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Syntheses, Biological Evaluation and QSAR Study on Antitumor Activity of 1,5-*N*,*N*′-Disubstituted-2-(substituted Benzenesulphonyl) Glutamamides

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Abstract—We have reported [unpublished data] the synthesis and QSAR of 5-substituted-2-(substituted benzenesulphonyl) glutamines which have shown the importance of steric factor on the aliphatic chain. *N*-Phthalyl isoglutamine, having the substitution at position 1 of the glutamic acid moiety, is the metabolite of recently approved thalidomide for different types of tumors by US FDA. Based on these, 36 new 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides were synthesized, as tools for further elucidation of the structural requirements for antitumor activity. All the synthesized compounds were tested for antitumor activity against Ehrlich Ascites Carcinoma (EAC) in Swiss albino mice using tumor weight as inhibitory parameter. Quantitative structure–activity relationship (QSAR) studies of these analogues revealed that the electron donating groups on the phenyl ring are found to be mandatory for the activity which was also proved by the negative coefficient of indicator parameter I_3, for NO_2 group on the phenyl ring. Molecular volume (MV) and steric factor at R_5 position also plays a role in ligand–receptor interactions.

Introduction

Glutamine[1] is an important nitrogen-carrying amino acid that may be conditionally essential, serving as a preferred respiratory fuel for rapidly proliferating cells, such as enterocytes and lymphocytes; a regulator of acid-base balance through the production of urinary ammonia; a carrier of nitrogen between tissues; and an important precursor of nucleic acids, nucleotides, amino sugars and proteins. Glutamine is a principal fuel utilized by rapidly growing tumors.[2] Numerous studies on glutamine metabolism in cancer indicate that many tumors are avid glutamine consumers in-vivo and in-vitro.[3] As a consequence of progressive tumor growth, host glutamine depletion develops and becomes a hallmark. This glutamine depletion occurs in part, because the tumor behaves as a 'glutamine trap' but also because of cytokine-mediated alterations in glutamine metabolism in host tissues. Glutamine supplies its amide nitrogen atoms in the biosynthesis of purines and pyrimidines through different amidotranferases.[4] It is found in much higher concentrations in tumor cells when compared with that of normal body cells. Hence the structural variants of glutamine attracted our attention to develop as possible antitumor agents which may act through glutamine and/or folic acid antagonism.

We previously reported the structural requirements of glutamines for possible antitumor activity. It has shown the importance of steric factors on the aliphatic chain of the substituted glutamine. It may play some role in ligand–receptor interactions. Moreover, isoglutamine, which is having 1-*N*-amide has reported[6] to have anticancer activity. Based on these, we report here 36 new 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides as derivatives of glutamine and/or glutamic acid. The work is a part of our composite program of Rational Drug Design of glutamine analogues[7] for their possible antitumor activity. These compounds possesses substitutions on the phenyl ring and aliphatic side chain at 1 and 5 positions as shown in Figure 1, unlike the previously reported glutamines which had the substitution only at the 5th position to exploit further structural requirements for the antitumor activity. QSAR studies have been performed, to further explore the chemical structural features at different substitutions over the ligand influencing biological activity (BA).

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Results and Discussion

1,5-*N*,*N*′-Disubstituted-2-(substituted benzenesulphonyl) glutamamides were synthesized in accordance with Scheme 1 and the chemistry behind the synthesis is explained under the experimental section. Physical data of the intermediates and the final compounds are furnished in Tables 1 and 2. All the title compounds were evaluated for antitumor activity against Ehrlich Ascites Carcinoma (EAC) in Swiss albino mice using percentage of tumor weight inhibition (%TI) as activity parameter. Antitumor activity data are reported in Table 3.

QSAR studies of 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides (Fig. 1) were performed by adopting Hansch analysis.[8] Molecular descriptors used in QSAR analysis are compiled in Tables 4 and 5. These parameters were subjected to correlation analysis and the resultant correlation matrix is shown in Table 6.

The following mathematical equations were developed in a stepwise fashion for modeling the antitumor activity by multiple regression analysis. Predictor variables with higher p values were removed in developing the equation to get more acceptable QSAR equation with statistical quality. Predicting potential of the final QSAR equations were justified by Leave-One-Out (LOO)[9] prediction. In LOO prediction, each compound of the list is deleted once from the data set and the regression equation obtained thereby was used to predict the activity of deleted compound. LOO predicted values are listed in Table 7.

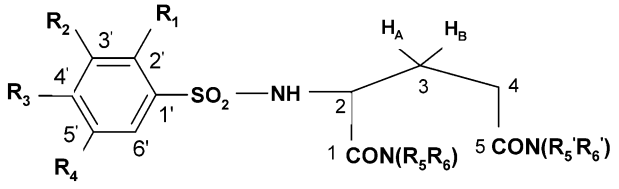
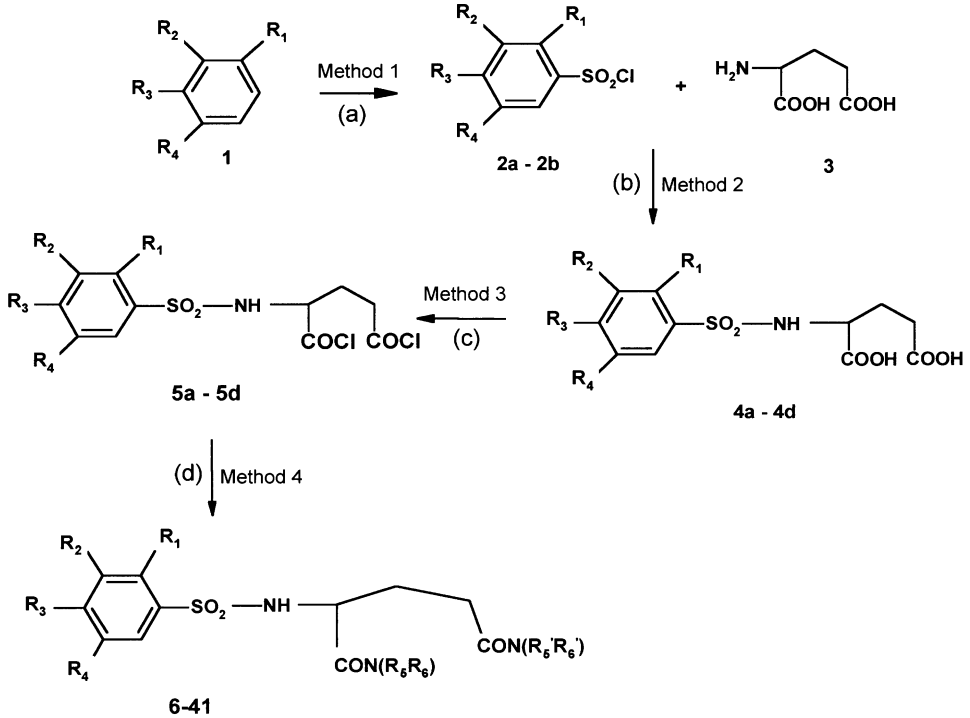


Figure 1. General structure for 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides.

$$\log(\mathrm{BA}) = 1.2002\ (\pm 0.1531) - 0.0976\ (\pm 0.0981)\ \Sigma\sigma + 0.1430\ (\pm 0.0378)\ \mathrm{EsR_5} + 0.2001\ (\pm 0.0545)\ \mathrm{I_1} + 0.3501\ (\pm 0.0769)\ \mathrm{MV} + 0.3537\ (\pm 0.0821)\ \mathrm{I_2}$$
$$n = 35,\quad \mathrm{R^2} = 0.5908,\quad \mathrm{F_{5,29}} = 8.37,\quad \mathrm{SEE} = 0.1157,\quad p = 0.00005,\quad \mathrm{DC} = 36 \qquad (1)$$

$$\log(\mathrm{BA}) = 1.2074\ (\pm 0.1350) - 0.1263\ (\pm 0.0870)\ \Sigma\sigma + 0.1540\ (\pm 0.0335)\ \mathrm{EsR_5} + 0.2066\ (\pm 0.0481)\ \mathrm{I_1} + 0.3580\ (\pm 0.0678)\ \mathrm{MV} + 0.3797\ (\pm 0.0729)\ \mathrm{I_2}$$
$$n = 34,\quad \mathrm{R^2} = 0.6775,\quad \mathrm{F_{5,28}} = 11.76,\quad \mathrm{SEE} = 0.1020,\quad p = 0.00000,\quad \mathrm{DC} = 36,\ 34 \qquad (2)$$

$$\log(\mathrm{BA}) = 1.1343\ (\pm 0.1289) - 0.1635\ (\pm 0.0821)\ \Sigma\sigma + 0.1550\ (\pm 0.0311)\ \mathrm{EsR_5} + 0.2388\ (\pm 0.0466)\ \mathrm{I_1} + 0.3931\ (\pm 0.0646)\ \mathrm{MV} + 0.3779\ (\pm 0.0675)\ \mathrm{I_2}$$
$$n = 33,\quad \mathrm{R^2} = 0.7325,\quad \mathrm{F_{5,27}} = 14.78,\quad \mathrm{SEE} = 0.0945,\quad p = 0.00000,\quad \mathrm{DC} = 36, 34, 15,\quad \mathrm{q^2} = 0.7337 \qquad (3)$$



Scheme 1. General synthetic protocol for 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides.

Table 1. Physical data for the intermediate compounds

Compd	R_1	R_2	R_3	R_4	mp (°C)	% Yield	Molecular formula	MW
2a	CH_3	H	H	NO_2	42–44	76.39	$C_7H_6N_1O_4S_1Cl$	235.5
2b	H	NO_2	CH_3	H	Liquid	83.54	$C_7H_6N_1O_4S_1Cl$	235.5
4a	H	H	CH_3	H	120–122	69.30	$C_{12}H_{15}N_1O_6S_1$	301.32
4b	CH_3	H	H	NO_2	138–140	73.20	$C_{12}H_{14}N_2O_8S_1$	346.32
4c	H	NO_2	CH_3	H	130–132	71.40	$C_{12}H_{14}N_2O_8S_1$	346.32
4d	H	H	H	H	145–147	56.66	$C_{11}H_{13}N_1O_6S_1$	287.29
5a	H	H	CH_3	H	110–112	79.70	$C_{12}H_{13}N_1O_4S_1Cl_2$	338.21
5b	CH_3	H	H	NO_2	99–100	88.55	$C_{12}H_{12}N_2O_6S_1Cl_2$	383.21
5c	H	NO_2	CH_3	H	85–87	74.90	$C_{12}H_{12}N_2O_6S_1Cl_2$	383.21
5d	H	H	H	H	108–110	71.57	$C_{11}H_{11}N_1O_4S_1Cl_2$	324.18

In all the equations, '*n*' represents number of data points; 'R' is multiple correlation coefficient, 'F' denotes F-statistic for the significance of each added variable at specified degrees of freedom, which explains the variances in experimental and predicted activities, SEE stands for standard error of the estimate, DC is Deleted Compound's number and q^2 is cross validated R^2.

