1.568	0.159	0.183
15	1.275	1.130	-0.246	-2.483	0.177	0.162
16	1.128	1.225	-0.051	-1.289	0.185	0.178
17	1.190	1.198	-0.155	-2.561	0.201	0.173
18	1.133	1.309	-0.146	-2.708	0.182	0.157
19	1.100	0.996	-0.141	-1.886	0.154	0.161
20	1.045	1.018	-0.043	-2.066	0.181	0.175
21	1.127	1.025	-0.233	-2.458	0.217	0.168
22	1.146	0.980	-0.109	-1.961	0.165	0.170
23	1.162	0.973	-0.046	-1.894	0.200	0.161
24	1.163	1.014	-0.103	-2.643	0.182	0.166
25	1.125	0.890	-0.166	-2.439	0.155	0.171
26	1.192	1.012	-0.179	-2.842	0.202	0.161
27	1.218	0.976	-0.099	-2.811	0.177	0.157
28	1.144	0.997	0.135	-2.255	0.213	0.167

Table 3. Correlation matrix

	LogBA	GATS2i	GATS4i	Mor29p	Mor21i	G3e	Gm
LogBA	1.000						
GATS2i	0.724	1.000					
GATS4i	-0.377	0.007	1.000				
Mor29p	-0.060	-0.424	-0.025	1.000			
Mor21i	-0.075	0.076	-0.052	0.309	1.000		
G3e	0.314	0.111	0.149	0.184	-0.086	1.000	
Gm	-0.183	-0.271	0.073	0.130	0.505	-0.166	1.000

Table 4. Regression parameters and quality of correlations.

Model No.	Parameters Used	A_i=(1.....6)	B	Se	R^2	R^2_A	F	Q=R/Se
1	GATS2i	1.1557(±0.2013)	0.2305	0.0661	0.5236	0.5077	32.971	10.947
2	GATS4i	-0.6443(±0.2890)	2.2549	0.0886	0.1421	0.1135	4.970	4.255
3	Mor29p	-0.0870(±0.2646)	1.5745	0.0955	0.0036	0.0000	0.108	0.628
4	Mor21i	-0.0190(±0.0463)	1.5463	0.0954	0.0056	0.0000	0.169	0.784
5	G3e	2.5975(±1.4342)	1.1035	0.0909	0.0986	0.0685	3.280	3.454
6	Gm	-3.0778(±3.0205)	2.1034	0.0941	0.0335	0.0012	1.038	1.945
7	GATS2i	1.1601(±0.1705)	0.9066	0.0559	0.6697	0.6469	29.394	14.640
	GATS4i	-0.6532(±0.1824)						
8.	GATS2i	1.3599(±0.2077)	0.0338	0.0617	0.5980	0.5703	21.573	12.533
	Mor29p	0.4374(±0.1888)						
9.	GATS2i	1.1716(±0.2016)	0.1480	0.0660	0.5406	0.5089	17.061	11.140
	Mor21i	-0.0332(±0.0321)						
10	G3e	1.9579(±1.0032)	-0.0818	0.0632	0.5789	0.5499	19.934	12.039
	GATS2i	1.1138(±0.1937)						
11	GATS2i	1.1619(±0.2126)	0.1826	0.0672	0.5238	0.4909	15.948	10.770
	Gm	0.2403(±2.2403)						
12	GATS2i	1.3573(±0.1703)	0.7051	0.0506	0.7391	0.7112	26.443	16.990
	GATS4i	-0.6421(±0.1650)						
	Mor29p	0.4227(±0.1548)						
13	GATS2i	1.1785(±0.1679)	0.8252	0.0550	0.6923	0.6594	21.001	15.128
	GATS4i	-0.6667(±0.1794)						
	Mor21i	-0.0385(±0.0268)						
14	G3e	2.4891(±0.7843)	0.5886	0.0488	0.7571	0.7310	29.084	17.830
	GATS2i	1.1073(±0.1497)						
	GATS4i	-0.7295(±0.1610)						
15	GATS2i	1.1797(±0.1798)	0.7609	0.0568	0.6715	0.6364	19.082	14.427
	GATS4i	-0.6589(±0.1857)						
	Gm	0.7616(±1.8991)						
16	G3e	2.0467(±0.7621)	0.4926	0.0458	0.7941	0.7636	26.035	19.457
	GATS2i	1.2660(±0.1577)						
	GATS4i	-0.7076(±0.1513)						
	Mor29p	0.3200(±0.1452)						
17.	G3e	2.3955(±0.7757)	0.5328	0.0481	0.7726	0.7389	22.937	18.274
	GATS2i	1.1247(±0.1480)						
	GATS4i	-0.7379(±0.1587)						
	Mor21i	-0.0320(±0.0235)						
18	G3e	2.6099(±0.7948)	0.2649	0.0489	0.7653	0.7305	22.008	17.890
	GATS2i	1.1463(±0.1551)						
	GATS4i	-0.7454(±0.1620)						
	Gm	1.6105(±1.6552)						
19	G3e	1.6223(±0.6892)	0.3297	0.0405	0.8451	0.8153	28.363	22.699
	GATS2i	1.3860(±0.1453)						
	GATS4i	-0.7124(±0.1337)						
	Mor21i	-0.0637(±0.0218)						
	Mor29p	0.4923(±0.1412)						
20	G3e	2.1632(±0.7758)	0.2136	0.0459	0.8003	0.7619	20.840	19.490
	GATS2i	1.2958(±0.1617)						
	GATS4i	-0.7220(±0.1526)						
	Gm	1.4004(±1.5589)						
	Mor29p	0.3118(±0.1460)						
21	G3e	1.7462(±0.5357)	-0.9067	0.0314	0.9103	0.8887	42.263	30.385
	GATS2i	1.5997(±0.1235)						
	GATS4i	-0.7733(±0.1048)						
	Gm	5.5553(±1.3036)						
	Mor21i	-0.1145(±0.0207)						
	Mor29p	0.5968(±0.1123)						