Dummy variable I_1, used for substitution at the R_6 and R_6' positions, which takes the value of '1' for the presence of any substituent at the R_6 and R_6' positions, otherwise '0' for absence or the presence of hydrogen. R_6 and R_6' substituents which replaces the acidic hydrogen atom of secondary amino group, has been found to play a major role for antitumor activity, which is evident from the positive coefficient of the indicator parameter I_1 in the above equations. This may be due to possible exclusion of interaction between acidic hydrogen with the solvent molecules at the receptor site and hence allows the ligand to come more closer to active site. Hammett's sigma ($\Sigma\sigma$) parameter was shown to be significant only at 70% in eq (1), but the compounds **34** and **15** were behaving as outliers with larger residuals. Hence step by step exclusion of these compounds in eqs (2) and (3), has improved statistical significance of the same to 95% level and also statistical quality of the equations improved with better predictive power. $\Sigma\sigma$ term is indicative of dipolar interactions between the

Table 2. Physical data for different 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides **6**–**41**

Compd	R_1	R_2	R_3	R_4	R_5	R_6	Mp (°C)	% Yield	Molecular formula	MW
6	H	H	H	H	*i*-Butyl	H	178–180	95.43	$C_{19}H_{31}N_3O_4S_1$	397.54
7	H	H	H	H	*i*-Propyl	H	172–173	92.20	$C_{17}H_{27}N_3O_4S_1$	369.49
8	H	H	H	H	CH_3	CH_3	166–168	82.71	$C_{13}H_{19}N_3O_4S_1$	313.38
9	H	H	H	H	C_2H_5	C_2H_5	169–171	78.84	$C_{19}H_{31}N_3O_4S_1$	397.54
10	H	H	CH_3	H	$C_6H_5CH_2$	H	158–160	94.31	$C_{25}H_{27}N_3O_4S_1$	479.59
11	H	H	CH_3	H	*n*-C_6H_{13}	H	139–141	73.34	$C_{23}H_{39}N_3O_4S_1$	467.67
12	H	H	CH_3	H	C_6H_{11}	H	196–198	83.69	$C_{23}H_{35}N_3O_4S_1$	449.60
13	H	H	CH_3	H	*i*-Propyl	H	213–215	79.6	$C_{17}H_{27}N_3O_4S_1$	369.40
14	H	H	CH_3	H	*i*-Butyl	H	194–196	82.3	$C_{19}H_{31}N_3O_4S_1$	413.58
15	H	H	CH_3	H	*i*-Propyl	*i*-Propyl	171–173	34.8	$C_{23}H_{39}N_3O_4S_1$	453.60
16	H	H	CH_3	H	CH_3	CH_3	199–200	80.8	$C_{15}H_{23}N_3O_4S_1$	341.40
17	H	H	CH_3	H	C_2H_5	C_2H_5	123–125	79.2	$C_{19}H_{37}N_3O_4S_1$	403.50
18	CH_3	H	H	NO_2	H	H	172–173	70.0	$C_{12}H_{16}N_4O_6S_1$	344.34
19	CH_3	H	H	NO_2	CH_3	H	201–210	65.0	$C_{14}H_{20}N_4O_6S_1$	372.40
20	CH_3	H	H	NO_2	C_2H_5	H	245	71.9	$C_{16}H_{24}N_4O_6S_1$	400.46
21	CH_3	H	H	NO_2	*n*-C_3H_7	H	255	76.3	$C_{18}H_{28}N_4O_6S_1$	428.51
22	CH_3	H	H	NO_2	*n*-C_4H_9	H	145	87	$C_{20}H_{32}N_4O_6S_1$	456.56
23	CH_3	H	H	NO_2	*i*-Propyl	H	250	66.6	$C_{18}H_{28}N_4O_6S_1$	428.51
24	CH_3	H	H	NO_2	*i*-Butyl	H	155–158	87	$C_{20}H_{32}N_4O_6S_1$	456.56
25	CH_3	H	H	NO_2	*i*-Propyl	*i*-Propyl	165–168	65	$C_{24}H_{40}N_4O_6S_1$	512.67
26	CH_3	H	H	NO_2	C_6H_5	H	102–105	71	$C_{24}H_{24}N_4O_6S_1$	496.54
27	CH_3	H	H	NO_2	C_6H_{11}	H	215	77.3	$C_{24}H_{36}N_4O_6S_1$	508.64
28	CH_3	H	H	NO_2	$C_6H_5CH_2$	H	158–160	73.68	$C_{26}H_{28}N_4O_6S_1$	524.59
29	CH_3	H	H	NO_2	*n*-C_5H_{11}	H	130–132	64.29	$C_{22}H_{36}N_4O_6S_1$	484.62
30	CH_3	H	H	NO_2	*n*-C_6H_{13}	H	123–125	85.61	$C_{24}H_{40}N_4O_6S_1$	512.67
31	CH_3	H	H	NO_2	CH_3	CH_3	142–144	78.36	$C_{16}H_{24}N_4O_6S_1$	400.46
32	H	NO_2	CH_3	H	CH_3	H	218–219	71.25	$C_{14}H_{20}N_4O_6S_1$	372.40
33	H	NO_2	CH_3	H	*n*-C_3H_7	H	204–206	88.57	$C_{18}H_{28}N_4O_6S_1$	428.51
34	H	NO_2	CH_3	H	*n*-C_4H_9	H	188–190	82.47	$C_{20}H_{32}N_4O_6S_1$	456.56
35	H	NO_2	CH_3	H	*n*-C_5H_{11}	H	112–114	77.9	$C_{22}H_{36}N_4O_6S_1$	484.62
36	H	NO_2	CH_3	H	*n*-C_6H_{13}	H	159–161	79.73	$C_{24}H_{40}N_4O_6S_1$	512.67
37	H	NO_2	CH_3	H	*i*-Propyl	H	200–201	29.5	$C_{18}H_{28}N_4O_6S_1$	428.51
38	H	NO_2	CH_3	H	*i*-Butyl	H	189–191	76.64	$C_{20}H_{32}N_4O_6S_1$	456.56
39	H	NO_2	CH_3	H	C_6H_{11}	H	216–218	77.66	$C_{24}H_{36}N_4O_6S_1$	508.64
40	H	NO_2	CH_3	H	$C_6H_5CH_2$	H	203–204	80.0	$C_{26}H_{28}N_4O_6S_1$	524.60
41	H	NO_2	CH_3	H	C_6H_5	H	196–198	79.67	$C_{24}H_{24}N_4O_6S_1$	496.54

Table 3. Antitumor activity and molecular volume of 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides

Compd No	R_1	R_2	R_3	R_4	R_5	R_6	MV[a]	% TI[b]	Log(BA)
6	H	H	H	H	*i*-Butyl	H	2.24416	59.20	1.77
7	H	H	H	H	*i*-Propyl	H	2.04425	31.33	1.49
8	H	H	H	H	CH_3	CH_3	1.84676	58.43	1.76
9	H	H	H	H	C_2H_5	C_2H_5	2.25252	85.21	1.93
10	H	H	CH_3	H	$C_6H_5CH_2$	H	2.59631	39.63	1.59
11	H	H	CH_3	H	*n*-C_6H_{13}	H	2.74550	50.40	1.70
12	H	H	CH_3	H	C_6H_{11}	H	2.61147	39.51	1.59
13	H	H	CH_3	H	*i*-Propyl	H	2.14619	42.46	1.62
14	H	H	CH_3	H	*i*-Butyl	H	2.34612	50.00	1.69
15	H	H	CH_3	H	*i*-Propyl	*i*-Propyl	2.75668	50.00	1.69
16	H	H	CH_3	H	CH_3	CH_3	1.95418	66.06	1.82
17	H	H	CH_3	H	C_2H_5	C_2H_5	2.35448	70.90	1.85
18	CH_3	H	H	NO_2	H	H	1.68596	64.20	1.81
19	CH_3	H	H	NO_2	CH_3	H	1.89286	22.69	1.36
20	CH_3	H	H	NO_2	C_2H_5	H	2.09288	26.61	1.42
21	CH_3	H	H	NO_2	*n*-C_3H_7	H	2.29263	33.18	1.52
22	CH_3	H	H	NO_2	*n*-C_4H_9	H	2.49247	37.50	1.57
23	CH_3	H	H	NO_2	*i*-Propyl	H	2.29303	20.00	1.30
24	CH_3	H	H	NO_2	*i*-Butyl	H	2.49282	70.30	1.85
25	CH_3	H	H	NO_2	*i*-Propyl	*i*-Propyl	2.90348	70.37	1.85
26	CH_3	H	H	NO_2	C_6H_5	H	2.53170	40.70	1.61
27	CH_3	H	H	NO_2	C_6H_{11}	H	2.75788	31.33	1.49
28	CH_3	H	H	NO_2	$C_6H_5CH_2$	H	2.74237	58.89	1.77
29	CH_3	H	H	NO_2	*n*-C_5H_{11}	H	2.69215	51.12	1.71
30	CH_3	H	H	NO_2	*n*-C_6H_{13}	H	2.89193	53.20	1.73
31	CH_3	H	H	NO_2	CH_3	CH_3	2.10074	55.11	1.74
32	H	NO_2	CH_3	H	CH_3	H	1.89192	20.51	1.31
33	H	NO_2	CH_3	H	*n*-C_3H_7	H	2.29193	34.04	1.53
34	H	NO_2	CH_3	H	*n*-C_4H_9	H	2.49175	74.85	1.87
35	H	NO_2	CH_3	H	*n*-C_5H_{11}	H	2.69166	58.44	1.76
36	H	NO_2	CH_3	H	*n*-C_6H_{13}	H	2.89145	12.69	1.10
37	H	NO_2	CH_3	H	*i*-Propyl	H	2.29215	28.16	1.45
38	H	NO_2	CH_3	H	*i*-Butyl	H	2.49203	52.10	1.71
39	H	NO_2	CH_3	H	C_6H_{11}	H	2.75725	45.45	1.66
40	H	NO_2	CH_3	H	$C_6H_5CH_2$	H	2.74202	68.84	1.84
41	H	NO_2	CH_3	H	C_6H_5	H	2.53108	66.66	1.82
STD[c]				Mitomycin-C				100.00	2.00

[a]MV is scaled by factor 0.01 for linear relation with other parameters.
[b]%TI is percentage inhibition of tumor weight.
[c]STD is standard drug (Mitomycin-C).

electron deficient active sites of the receptor and the electron rich phenyl ring of the glutamamide, which is represented by its negative coefficient.

The positive steric term (Es R_5) at the R_5 position suggests that the steric bulk at R_5 substitution is detrimental to the activity. It explains that the smaller substituents at the R_5 position are conductive to biological activity. Molecular volume has the positive contribution to the activity and necessitates for still larger volume of the ligands for more accurate fit into the active sites.

Table 4. Aromatic substituent constants used in deriving QSAR equations[12]

Substituent	π	σ	MR	Es	F	R
H	0.00	0.00 (σ−p, σ−m) −0.06 (σ−o)	0.103	0.00	0.00	0.00
CH_3	0.56	−0.17 (σ−p) −0.36 (σ−o)	0.565	−1.24	−0.04	−0.13
NO_2	−0.28	0.71 (σ−m)	0.736	−2.52	0.67	0.16

By the introduction of an indicator variable I_3 for the presence of NO_2 group at the 3′ and 5′ positions on the benzene ring yielded the following eq (4).

$$\log(BA) = 1.0863\ (\pm 0.1230) + 0.1412\ (\pm 0.0286)\ \mathrm{Es}R_5 + 0.2357\ (\pm 0.0439)\ I_1 + 0.4094\ (\pm 0.0622)\ \mathrm{MV} + 0.3537\ (\pm 0.0646)\ I_2 - 0.0972\ (\pm 0.0363)\ I_3$$
$$n = 33, \quad R^2 = 0.7574, \quad F_{5,27} = 16.86, \quad \mathrm{SEE} = 0.0900, \quad p = 0.00000, \quad \mathrm{DC} = 36,\ 34, 15, \quad q^2 = 0.7583 \qquad (4)$$

The above equation explains around 75% of the variances in the activity data and all the parameters are significant at 99% level. Predicted and residual values of log(BA) as obtained from eq (4) are listed in Table 7. The negative Σσ term in eq (3) and the negative coefficient of indicator variable I_3 in eq (4) represents that the electron withdrawing group on the phenyl ring is detrimental to the activity or it requires high electron density on the aromatic ring system to interact with electron deficient receptor sites.

Indicator parameter I_2, that takes the value '1' for isobutyl group at the R_5 and R_5' positions, otherwise '0' for any other substitution or hydrogen. Isobutyl group found to be conductive to the activity [eq (4)] as evident from its positive coefficient. But when isobutyl group was combined with isopropyl group to a common indicator parameter resulted in insignificant model. The apparent reason may be the lengthy alkyl groups with branched end helps in improving the activity than the corresponding normal alkyl chains.

The following eq (5) explains the possible hydrophobic interactions between the R_5 substituents with the active site.

$$\log (BA) = 1.7056\ (\pm 0.0752) + 0.0893\ (\pm 0.0146)\ \pi R_5 + 0.1710\ (\pm 0.0326)\ Es\ R_5 + 0.3708\ (\pm 0.0500)\ I_1 + 0.3705\ (\pm 0.0667)\ I_2$$
$$n = 33, \quad R^2 = 0.7249, \quad F_{4,28} = 18.45, \quad SEE = 0.0941, \quad p = 0.00000, \quad DC = 36,\ 34,\ 15 \qquad (5)$$

All the parameters in the above equation are significant at the 99% level and also the equation explains around 73% of the variances in the activity. Various other combinations of the parameters were tried, but eqs (3) and (4) were only proved to be better predictive and statistically of good quality as evident from LOO prediction results furnished in Table 7. The compounds **36**, **34** and **15** had shown their predicted activities much higher than observed ones, hence the stepwise deletion of these compounds drastically improved the statistical quality of the equations from eq (1) to (3). The F value has increased from 8.37 to 14.78 and the correlation coefficient R value has raised to 0.8558. Also, eq (3) explains 73.25% of the variances in activity. Replacement of $\Sigma\sigma$ with indicator I_3 has produced the equally accurate eq (4). The negative coefficient of indicator parameter I_3 representing NO_2 group on the 3rd and 5th positions of the phenyl ring, indicates that it is detrimental to the activity or produces untoward side effects. It explains 75.74% of the variances in the activity. The R value further rose to 0.8703. Statistical quality and preditive potentail of this equation is further explained by LOO prediction and the predicted values are furnished in Table 7.

Table 5. Aliphatic substituent constants used in deriving QSAR equations[12]

Substituent	π	MR	Es
H	0.00	0.103	0.00
CH_3	0.04	0.357	−1.24
C_2H_5	0.56	0.817	−1.31
n-C_3H_7	1.09	1.29	−1.43
n-C_4H_9	1.62	1.747	−1.63
n-C_5H_{11}	2.15	2.217	−1.64
n-C_6H_{13}	2.68	2.677	−1.54
C_6H_{11}	2.07	2.497	−1.81
i-Propyl	0.87	1.287	−1.71
i-Butyl	1.49	1.747	−2.17
C_6H_5	2.27	2.277	−1.01
$C_6H_5CH_2$	2.06	2.867	−1.51

MR values are scaled by factor of 0.1 as usual.

Conclusion

All the title compounds have shown different inhibitions on EAC depending on the substitution pattern. A QSAR study was performed to identify the structural features influencing antitumor activity. From the QSAR study, it is clear that glutamamides requires high electron density, that is electron-donating groups on the phenyl ring or at least electronegative groups should not be used for the dipolar interactions with electron deficient receptor surface. This is evident from the negative $\Sigma\sigma$ term and negative indicator parameter I_3 in eq (4) for NO_2 group on phenyl ring. Indicator parameter I_2 representing isobutyl group at R_5 indicates the possible improvement in activity with the substitution of branched alkyl groups with more than four carbons at R_5 and R_5' positions. Displacement of acidic hydrogen atoms of imino groups with substituents R_6 and R_6', shown by the indicator variable I_1 has improved the biological activity. Lower coefficient of hydrophobic term necessitates for substitution elsewhere, apart from the positions where congener series possesses to ensure the ligand to enter into the hydrophobic pocket of the receptor. Introducing some linker chains between phenyl ring and imino group of SO_2NH or substitution elsewhere may increase molecular volume and hydrophobic character for more potent activity.

Table 6. Correlation matrix for the descriptors used in developing QSAR equations

	Σπ	Σσ	ΣMR	ΣF	ΣR	ΣEs	πR_5	MRR_5	EsR_5	MV	Log(BA)
Σπ	1	−0.5	0.01	−0.3	−0.75	0.04	0.18	0.16	−0.06	0.22	0.01
Σσ	−0.47	1	0.88	0.98	0.93	−0.9	0	0.07	0.16	0.13	−0.23
ΣMR	0.01	0.88	1	0.95	0.65	−1	0.1	0.17	0.15	0.26	−0.25
ΣF	−0.31	0.98	0.95	1	0.86	−0.96	0.04	0.11	0.16	0.18	−0.24
ΣR	−0.75	0.93	0.65	0.86	1	−0.69	−0.07	−0.01	0.14	0	−0.17
ΣEs	0.04	−0.9	−1	−1	−0.69	1	−0.09	−0.16	−0.15	−0.25	0.25
πR_5	0.18	0	0.1	0.04	−0.07	−0.09	1	0.88	−0.57	0.87	−0.05
MRR_5	0.16	0.07	0.17	0.11	−0.01	−0.16	0.88	1	−0.43	0.86	0.01
EsR_5	−0.06	0.16	0.15	0.16	0.14	−0.15	−0.57	−0.43	1	−0.45	0.04
MV	0.22	0.13	0.26	0.18	0	−0.25	0.87	0.86	−0.45	1	0.1
Log(BA)	0.01	−0.2	−0.3	−0.2	−0.17	0.25	−0.05	0.01	0.04	0.1	1

Experimental

Synthesis

Chemistry. 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides were synthesized in accordance with Scheme 1. Substituted benzene **1** upon chlorosulphonation[10] yielded corresponding sulphonyl chlorides **2a**–**2b** except in case of p-tosyl chloride and benzenesulphonyl chloride, which were the commercial products purchased. This halide proved to be versatile synthon in the subsequent step in the preparation of substituted benzenesulphonyl glutamic acids **4**. With the application of the Schotton–Bauman reaction, 2-(substituted benzenesulphonyl) glutamic acids were prepared **4a**–**4d** by one step condensation of **2** with L-glutamic acid **3**. Further halogenation of resultant diacid **4** with thoinyl chloride resulted in corresponding acid dichlorides **5a**–**5d** with the release of two molecules of water. Nucleophilic displacement of chloro groups of 2-(substituted benzenesulphonyl) glutamic acid dichlorides **5a**–**5d** with different amines[11] yielded corresponding diamides **6**–**41** as amorphous or crystalline products with varying yields.

General. All the meting points were determined on Mel-Temp II melting point apparatus and are uncorrected. Elemental or micro analyses (C, H, N) of the compounds were performed on 2400 Series II CHN analyser of Perkin-Elmer. Infrared spectra were performed on M-500 Model IR spectrophotometer of Buck Scientific, using KBr discs. The frequencies are expressed in cm^{-1}. ^1H NMR spectra were recorded on Bruker DRX 500, Bruker (300 MHz), Varian gemini (200 MHz) and Bruker RDX (200 MHz) using Tetramethyl Silane (Me_4Si) as an internal standard for solutions in $CDCl_3$ and DMSO-d_6. Chemical shifts are expressed in δ ppm (parts per million) down field from Me_4 Si and the coupling constant J in Hz. Splitting patterns have been designated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet). Position of hydrogens described in ^1H NMR interpretation are as per general structure (Fig. 1) and substitutions at the R_5' and R_6' positions has taken the superscript '″' (double dash) and the substitution at R_5 and R_6 has taken the superscript '‴' (triple dash). The mass spectra (FAB) were recorded on JEOL-JMS-SX-102 mass spectrometer. *p*-Nitro benzyl alcohol (PNBA) was used as matrix (M^+) which showed the $M+1$ peak at 154, $2M+1$ peak at 307. Reactions were monitored by analytical thin layer chromatography performed on silica gel G plates. The spots were located keeping the TLC plates in iodine chamber.

Table 7. Observed and calculated antitumor activities as per eqs (3) and (4)

Compd	Observed	Eq (3)			Eq (4)		
		Pred	Residual	LOO pred	Pred	Residual	LOO pred
6	1.77	1.72	0.05	1.70	1.75	0.02	1.73
7	1.49	1.41	0.09	1.39	1.44	0.05	1.42
8	1.76	1.71	0.05	1.70	1.73	0.03	1.77
9	1.92	1.85	0.07	1.84	1.87	0.05	1.86
10	1.59	1.71	−0.11	1.74	1.72	−0.12	1.75
11	1.70	1.76	−0.06	1.78	1.77	−0.07	1.79
12	1.59	1.63	−0.03	1.63	1.64	−0.04	1.65
13	1.62	1.47	0.15	1.43	1.48	0.14	1.45
14	1.69	1.79	−0.09	1.83	1.79	−0.08	1.82
16	1.82	1.78	0.03	1.77	1.77	0.04	1.76
17	1.85	1.92	−0.06	1.94	1.92	−0.06	1.93
18	1.80	1.74	0.06	1.62	1.78	0.03	1.71
19	1.35	1.44	−0.08	1.45	1.41	−0.05	1.43
20	1.42	1.49	−0.06	1.50	1.48	−0.05	1.48
21	1.52	1.53	−0.01	1.53	1.52	−0.00	1.52
22	1.57	1.55	0.02	1.55	1.55	0.02	1.55
23	1.30	1.45	−0.14	1.46	1.44	−0.14	1.46
24	1.84	1.76	0.08	1.73	1.75	0.09	1.71
25	1.84	1.93	−0.07	1.97	1.93	−0.08	1.97
26	1.60	1.76	−0.15	1.78	1.74	−0.13	1.76
27	1.49	1.59	−0.10	1.61	1.61	−0.11	1.62
28	1.76	1.67	0.08	1.68	1.68	0.08	1.68
29	1.71	1.63	0.08	1.62	1.63	0.07	1.62
30	1.72	1.74	−0.01	1.74	1.74	−0.01	1.74
31	1.74	1.76	−0.01	1.76	1.73	0.01	1.73
32	1.31	1.44	−0.12	1.46	1.41	−0.10	1.43
33	1.53	1.53	−0.00	1.53	1.52	0.01	1.52
35	1.76	1.63	0.14	1.61	1.63	0.13	1.62
37	1.45	1.45	0.00	1.44	1.44	0.00	1.44
38	1.72	1.76	−0.04	1.78	1.75	−0.03	1.76
39	1.66	1.60	0.05	1.59	1.61	0.05	1.60
40	1.84	1.69	0.15	1.67	1.68	0.15	1.67
41	1.82	1.76	0.06	1.75	1.74	0.08	1.72

LOO pred, Leave-One-Out predicted values; Compd, compound number.

General synthetic procedures

Method 1. Substituted benzenesulphonyl chloride 2a–2b. To a mixture of substituted benzene (0.1 mol) in chloroform (50 mL), in an 500 mL flask equipped with dropping funnel, thermometer, reflux condensor, was added chlorosulphonic acid (0.25 mol) dropwise over a period of 45–60 min. The reaction mixture was stirred magnetically at 0 °C in a bath containing freezing mixture of ice and salt. Chlorosulphonic acid was added in such a rate that the temperature of the reaction mixture does not exceed 5 °C. After the complete addition of chlorosulphonic acid, the reaction mixture was stirred for another 45 min at room temperature and the mixture was poured onto crushed ice. The product was extracted with three 50-mL portions of chloroform, dried overnight over anhydrous sodium sulphate. Chloroform was distilled off. The product was sufficiently pure which was not attempted for further purification. It has been taken for the next step.