Comp. No.	Obs. Log (TWI)	Est. Log (TWI)	Residual
1	1.668	1.602	0.066
2	1.801	1.783	0.018
3	1.536	1.543	-0.007
4	1.424	1.399	0.025
5	1.605	1.606	-0.001
6	1.602	1.622	-0.020
7	1.717	1.739	-0.022
8	1.678	1.645	0.033
9	1.683	1.712	-0.029
10	1.751	1.765	-0.014
11	1.749	1.763	-0.014
12	1.683	1.691	-0.008
13	1.631	1.634	-0.003
14	1.348	1.328	0.020
15	1.646	1.605	0.041
16	1.366	1.379	-0.013
17	1.551	1.583	-0.032
18	1.340	1.306	0.034
19	1.300	1.378	-0.078
20	1.602	1.477	0.125
21	1.510	1.558	-0.048
22	1.516	1.561	-0.045
23	1.660	1.633	0.027
24	1.655	1.651	0.004
25	1.586	1.605	-0.019
26	1.706	1.683	0.023
27	1.788	1.731	0.057
28	1.832	1.791	0.041

Table 6. Cross validated parameters for the best obtained models.

Model No.	Parameters used	PRESS/SSY	R^2_{cv}	S_{PRESS}	PSE
1	GATS2i	0.9099	0.0901	0.1046	0.1012
7	GATS2i GATS4i	0.4933	0.5067	0.0886	0.0843
14	GATS2i GATS4i G3e	0.3209	0.6791	0.0773	0.0723
16	GATS2i GATS4i G3e Mor29p	0.2593	0.7407	0.0725	0.0666
19	GATS2i GATS4i G3e Mor21i Mor29p	0.1833	0.8167	0.0641	0.0577
21	GATS2i GATS4i G3e Mor29p Mor21i Gm	0.0986	0.9014	0.0497	0.0439

Table 7. Ridge analysis for the best five-parametric model.

Model No.	Parameters used	VIF	Tolerence	Eigenvalue	Condition no.
21	GATS2i	0.6009	1.6643	1.8028	1.00
	GATS4i	0.9551	1.0470	1.2623	1.43
	Mor29p	0.5999	1.6670	1.1206	1,61
	Mor21i	0.5430	1.8418	0.9920	1.82
	G3e	0.8563	1.1678	0.5769	3.12
	Gm	0.5981	1.6719	0.2451	7.35

CONCLUSION:

2D-autocorelation, 3D MORSE, and WHIM are the best parameters for modeling the activity of present set of compound. The positive coefficients are increasing the activity and negative coefficients have retarding effect towards the activity.

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