Method 2. 2-(Substituted benzene sulphonyl) glutamic acid 4a–4e. L-Glutamic acid (14.7 g: 0.1 mol) was taken in a 250 mL conical flask and sodium hydroxide solution (2 N) was added slowly till all the glutamic acid dissolves and mixture becomes distinctly alkaline to phenolphthalein. The reaction mixture was stirred on the magnetic stirrer with temperature maintained at 70 °C using hot water bath. Substituted benzenesulphonyl chloride (0.15 mol) was added in small portions with constant stirring and time to time addition of sodium hydroxide (2 N) to keep the reaction mixture alkaline. The reaction was continued until a clear homogeneous solution results or the thin layer chromatography showed the reaction to be complete. After the reaction was over, it was allowed to cool to room temperature and filtered to separate undissolved solid matter if any. The filtrate was acidified with concentrated hydrochloric acid and saturated with sodium chloride. The product was extracted with three 50 mL portions of ethyl acetate. Ethyl acetate layer was washed with brine solution (15 mL) and dried overnight over anhydrous sodium sulphate. The solvent was distilled off to get the product.

2-(4′-Methyl benzenesulphonyl) glutamic acid (4a). IR (KBr, cm^{-1}): 3253, 3031(Ar–C–H str), 2871 (Ali C-H str), 1698 (C=O str), 1409, 1334 and 1150 (S=O str of SO_2NH), 985, 816 (Ar–C–H def), 658. Anal. $C_{12}H_{15}N_1O_6S_1$ (C, H, N) calcd: 47.84, 4.98, 4.04; found: 47.64, 4.78, 4.02.

2-(2′-Methyl-5′-nitro benzenesulphonyl) glutamic acid (4b). IR (KBr, cm^{-1}): 3531, 3366, 3031 (Ar–C–H str), 2871 (Ali C–H str), 1679 (C=O str), 1515 (N=O str of Ar–NO_2), 1337, 1191 (S=O str of SO_2NH), 914, 792 & 733 (Ar–C–H def), 626. Anal. $C_{12}H_{14}N_2O_8S_1$ (C, H, N) calcd: 41.62, 4.05, 8.09; found: 41.72, 4.18, 8.21.

2-(4′-Methyl-3′-nitro benzenesulphonyl) glutamic acid (4c). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.42 (d, 1H, H-2′), 8.05 (m, 1H, SO_2NH), 7.96 (dd, 1H, H-6′), 7.53 (d, 1H, H-5′), 3.88 (m, 1H, H-2), 2.58 (s, 3H, Ar–CH_3), 2.30 (m, 2H, H_2-4), 2.02 (m, 2H, H_A-3), 1.82 (m, 1H, H_B-3). IR (KBr, cm^{-1}): 3227, 3031(Ar–C–H str), 2861 (ali C–H str), 1694 (C=O str), 1512 (N=O str of Ar–NO_2), 1404, 1336 and 1165 (S=O str of SO_2NH), 1104, 894, 713 (Ar–C–H def), 661. Anal. $C_{12}H_{14}N_2O_8S_1$ (C, H, N) calcd: 41.62, 4.05, 8.09; found: 41.59, 3.95, 8.12.

2-(Benzenesulphonyl) glutamic acid (4d). IR (KBr, cm^{-1}): 3191, 3031 (Ar–C–H str), 2881 (ali C–H str), 1726 (C=O str), 1695, 1428, 1375, 1303 and 1155 (S=O str of SO_2NH), 970, 888, 765 and 724 (Ar–C–H def). Anal. $C_{11}H_{13}N_1O_6S_1$ (C, H, N) calcd: 45.99, 4.53, 4.88; found: 45.96, 4.52, 4.62.

Method 3. Synthesis of 2-(substituted benzenesulphonyl)-1,5-glutamic acid dichloride (5). Substituted benzenesulphonyl glutamic acid (1 equivalent) was taken in 100-mL two-necked flask fitted with dropping funnel and reflux condenser connected at the top to a gas absorption trap. Thionyl chloride (1.2 equivalent) was added dropwise from the dropping funnel. The reaction set up was heated on a water bath. Thionyl chloride was added for a period of 30–40 min with occasional stirring. After the complete addition, the reaction mixture was further heated for additional 30 min or until the evolution of HCl gas ceases. Apparatus was then rearranged and excess of $SOCl_2$ was removed by distilling with three 10-mL portions of dry benzene under reduced pressure. The resultant dichloride was sufficiently pure for the subsequent reactions and hence the further purification was not attempted to avoid unnecessary decomposition.

Method 4. Synthesis of 2-(substituted benzenesulphonyl)-1,5-*N*,*N*-dialkyl glutamamides 6–41. A 50-mL round bottomed flask containing 2-(substituted benzenesulphonyl)-1,5-dicarboxylic acid dichloride (1 equivalent) in 10 mL of dry benzene was fitted with reflux condenser. Acyl chloride was added with excess of amine (2.5 equivalent) and refluxed on the water bath for 30 min or until the thin layer chromatography showed the reaction to be complete. Benzene was distilled out and the reaction mixture was acidified with dilute hydrochloric acid to remove any traces of unreacted amine. It was then filtered at the pump and recrystallized from dilute ethanol. All the resultant glutamamides were characterized and hence the structures of corresponding acid dichlorides.

1,5-*N*,*N*′-di *i*-Butyl-2-(benzenesulphonyl) glutamamide (6). MS (FAB): $M+H^+$ peak at m/z 398. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (m, 2H, H-2′, H-6′), 7.37–7.26 (m, 2H, H-3′, H-4′, H-5′), 7.11 (s, 1H, SO_2NH), 6.88 (m, 1H, CONH), 5.76 (m, 1H, CONH), 3.60 (m, 1H, H-2), 3.15 (m, 2H, CH_2-1‴), 3.02 (m, 2H, CH_2-1″), 1.99–1.71 (m, 4H, H_2-4, H_2-3), 1.10–0.91 (m, 14H, CH-2‴, CH-2″, CH_3-3‴ CH_3-4‴, CH_3-3″ CH_3-4″). IR (KBr, cm^{-1}): 3250, 3176 (N–H str of CONH), 3035 (Ar–C–H str), 2903 and 2875 (ali C–H str), 1632, 1437 (ali C–H def), 1328 and 1158 (S=O str of SO_2NH, 1086, 970, 752 and 721 (Ar–C–H def), 684. Anal. $C_{19}H_{31}N_3O_4S_1$ (C, H, N) calcd: 57.43, 7.80, 10.58; found: 57.35, 7.74, 10.40.

1,5-*N*,*N*′-di *i*-Propyl-2-(benzenesulphonyl) glutamamide (7). MS (FAB): $M+H^+$ peak at *m*/*z* 370. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (m, 2H, H-2′, H-6′), 7.36–7.25 (m, 2H, H-3′, H-4′, H-5′), 7.09 (s, 1H, SO_2NH), 6.40 (m, 1H, CONH), 5.79 (m, 1H, CONH), 3.96 (m, 1H, CH-1‴), 3.87 (m, 1H, CH-1″), 3.48 (m, 1H, H-2), 2.31 (m, 1H, H_A-3), 2.12 (m, 1H, H_B-3), 1.97 (m, 2H, H_2-4,), 1.35–1.21 (m, 6H, CH_3-2‴, CH_3-3‴), 0.97–0.89 (m, 6H, CH_3-2″, CH_3-3″). IR (KBr, cm^{-1}): 3241, 3178 (N–H str of CONH), 3001 (Ar–C–H str), 2878 (ali C–H str), 1624, 1529, 1437 (ali C–H def), 1328 and 1152 (S=O str of SO_2NH), 1084, 773, 748 and 714 (Ar–C–H def), 675. Anal. $C_{17}H_{27}N_3O_4S_1$ (C, H, N) calcd: 55.28, 7.32, 11.38; found: 55.18, 7.28, 11.70.

1,5-*N*,*N*′-di-(Dimethyl)-2-(benzenesulphonyl) glutamamide (8). MS (FAB): $M+H^+$ peak at *m*/*z* 314. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (m, 2H, H-2′, H-6′), 7.42–7.29 (m, 3H, H-3′, H-4′, H-5′), 7.11 (s, 1H, SO_2NH), 3.11 (m, 6H, CH_3-1‴, CH_3-2‴), 2.95 (m, 6H, CH_3-1″, CH_3-2″), 2.60 (m, 1H, H-2), 2.31 (m, 2H, H_2-4), 1.86 (m, 1H, H_A-3), 1.54 (m, 1H, H_B-3). IR (KBr, cm^{-1}): 3371, 3032 (Ar–C–H str), 2875 (ali C–H str), 1632 (C=O str overlapped with N–H bend), 1480, 1342 and 1158 (S=O str of SO_2NH), 1117, 757 and 702 (Ar–C–H def), 662. Anal. $C_{13}H_{19}N_3O_4S_1$ (C, H, N) calcd: 49.84, 6.07, 13.41; found: 49.75, 6.21, 13.42.

1,5-*N*,*N*′-di-(Diethyl)-2-(benzenesulphonyl) glutamamide (9). MS (FAB): $M+H^+$ peak at *m*/*z* 398. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 (m, 2H, H-2′, H-6′), 7.62–7.46 (m, 3H, H-3′, H-4′, H-5′), 7.10 (m, 1H, SO_2NH), 3.52 (m, 1H, H-2), 3.48–3.32 (m, 8H, N–CH_2-1‴, N-CH_2-3‴, N–CH_2-1″, N–CH_2-3″), 2.66 (m, 2H, H_2-4), 2.42 (m, 1H, H_A-3), 2.36 (m, 1H, H_B-3), 1.31 (m, 6H, CH_3-2‴, CH_3-4‴), 1.15 (m, 6H, CH_3-2″, CH_3-4″). IR (KBr, cm^{-1}): 3035 (Ar–C–H str), 2881 (ali C–H str), 1634 (C=O str), 1440 (ali C–H def), 1345 and 1164 (S=O str of SO_2NH), 1114, 765 and 722 (Ar–C–H def), 684. Anal. $C_{19}H_{31}N_3O_4S_1$ (C, H, N) calcd: 57.43, 7.81, 10.58; found: 57.34, 7.91, 10.30.

1,5-*N*,*N*′-di-Benzyl-2-(4′-methyl benzenesulphonyl) glutamamide (10). MS (FAB): $M+H^+$ peak at *m*/*z* 480. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65 (d, 2H, H-2′, H-6′), 7.48–7.19 (m, 13H, H-3′, H-5′, SO_2NH, ph-protons), 6.83 (m, 2H, CONH-1, CONH-5), 4.38 (m, 2H, CH_2-ph), 4.35 (m, 2H, CH_2-ph), 3.79 (m, 1H, H-2), 2.39 (s, 3H, Ar–CH_3), 2.35 (m, 2H, H_2-4), 2.09–1.94 (m, 2H, H_2-3). IR (KBr, cm^{-1}): 3295, 3196 (N–H str of CONH), 2975, 2874, 1700 (C=O str of CONH), 1554, 1441, 1324 and 1154 (S=O str of SO_2NH), 981, 791, 719 (Ar–C–H def), 691, 677. Anal. $C_{25}H_{27}N_3O_4S_1$ (C, H, N) calcd: 62.63, 5.63, 8.76; found: 62.43, 5.43, 8.54.

1,5-*N*,*N*′-di *n*-Hexyl-2-(4′-methyl benzenesulphonyl) glutamamide (11). MS (FAB): $M+H^+$ peak at *m*/*z* 468. ^{1}H NMR (200 MHz, DMSO): δ 8.30 (m, 1H, SO_2NH), 8.00 (m, 2H, H-2′, H-6′), 7.87 (m, 2H, H-3′, H-5′), 7.57 (m, 2H, CONH-1, CONH-5), 3.98 (m, 1H, H-2), 3.21 (m, 2H, N–CH_2-1‴), 3.03 (m, 2H, N–CH_2-1″), 2.59 (s, 3H, Ar–CH_3), 2.27 (m, 2H, H_2-4), 1.88 (m, 2H, H_2-3), 1.57–1.39 (m, 16H, CH_2-2″, CH_2-3″, CH_2-4″, CH_2-5″, CH_2-2‴, CH_2-3‴ CH_2-4‴, CH_2-5‴), 1.08 (m, 6H, CH_3-6″, CH_3-6‴). IR (KBr, cm^{-1}): 3299, 3232, 3170 (N–H str of CONH), 3021 (Ar–C–H str), 2897, 2877 (ali C–H str), 1643 (C=O str), 1625, 1543, 1444 (ali C–H def), 1328, 1313 and 1157 (S=O str of SO_2NH), 1084, 970, 710, 672 (Ar–C–H def). Anal. $C_{23}H_{39}N_3O_4S_1$ (C, H, N) calcd: 59.10, 8.35, 8.99; found: 59.09, 8.07, 8.84.

1,5-*N*,*N*′-di-Cyclohexyl-2-(4′-methyl benzenesulphonyl) glutamamide (12). MS (FAB): $M+H^+$ peak at *m*/*z* 450. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (m, 2H, H-2′, H-6′), 7.28 (d, 2H, H-3′, H-5′), 7.01 (s, 1H, SO_2NH), 6.62 (d, 1H, CONH), 6.46 (d, 1H, CONH), 3.76 (m, 1H, H-2), 3.68 (m, 1H, CH-1‴), 3.62–3.46 (m, 1H, CH-1″), 2.40 (s, 3H, Ar–CH_3), 2.35–2.20 (m, 2H, H_2-3), 2.13–2.07 (m, 2H, H_2-4), 1.92–1.00 (m, 20H, cyclohexyl protons). IR (KBr, cm^{-1}): 3240, 3187 (N–H str of CONH), 2876, 2804 (ali C–H str), 1626 (C=O str), 1531, 1436 (ali C–H def), 1326 and 1155 (S=O str of SO_2NH), 1083, 664 (Ar–C–H def). Anal. $C_{23}H_{35}N_3O_4S_1$ (C, H, N) calcd: 61.47, 7.79, 9.35; found: 61.54, 8.11, 9.13.

1,5-*N*,*N*′-di *i*-Propyl-2-(4′-methyl benzenesulphonyl) glutamamide (13). MS (FAB): $M+H^+$ peak at *m*/*z* 370. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, 2H, *J* = 8.20, H-2′, H-6′), 7.26 (d, 2H, *J* = 7.97, H-3′, H-5′), 7.05 (s, 1H, SO_2NH), 6.56 (d, 1H, CONH), 5.59 (d, 1H, CONH), 4.06 (m, 1H, CH-1″), 3.87 (m, 1H, CH-1‴), 3.57 (m, 1H, H-2), 2.40 (s, 3H, Ar–CH_3), 2.32 (m, 1H, H_A-3), 2.08 (m, 1H, H_B-3), 1.89–1.85 (m, 2H, H_2-4), 1.19–1.16 (m, 6H, CH_3-2‴, CH_3-3‴), 1.07 (m, 3H,CH_3-2″), 0.97 (m, 3H, CH_3-3″).IR (KBr, cm^{-1}): 3238, 3176 (N–H str of CONH), 2912 and 2876 (ali C–H str), 1623, 1531, 1433 (ali C–H def), 1328 and 1152 (S=O str of SO_2NH), 1083, 671 (Ar–C–H def). Anal. $C_{17}H_{27}N_3O_4S_1$ (C, H, N) calcd: 55.28, 7.32, 11.38; found: 55.27, 7.52, 11.57.

1,5-*N*,*N*′-di *i*-Butyl-2-(4′-methyl benzenesulphonyl) glutamamide (14). MS (FAB): $M+H^+$ peak at *m*/*z* 412. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 (m, 2H, H-2′, H-6′), 7.28–7.17 (m, 3H, H-3′, H-5′, SO_2NH), 6.87 (m, 1H, CONH), 5.75 (m, 1H, CONH), 3.61 (m, 1H, H-2), 3.08 (m, 2H, N–CH_2-1‴), 2.96 (m, 2H, N–CH_2-1″), 2.40 (s, 3H, Ar–CH_3), 1.93–1.62 (m, 4H, H_2-3, H_2-4), 1.32–1.20 (m, 2H, CH-2″, CH-2‴), 0.94–0.80 (m, 12H, CH_3-3″, CH_3-4″, CH_3-3‴, CH_3-4‴). IR (KBr, cm^{-1}): 3299, 3240, 3167 (N–H str of CONH), 3032 (Ar–C–H str), 2900, 2876 (ali C–H str), 1648, 1628, 1538, 1443, 1424 (ali C–H def), 1334 and 1312, 1158 (S=O str of SO_2NH), 1084, 972, 745, 699 (Ar–C–H def), 671. Anal. $C_{20}H_{33}N_3O_4S_1$ (C, H, N) calcd: 55.20, 7.51, 10.17; found: 55.17, 7.49, 10.18.

1,5-*N*,*N*′-di-(Diisopropyl)-2-(4′-methyl benzenesulphonyl) glutamamide (15). MS (FAB): $M+H^+$ peak at *m*/*z* 454. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 8.20, H-2′, H-6′), 7.28 (d, 2H, *J* = 8.18, H-3′, H-5′), 7.00 (s, 1H, SO_2NH), 4.06 (m, 2H, CH-1″, CH-4″), 3.87–3.79 (m, 2H, CH-1‴, CH-4‴), 3.56 (m, 1H, H-2), 2.40 (s, 3H, Ar–CH_3), 2.33 (m, 1H, H_A-3), 2.09 (m, 1H, H_B-3), 1.90–1.85 (m, 2H, H_2-4), 1.23–1.14 (m, 12H, CH_3-2‴, CH_3-3‴, CH_3-5‴, CH_3-6‴), 1.06–0.84 (m, 12H, CH_3-2″,

CH_3-3″, CH_3-5″, CH_3-6″). IR (KBr, cm^{-1}): 3033 (Ar–C–H str), 2909, 2878 (ali C–H str), 1637 (C=O str overlapped with N–H bend), 1436 (ali C–H def), 1345 and 1159 (S=O str of SO_2NH), 956, 747 and 702 (Ar–C–H def), 662. Anal. $C_{23}H_{39}N_3O_4S_1$ (C, H, N) calcd: 60.93, 8.61, 9.27; found: 60.84, 8.59, 9.27.

1,5-*N*,*N*′-di-(Dimethyl)-2-(4′-methyl benzenesulphonyl) glutamamide (16). MS (FAB): $M+H^+$ peak at *m*/*z* 342. ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 (m, 2H, H-2′, H-6′), 7.29 (m, 2H, H-3′, H-5′), 5.27 (m, 1H, SO_2NH), 3.16 (m, 6H, CH_3-1‴, CH_3-2‴), 3.01 (m, 6H, CH_3-1″, CH_3-2″), 2.65 (m, 1H, H-2), 2.58 (s, 3H, Ar–CH_3), 2.38 (m, 2H, H_2-4), 1.98 (m, 1H, H_A-3), 1.60 (m, 1H, H_B-3). IR (KBr, cm^{-1}): 3371, 3031 (Ar–C–H str), 2877 (ali C–H str), 1637 (C=O str overlapped with N–H bend), 1480, 1343 and 1158 (S=O str of SO_2NH), 1116, 756 and 707 (Ar–C–H def), 667, 614. Anal. $C_{15}H_{23}N_3O_4S_1$ (C, H, N) calcd: 52.78, 6.74, 12.32; found: 52.67, 6.59, 12.14.

1,5-*N*,*N*′-di (Diethyl)-2-(4′-methyl benzenesulphonyl) glutamamide (17). MS (FAB): $M+H^+$ peak at *m*/*z* 404. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (m, 2H, H-2′, H-6′), 7.29 (m, 2H, H-3′, H-5′), 5.19 (m, 1H, SO_2NH), 3.54–3.31 (m, 8H, CH_2-1″, CH_2-3″, CH_2-1‴, CH_2-3‴), 2.74–2.66 (m, 1H, H-2), 2.41 (s, 3H, Ar–CH_3), 2.39–2.34 (m, 2H, H_2-3), 1.96 (m, 2H, H_2-4), 1.31 (m, 6H, CH_3-2‴, CH_3-4‴), 1.16 (m, 6H, CH_3-2″, CH_3-4″). IR (KBr, cm^{-1}): 3378, 2922 and 2878 (Ali C–H str), 1635 (C=O str), 1453 (ali C–H def), 1344 and 1160 (S=O str of SO_2NH), 954, 745 and 668 (Ar–C–H def). Anal. $C_{19}H_{37}N_3O_4S_1$ (C, H, N) calcd: 56.57, 8.03, 10.23; found: 56.78, 8.14, 10.40.

2-(2′-Methyl-5′-nitro benzenesulphonyl) glutamamide (18). MS (FAB): $M+H^+$ peak at *m*/*z* 345. ^1H NMR (200 MHz, $CDCl_3$): δ 8.70 (d, 1H, H-6′), 8.30 (dd, 1H, H-4′), 7.55 (d, 1H, H-3′), 7.45 (m, 1H, SO_2NH), 7.10 (m, 2H, $CONH_2$-1), 6.71 (m, 2H, $CONH_2$-5), 3.73 (m, 1H, H-2), 2.70 (s, 3H, Ar–CH_3), 2.24 (m, 2H, H_2-4), 1.90 (m, 2H, H_2-3). IR (KBr, cm^{-1}): 3394, 3353, 3301 (N–H str of CONH), 3049 (Ar–C–H str, assymmetric), 1652 (C=O str), 1619, 1506 (N=O str of Ar–NO_2), 1418, 1337, 1301, 1148 (S=O str of SO_2NH), 1055, 783, 736, 713 (Ar–C–H def). Anal. $C_{12}H_{16}N_4O_6S_1$ (C, H, N) calcd: 41.86, 4.65, 16.28; found: 41.84, 4.63, 16.24.

1,5-*N*,*N*′-di-Methyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (19). MS (FAB): $M+H^+$ peak at *m*/*z* 373. ^1H NMR (200 MHz, $CDCl_3$): δ 8.67 (d, 1H, H-6′), 8.26 (m, 1H, H-4′), 8.10 (m, 1H, SO_2NH), 7.60 (m, 1H, CONH-1), 7.43(m, 1H, CONH-5), 3.72 (m, 1H, H-2), 2.70 (s, 3H, Ar–CH_3), 2.66 (m, 3H, N–CH_3-1‴), 2.39 (m, 3H, N–CH_3-1″), 2.19 (m, 2H, H_2-4), 1.85 (m, 2H, H_2-3). IR (KBr, cm^{-1}): 3234 (N–H str of CONH), 3033 (Ar–C–H str, asymmetric), 2889 (ali C–H str), 1636, 1555, 1507 (N=O str of Ar–NO_2, asymmetric), 1421 (ali C-H def), 1336, 1314, 1149 (S=O str of SO_2NH), 1115, (C–N str of Ar–NO_2), 793 and 736 (Ar–C–H def). Anal. $C_{14}H_{20}N_4O_6S_1$ (C, H, N) calcd: 45.16, 5.38, 15.05; found: 45.28, 5.42, 15.10.

1,5-*N*,*N*′-Diethyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (20). MS (FAB): $M+H^+$ peak at *m*/*z* 401, 136. ^1H NMR (200 MHz, $CDCl_3$): δ 8.72 (d, 1H, $J=2.42$, H-6′), 8.25 (dd, 1H, $J_1=2.44$, $J_2=8.36$, H-4′), 7.60 (d, 1H, $J=8.46$, H-3′), 7.50 (m, 1H, SO_2NH), 7.42 (m, 1H, CONH-1), 6.99(m, 1H, CONH-5), 3.73 (m, 1H, H-2), 3.23 (m, 2H, N–CH_2-1‴), 2.95 (m, 2H, N–CH_2-1″), 2.70 (s, 3H, Ar–CH_3), 2.27 (m, 2H, H_2-4), 1.92 (m, 2H, H_2-3), 1.13 (m, 3H, CH_3-2‴), 0.90 (m, 3H, CH_3-2″). IR (KBr, cm^{-1}): 3232 (N–H str of CONH), 3037 (Ar–C–H str), 2923, 2882 and 2825 (ali C–H str), 1627 (C=O str overlapped with N–H bend), 1540, 1511 (N=O str of Ar–NO_2, asymmetric), 1427 (ali C–H def), 1339 and 1154 (S=O str of SO_2NH), 1117, 884 (C–N str of Ar–NO_2), 795 and 734 (Ar–C–H def). Anal. $C_{16}H_{24}N_4O_6S_1$ (C, H, N) calcd: 48.00, 6.00, 14.00; found: 48.12, 6.21, 14.31.

1,5-*N*,*N*′-di *n*-Propyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (21). MS (FAB): $M+H^+$ peak at *m*/*z* 429. ^1H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, 1H, $J=2.35$, H-6′), 8.27 (dd, 1H, $J_1=2.37$, $J_2=8.34$, H-4′), 7.49 (d, 1H, $J=8.38$, H-3′), 7.11 (s, 1H, SO_2NH), 6.88 (t, 1H, CONH), 5.80(t, 1H, CONH), 3.70 (m, 1H, H-2), 3.28–3.14 (m, 2H, CH_2-1‴), 3.10–3.00 (m, 2H, CH_2-1″), 2.81 (s, 3H, Ar–CH_3), 2.46 (m, 1H, H_A-3), 2.31 (m, 1H, H_B-3), 2.00–1.91 (m, 2H, H_2-4), 1.59–1.52 (m, 2H, CH_2-2‴), 1.40–1.32 (m, 2H, CH_2-2″), 0.96 (t, 3H, CH_3-3‴). 0.79 (t, 3H, CH_3-3″). IR (KBr, cm^{-1}): 3222 (N–H str of CONH), 3032 (Ar–C–H str, assymmetric), 2906, 2880 (ali C–H str), 1627, 1541, 1512 (N=O str of Ar–NO_2, asymmetric), 1422 (ali C–H def), 1339, 1310, 1151 (S=O str of SO_2NH), 1116, 882 (C–N str of Ar–NO_2), 795 and 736 (Ar–C–H def), 604. Anal. $C_{18}H_{28}N_4O_6S_1$ (C, H, N) calcd: 50.47, 6.54, 13.08; found: 50.52, 6.57, 13.03.

1,5-*N*,*N*′-di *n*-Butyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (22). MS (FAB): $M+H^+$ peak at *m*/*z* 457. ^1H NMR (200 MHz, $CDCl_3$): δ 8.71 (d, 1H, H-6′), 8.25 (dd, 1H, H-4′), 7.60 (d, 1H, H-3′), 7.49 (s, 1H, SO_2NH), 7.41 (m, 1H, CONH), 6.97 (m, 1H, CONH), 3.72 (m, 1H, H-2), 3.24 (m, 2H, CH_2-1‴), 2.94 (m, 2H, CH_2-1″), 2.70 (s, 3H, Ar–CH_3), 2.30 (m, 2H, H_2-3), 1.94 (m, 2H, H_2-4), 1.52–1.20 (m, 8H, CH_2-2‴, CH_2-3‴, CH_2-2″, CH_2-3″), 0.96–0.84 (m, 6H, CH_3-4‴, CH_3-4″). IR (KBr, cm^{-1}): 3232 (N–H str of CONH), 3031 (Ar–C–H str, assymmetric), 2897, 2876 (ali C–H str), 1628, 1545, 1505 (N=O str of Ar–NO_2, asymmetric), 1423 (ali C–H def), 1338, 1306, 1150 (S=O str of SO_2NH), 1113, 733 (Ar–C–H def). Anal. $C_{20}H_{32}N_4O_6S_1$ (C, H, N) calcd: 52.63, 7.02, 12.28; found: 52.23, 6.78, 12.21.

1,5-*N*,*N*′-di *i*-Propyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (23). MS (FAB): $M+H^+$ peak at *m*/*z* 429. ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, 1H, $J=1.96$, H-6′), 8.26 (dd, 1H, $J_1=2.16$, $J_2=8.32$, H-4′), 7.49 (d, 1H, $J=8.32$, H-3′), 6.93 (m, 1H, SO_2NH), 6.61 (m, 1H, CONH-1), 5.52 (m, 1H, CONH-5), 4.07 (m, 1H, N–CH-1‴), 3.81 (m, 1H, N–CH-1″), 3.64 (m, 1H, H-2), 2.81 (s, 3H, Ar–CH_3), 2.43 (m, 1H, H_A-3), 2.27 (m, 1H, H_B-3), 1.94 (m, 2H, H_2-4), 1.25–1.16 (m, 6H, CH_3-2″, CH_3-3″), 1.08–0.90 (m, 6H, CH_3-2‴, CH_3-3‴).

IR (KBr, cm^{-1}): 3228 (N–H str of CONH), 3030 (Ar–C–H str), 2916, 2879 and 2822 (ali C–H str), 1633 (C=O str overlapped with N–H bend), 1616, 1533, 1513 (N=O str of Ar–NO_2, asymmetric), 1454 (ali C–H def), 1337 and 1155 (S=O str of SO_2NH), 1116, 988, 882 (C–N str of Ar–NO_2), 793 and 734 (Ar–C–H def), 612. Anal. $C_{18}H_{28}N_4O_6S_1$ (C, H, N) calcd: 50.47, 6.54, 13.08; found: 50.62, 6.71, 13.02.

1,5-*N*,*N*′-di *i*-Butyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (24). MS (FAB): $M+H^+$ peak at *m*/*z* 458, 136. ^1H NMR (200 MHz, $CDCl_3$): δ 8.92 (d, 1H, $J=2.40$, H-6′), 8.33 (dd, 1H, $J_1=2.42$, $J_2=8.34$, H-4′), 7.50 (d, 1H, $J=8.34$, H-3′), 7.15 (m, 1H, SO_2NH), 6.22 (m, 1H, CONH-1), 4.75 (m, 1H, CONH-5), 3.70 (m, 1H, H-2), 3.16 (m, 2H, N-CH_2-1‴), 2.92 (m, 2H, N-CH_2-1″), 2.77 (s, 3H, Ar–CH_3), 2.38 (m, 2H, H_2-4), 1.84 (m, 2H, H_2-3), 1.58–1.48 (m, 2H, CH-2″, CH-2‴), 0.96 (m, 6H, CH_3-3‴, CH_3-4‴), 0.77 (m, 6H, CH_3-3″, CH_3-4″). IR (KBr, cm^{-1}): 3237 (N–H str of CONH), 3042 (Ar–C–H str), 2905 and 2823 (ali C–H str), 1634 (C=O str overlapped with N–H bend), 1546, 1511 (N=O str of Ar–NO_2, asymmetric), 1456 (ali C–H def), 1338 and 1162 (S=O str of SO_2NH), 1118, 888 (C–N str of Ar–NO_2), 795 and 736 (Ar–C–H def), 611. Anal. $C_{20}H_{32}N_4O_6S_1$ (C, H, N) calcd: 52.63, 7.01, 12.28; found: 52.64, 6.92, 12.34.

1,5-*N*,*N*′-di-(Diisopropyl)-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (25). MS (FAB): $M+H^+$ peak at *m*/*z* 513. ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, 1H, $J=2.16$, H-6′), 8.24 (dd, 1H, $J_1=2.16$, $J_2=8.36$, H-4′), 7.51 (d, 1H, $J=8.36$, H-3′), 6.93 (m, 1H, SO_2NH), 4.20 (m, 2H, N–CH-1‴, N–CH-4‴), 3.94 (m, 2H, N–CH-1″, N–CH-4″), 3.52 (m, 1H, H-2), 2.81 (s, 3H, Ar–CH_3), 2.34 (m, 1H, H_A-3), 2.18 (m, 1H, H_B-3), 1.82 (m, 2H, H_2-4), 1.45–1.11 (m, 12H, CH_3-2″, CH_3-3″, CH_3-5″, CH_3-6″), 1.08–0.81 (m, 12H, CH_3-2‴, CH_3-3‴, CH_3-5‴, CH_3-6‴). IR (KBr, cm^{-1}): 3399, 3050 (Ar–C–H str), 2915 and 2880 (ali C–H str), 1632 (C=O str), 1509 (N=O str of Ar–NO_2, asymmetric), 1457, 1438 (ali C–H def), 1337 and 1164 (S=O str of SO_2NH), 1116, 887 (C–N str of Ar–NO_2), 794 and 737 (Ar–C–H def), 613. Anal. $C_{24}H_{40}N_4O_6S_1$ (C, H, N) calcd: 56.25, 7.81, 10.94; found: 56.42, 7.95, 10.89.

1,5-*N*,*N*′-di-Phenyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (26). MS (FAB): $M+H^+$ peak at *m*/*z* 497. ^1H NMR (500 MHz, $CDCl_3$): δ 8.95 (d, 1H, $J=2.09$, H-6′), 8.31 (dd, 1H, $J_1=2.26$, $J_2=8.39$, H-4′), 7.88 (s, 1H, SO_2NH), 7.54–7.16 (d, 11H, H-3′, phenyl protons), 2.85 (m, 1H, H-2), 2.78 (s, 3H, Ar–CH_3), 2.51–2.43 (m, 4H, H_2-3, H_2-4). IR (KBr, cm^{-1}): 3256 (N–H str of CONH), 3027 (Ar–C–H str), 2877, 1673 (C=O str), 1588, 1514 (N=O str of Ar–NO_2, asymmetric), 1455, 1351, 1332 and 1166 (S=O str of SO_2NH), 1112, 882 (C–N str of Ar–NO_2), 795 and 734 (Ar–C–H def), 691, 611. Anal. $C_{24}H_{24}N_4O_6S_1$ (C, H, N) calcd: 58.06, 4.84, 11.29; found: 57.95, 4.71, 11.21.

1,5-*N*,*N*′-di Cyclohexyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (27). MS (FAB): $M+H^+$ peak at *m*/*z* 509. ^1H NMR (200 MHz, DMSO-d_6): δ 8.27 (d, 1H, H-6′), 8.18 (dd, 1H, H-4′), 7.98 (d, 1H, H-3′), 7.69–7.51 (m, 3H, SO_2NH, CONH, CONH), 3.71 (m, 1H, H-2), 3.49 (m, 1H, H-1″), 3.19 (m, 1H, H-1‴), 2.56 (s, 3H, Ar–CH_3), 2.49 (m, 2H, H_2-4), 2.05 (m, 1H, H_A-3), 1.95 (m, 1H, H_B-3), 1.70–0.70 (m, 22H, cyclohexyl protons). IR (KBr, cm^{-1}): 3304, 3228 (N–H str of CONH), 3041 (Ar–C–H str), 2879 and 2806 (ali C–H str), 1647 (C=O str), 1512 (N=O str of Ar–NO_2, asymmetric), 1339 and 1161 (S=O str of SO_2NH), 1119, 887 (C–N str of Ar–NO_2), 796 and 735 (Ar–C–H def), 610. Anal. $C_{24}H_{36}N_4O_6S_1$ (C, H, N) calcd: 56.69, 7.09, 11.02; found: 56.84, 7.21, 11.34.

1,5-*N*,*N*′-di Benzyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (28). MS (FAB): $M+H^+$ peak at *m*/*z* 525. ^1H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 1H, $J=1.78$, H-6′), 8.20 (dd, 1H, $J_1=1.94$, $J_2=8.33$, H-4′), 7.41 (d, 1H, $J=8.37$, H-3′), 7.36–7.19 (m, 10H, phenyl protons), 7.04 (m, 2H, SO_2NH, CONH), 6.10 (m, 1H, CONH), 4.39 (m, 2H, CH_2-ph-1‴), 4.22 (m, 2H, CH_2-ph-1″), 3.79 (m, 1H, H-2), 2.76 (s, 3H, Ar–CH_3), 2.47 (m, 1H, H_A-3), 2.31 (m, 1H, H_B-3), 1.99 (m, 2H, CH_2-4). IR (KBr, cm^{-1}): 3282, 3205 (N–H str of CONH), 3034 (Ar–C–H str), 2876 and 2816 (ali C–H str), 1632 (C=O str overlapped with N–H bend), 1512 (N=O str of Ar–NO_2, asymmetric), 1441 (ali C–H def), 1338 and 1162 (S=O str of SO_2NH), 886 (C–N str of Ar–NO_2), 796 and 734 (Ar–C–H def), 696. Anal. $C_{26}H_{28}N_4O_6S_1$ (C, H, N) calcd: 59.54, 5.34, 10.69; found: 59.74, 5.43, 10.64.

1,5-*N*,*N*′-di *n*-Pentyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (29). MS (FAB): $M+H^+$ peak at *m*/*z* 485. ^1H NMR (200 MHz, $CDCl_3$): δ 8.71 (d, 1H, H-6′), 8.25 (dd, 1H, H-4′), 7.70 (d, 1H, H-3′), 7.48 (s, 1H, SO_2NH), 7.39 (m, 1H, CONH), 6.94 (m, 1H, CONH), 3.69 (m, 1H, H-2), 3.21 (m, 2H, CH_2-1‴), 2.91 (m, 2H, CH_2-1″), 2.70 (s, 3H, Ar–CH_3), 2.29 (m, 2H, H_2-3), 1.91 (m, 2H, H_2-4), 1.50–1.13 (m, 12H, CH_2-2‴, CH_2-3‴, CH_2-4‴, CH_2-2″, CH_2-3″, CH_2-4″), 0.94–0.80 (m, 6H, CH_3-5‴, CH_3-5″). IR (KBr, cm^{-1}): 3228 (N–H str of CONH), 3031 (Ar–C–H str), 2877 (ali C–H str), 1629, 1538, 1512 (N=O str of Ar–NO_2, asymmetric), 1455, 1444 (ali C–H def), 1339 and 1150 (S=O str of SO_2NH), 1116, 881 (C–N str of Ar–NO_2), 793 and 734 (Ar–C–H def). Anal. $C_{22}H_{36}N_4O_6S_1$ (C, H, N) calcd: 54.54, 7.44, 11.57; found: 54.55, 7.46, 11.59.

1,5-*N*,*N*′-di *n*-Hexyl-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (30). MS (FAB): $M+H^+$ peak at *m*/*z* 513. ^1H NMR (200 MHz, $CDCl_3$): δ 8.72 (d, 1H, $J=2.03$, H-6′), 8.26 (dd, 1H, $J_1=2.18$, $J_2=8.34$, H-4′), 7.49 (d, 1H, $J=8.31$, H-3′), 7.13 (m, 1H, SO_2NH), 6.87 (m, 1H, CONH-1), 5.78 (m, 1H, CONH-5), 3.69 (m, 1H, H-2), 3.25 (m, 2H, N-CH_2-1‴), 3.04 (m, 2H, N–CH_2-1″), 2.81 (s, 3H, Ar–CH_3), 2.36 (m, 2H, H_2-4), 1.94 (m, 2H, H_2-3), 1.52–1.21 (m, 16H, CH_2-2″, CH_2-3″, CH_2-4″, CH_2-5″, CH_2-2‴, CH_2-3‴, CH_2-4‴, CH_2-5‴), 0.88 (m, 6H, CH_3-6″, CH_3-6‴). IR (KBr, cm^{-1}): 3232 (N–H str of CONH), 3037, 3028 (Ar–C–H str), 2872 and 2807 (ali C–H str), 1633 (C=O str overlapped with N–H bend), 1550, 1504 (N=O str of Ar–NO_2, asymmetric), 1454 (ali C–H def), 1338, 1313 and 1148 (S=O

str of SO_2NH), 1117, 882 (C–N str of Ar–NO_2), 792 and 737 (Ar–C–H def). Anal. $C_{24}H_{40}N_4O_6S_1$ (C, H, N) calcd: 56.25, 7.81, 10.94; found: 56.34, 7.98, 10.93.

1,5-*N*,*N*′-di (Dimethyl)-2-(2′-methyl-5′-nitro benzenesulphonyl) glutamamide (31). MS (FAB): $M+H^+$ peak at m/z 401. ^1H NMR (500 MHz, $CDCl_3$): δ 8.91 (d, 1H, $J=2.35$, H-6′), 8.30 (dd, 1H, $J_1=2.35$, $J_2=8.45$, H-4′), 7.48 (d, 1H, $J=8.45$, H-3′), 7.11 (s, 1H, SO_2NH), 3.71 (m, 1H, H-2), 3.18 (m, 6H, CH_3-1‴, CH_3-2‴), 3.00 (m, 6H, CH_3-1″, CH_3-2″), 2.83 (s, 3H, Ar–CH_3), 2.76 (m, 2H, H_2-3), 2.06 (m, 2H, H_2-4). IR (KBr, cm^{-1}): 3037 (Ar–C–H str, assymmetric), 2888 (ali C–H str), 1640 (C=O str overlapped with N–H bend), 1511 (N=O str of Ar–NO_2, asymmetric), 1348, 1332 and 1164 (S=O str of SO_2NH), 1126, 956, 885 (C–N str of Ar–NO_2), 794 and 736 (Ar–C–H def), 634. Anal. $C_{16}H_{24}N_4O_6S_1$ (C, H, N) calcd: 48.00, 6.00, 14.00; found: 48.34, 6.21, 13.84.

1,5-*N*,*N*′-di Methyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (32). MS (FAB): $M+H^+$ peak at m/z 373. ^1H NMR (200 MHz, DMSO-d_6): δ 8.27 (d, 1H, H-2′), 7.90 (dd, 1H, H-6′), 8.00 (d, 1H, H-5′), 7.63 (m, 3H, SO_2NH, CONH, CONH), 3.7 (m, 1H, H-2), 2.60 (s, 3H, Ar–CH_3), 2.50 (m, 2H, H_2-4), 2.30 (m, 6H, N–CH_3-1‴, N–CH_3-1″), 2.04 (m, 1H, H_A-3), 1.70 (m, 1H, H_B-3). IR (KBr, cm^{-1}): 3255, 3179 (N–H str of CONH), 3039 (Ar–C–H str), 2897 (ali C–H str), 1629 (C=O str overlapped with N–H bend), 1547, 1525 (N=O str of Ar–NO_2, asymmetric), 1443 (ali C–H def), 1338 and 1164 (S=O str of SO_2NH), 978, 878 (C–N str of Ar–NO_2), 798 and 749 (Ar–C–H def), 663. Anal. $C_{14}H_{20}N_4O_6S_1$ (C, H, N) calcd: 45.16, 5.38, 15.05; found: 45.41, 5.25, 15.10.

1,5-*N*,*N*′-di *n*-Propyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (33). MS (FAB): $M+H^+$ peak at m/z 429. ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, 1H, $J=1.72$, H-2′), 7.95 (dd, 1H, $J_1=1.81$, $J_2=8.03$, H-6′), 7.54 (d, 1H, SO_2NH), 7.49 (d, 1H, $J=8.07$, H-5′), 6.88 (t, 1H, CONH), 5.65 (t, 1H, CONH), 3.68 (m, 1H, H-2), 3.29–3.18 (m, 2H, CH_2-1‴), 3.15–3.07 (m, 2H, CH_2-1″), 2.66 (s, 3H, Ar–CH_3), 2.40 (m, 1H, H_A-3), 2.16 (m, 1H, H_B-3), 1.99–1.84 (m, 2H, H_2-4), 1.54 (m, 2H, CH_2-2‴), 1.43 (m, 2H, CH_2-2″), 0.95 (t, 3H, $J_1=7.39$, $J_2=14.84$, CH_3-3‴), 0.85 (t, 3H, $J_1=7.39$, $J_2=14.82$, CH_3-3‴). IR (KBr, cm^{-1}): 3240, 3167 (N–H str of CONH), 3034 (Ar–C–H str), 2907 and 2878 (ali C–H str), 1638, 1625, 1516 (N=O str of Ar–NO_2), 1423, 1338 and 1163 (S=O str of SO_2NH), 881 (C–N str of Ar–NO_2), 757 (Ar–C–H def), 664. Anal. $C_{18}H_{28}N_4O_6S_1$ (C, H, N) calcd: 50.47, 6.54, 13.08; found: 50.34, 6.42, 13.21.

1,5-*N*,*N*′-di *n*-Butyl-2-(4-methyl-3-nitro benzenesulphonyl) glutamamide (34). MS (FAB): $M+H^+$ peak at m/z 457. ^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (d, 1H, $J=1.85$, H-2′), 7.96 (dd, 1H, $J_1=1.89$, $J_2=8.04$, H-6′), 7.54 (d, 1H, $J=6.85$, SO_2NH), 7.49 (d, 1H, $J=8.17$, H-5′), 6.90 (m, 1H, CONH), 5.73 (m, 1H, CONH), 3.70 (m, 1H, H-2), 3.26 (m, 2H, N–CH_2-1‴), 3.13 (m, 2H, N–CH_2-1″), 2.66 (s, 3H, Ar–CH_3), 2.37 (m, 1H, H_A-3), 2.19 (m, 1H, H_B-3), 1.92 (m, 2H, H_2-4), 1.53–1.21 (m, 8H, CH_2-2″, CH_2-3″, CH_2-2‴, CH_2-3‴), 0.97–0.85 (m, 6H, CH_3-4″, CH_3-4‴). IR (KBr, cm^{-1}): 3240, 3172 (N–H str of CONH), 3026 (Ar–C–H str), 2904, 2878 and 2817 (ali C–H str), 1638 (C=O str overlapped with N–H bend), 1624, 1537, 1517 (N=O str of Ar–NO_2, asymmetric), 1442 (ali C–H def), 1336 and 1163 (S=O str of SO_2NH), 1109, 882 (C–N str of Ar–NO_2), 799 and 753 (Ar–C–H def), 664. Anal. $C_{20}H_{32}N_4O_6S_1$ (C, H, N) calcd: 52.63, 7.02, 12.28; found: 52.81, 7.21, 11.92.

1,5-*N*,*N*′-di *n*-Pentyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (35). MS (FAB): $M+H^+$ peak at m/z 485. ^1H NMR (200 MHz, DMSO-d_6): δ 8.50 (d, 1H, H-2′), 8.20 (dd, 1H, H-6′), 7.50 (d, 1H, H-5′), 7.15 (d, 1H, SO_2NH), 5.87 (m, 1H, CONH), 4.65 (m, 1H, CONH), 3.40–3.20 (m, 4H, N–CH_2-1″, N–CH_2-1‴), 3.10 (m, 1H, H-2), 2.70 (s, 3H, Ar–CH_3), 2.65 (m, 2H, H_2-4), 2.40 (m, 1H, H_A-3), 2.15 (m, 1H, H_B-3), 1.70–1.10 (m, 12H, CH_2-2″, CH_2-3″, CH_2-4″, CH_2-2‴, CH_2-3‴, CH_2-4‴), 0.90 (m, 6H, CH_3-5″, CH_3-5‴). IR (KBr, cm^{-1}): 3270 (N–H str of CONH), 3028 (Ar–C–H str), 2876 and 2815 (ali C–H str), 1662 (C=O str), 1641 (N–H bend of CONH), 1518 (N=O str of Ar–NO_2, asymmetric), 1441 (ali C–H def), 1354, 1339 and 1169 (S=O str of SO_2NH), 1117, 886 (C–N str of Ar–NO_2), 798 and 711 (Ar–C–H def), 657, 613. Anal. $C_{22}H_{36}N_4O_6S_1$ (C, H, N) calcd: 54.54, 7.44, 11.57; found: 54.57, 7.42, 11.15.

1,5-*N*,*N*′-di *n*-Hexyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (36). MS (FAB): $M+H^+$ peak at m/z 513. ^1H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 1H, $J=1.92$, H-2′), 7.95 (dd, 1H, $J_1=1.92$, $J_2=8.03$, H-6′), 7.56 (d, 1H, $J=6.81$, SO_2NH), 7.48 (d, 1H, $J=1.92$, H-5′), 6.90 (m, 1H, CONH), 5.72(m, 1H, CONH), 3.70 (m, 1H, H-2), 3.25 (m, 2H, N-CH_2-1‴), 3.12 (m, 2H, N–CH_2-1″), 2.66 (s, 3H, Ar–CH_3), 2.41–2.34 (m, 1H, H_A-3), 2.18 (m, 1H, H_B-3), 1.96–1.86 (m, 2H, H_2-4), 1.53–1.22 (m, 16H, CH_2-2″, CH_2-3″, CH_2-4″, CH_2-5″, CH_2-2‴, CH_2-3‴, CH_2-4‴, CH_2-5‴), 0.88 (m, 6H, CH_3-6″, CH_3-6‴). IR (KBr, cm^{-1}): 3236, 3166 (N–H str of CONH), 3026 (Ar–C–H str), 2875 and 2810 (ali C–H str), 1641 (C=O str overlapped with N–H bend), 1625, 1539, 1518 (N=O str of Ar–NO_2, asymmetric), 1442 (ali C–H def), 1337 and 1163 (S=O str of SO_2NH), 1110, 882 (C–N str of Ar–NO_2), 799 and 753 (Ar–C–H def), 664. Anal. $C_{24}H_{40}N_4O_6S_1$ (C, H, N) calcd: 56.25, 7.81, 10.94; found: 56.34, 7.92, 10.84.

1,5-*N*,*N*′-di *i*-Propyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (37). MS (FAB): $M+H^+$ peak at m/z 429. ^1H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, 1H, $J=1.77$, H-2′), 7.96 (dd, 1H, $J_1=1.84$, $J_2=8.03$, H-6′), 7.60 (s, 1H, SO_2NH), 7.50 (d, 1H, $J=8.09$, H-5′), 7.21 (d, 1H, CONH), 6.74 (d, 1H, CONH), 4.01 (m, 1H, H-2), 3.73 (m, 2H, CH_2-1″, CH-1‴), 2.64 (s, 3H, Ar–CH_3), 2.32–2.26 (m, 1H, H_A-3), 2.22–2.17 (m, 1H, H_B-3), 1.95–1.80 (m, 2H, H_2-4), 1.16–1.13 (m, 6H, CH_3-2‴, CH_3-3‴), 1.00 (d, 3H, $J=6.57$, CH_3-2″), 0.92 (d, 3H, $J=6.55$, CH_3-3″. IR (KBr, cm^{-1}): 3237, 3186 (N–H str of CONH), 3027 (Ar–C–H str), 2918 and 2878 (ali C–H str), 1623, 1539, 1518, 1444 (ali C–H def), 1334 (S=O str of SO_2NH, asymmetric), 1164 (S=O str of

SO_2NH, symmetric), 1093, 982, 895 (C–N str of Ar–NO_2), 754 (Ar–C–H def), 662. Anal. $C_{18}H_{28}N_4O_6S_1$ (C, H, N) Calcd: 50.47, 6.54, 13.08; Found: 50.21, 6.48, 13.31.

1,5-*N*,*N*′-di *i*-Butyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (38). MS (FAB): $M+H^+$ peak at m/z 457. ^1H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 1H, $J=1.71$, H-2′), 7.95 (dd, 1H, $J_1=1.83$, $J_2=8.04$, H-6′), 7.54 (d, 1H, $J=6.69$, SO_2NH), 7.48 (d, 1H, $J=8.04$, H-5′), 6.94 (m, 1H, CONH), 5.71 (m, 1H, CONH), 3.70 (m, 1H, H-2), 3.10 (m, 2H, CH_2-1″), 2.98 (m, 2H, CH_2-1‴), 2.65 (s, 3H, Ar–CH_3), 2.41 (m, 1H, H_A-3), 2.20 (m, 1H, H_B-3), 1.92 (m, 2H, H_2-4), 1.72 (m, 2H, CH-2″, CH-2‴), 0.93 (m, 6H, CH_3-3″, CH_3-4″), 0.83 (m, 6H, CH_3-3‴, CH_3-4‴). IR (KBr, cm^{-1}): 3250, 3165 (N–H str of CONH), 3032 (Ar–C–H str), 2901 and 2823 (ali C–H str), 1644 (C=O str overlapped with N–H bend), 1625, 1533, 1517 (N=O str of Ar–NO_2, asymmetric), 1442 (ali C–H def), 1335 and 1163 (S=O str of SO_2NH), 1109, 882 (C–N str of Ar–NO_2), 798 and 752 (Ar–C–H def), 666. Anal. $C_{20}H_{32}N_4O_6S_1$ (C, H, N) calcd: 52.63, 7.02, 12.28; found: 52.21, 7.21, 12.29.

1,5-*N*,*N*′-di Cyclohexyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (39). MS (FAB): $M+H^+$ peak at m/z 509. ^1H NMR (200 MHz, DMSO-d_6): δ 8.25 (d, 1H, H-2′), 8.12 (dd, 1H, H-6′), 7.90 (d, 1H, H-5′), 7.70–7.50 (m, 3H, SO_2NH, CONH, CONH), 3.70 (m, 1H, H-2), 3.47 (m, 1H, H-1″), 3.17 (m, 1H, H-1‴), 2.56 (s, 3H, Ar–CH_3), 2.49 (m, 2H, H_2-4), 2.10 (m, 1H, H_A-3), 2.00 (m, 1H, H_B-3), 1.70–0.70 (m, 22H, cyclohexyl protons). IR (KBr, cm^{-1}): 3234 (N–H str of CONH), 3032 (Ar–C–H str), 2876 and 2805 (ali C–H str), 1626 (C=O str overlapped with N–H bend), 1536, 1517 (N=O str of Ar–NO_2, asymmetric), 1436 (ali C–H def), 1335 and 1162 (S=O str of SO_2NH), 1107, 886 (C–N str of Ar–NO_2), 796 and 755 (Ar–C–H def), 662. Anal. $C_{24}H_{36}N_4O_6S_1$ (C, H, N) calcd: 56.69, 7.09, 11.02; found: 56.59, 7.16, 11.21.

1,5-*N*,*N*′-di Benzyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (40). MS (FAB): $M+H^+$ peak at m/z 525. ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, 1H, $J=1.94$, H-2′), 8.18 (dd, 1H, $J_1=1.94$, $J_2=8.33$, H-5′), 7.41 (d, 1H, $J=8.34$, H-4′), 7.40–7.21 (m, 10H, phenyl protons), 6.98 (m, 2H, SO_2NH, CONH), 6.10 (m, 1H, CONH), 4.42 (m, 2H, CH_2-ph-1‴), 4.24 (m, 2H, CH_2-ph-1″), 3.78 (m, 1H, H-2), 2.76 (s, 3H, Ar–CH_3), 2.45 (m, 1H, H_A-3), 2.34 (m, 1H, H_B-3), 2.00 (m, 2H, CH_2-4). IR (KBr, cm^{-1}): 3232, 3165 (N–H str of CONH), 3031 (Ar–C–H str), 2871, 1625 (C=O str), 1535, 1515 (N=O str of Ar–NO_2), 1441, 1337 and 1161 (S=O str of SO_2NH), 1103, 694 (Ar–C–H def), 662. Anal. $C_{26}H_{28}N_4O_6S_1$ (C, H, N) calcd: 59.54, 5.34, 10.69; found: 56.59, 5.64, 10.62.

1,5-*N*,*N*′-di Phenyl-2-(4′-methyl-3′-nitro benzenesulphonyl) glutamamide (41). MS (FAB): $M+H^+$ peak at m/z 497. ^1H NMR (500 MHz, $CDCl_3$): δ 8.97 (d, 1H, $J=2.11$, H-2′), 8.33 (dd, 1H, $J_1=2.15$, $J_2=8.40$, H-6′), 7.92 (s, 1H, SO_2NH), 7.57–7.21 (d, 11H, H-4′, phenyl protons), 2.89 (m, 1H, H-2), 2.78 (s, 3H, Ar–CH_3), 2.60–2.46 (m, 4H, H_2-3, H_2-4). IR (KBr, cm^{-1}): 3288, 3184 (N–H str of CONH), 3013 (Ar–C–H str), 1679 (C=O str), 1519 (N=O str of Ar–NO_2), 1452, 1335 and 1162 (S=O str of SO_2NH), 1109, 898 (C–N str of Ar–NO_2), 753, 689 (Ar–C–H def), 663. Anal. $C_{24}H_{24}N_4O_6S_1$ (C, H, N) calcd: 58.06, 4.84, 11.29; found: 57.83, 4.79, 11.13.

Pharmacology

Antitumor activity of the title compounds was evaluated by dissolving them in phosphate buffered saline (PBS) or by suspending in PBS with 2% Tween 80 (where and when necessary), with a dose of 2 mmol/kg/day for 7 consecutive days, 24 h after intraperitoneal inoculation of mice with 2×10^6 EAC cells on day zero. On day 8, animals were sacrificed and tumor weight was determined. For the tumor growth inhibition, antitumor activity was assessed on the basis of the percentage tumor inhibition (% TI), calculated from mean tumor weight treated (T) and control (C) mice on the day of evaluation. The% TI was calculated as $(1-T/C)\times100$.

Antitumor screening protocol

EAC (Ehrlich Ascites Carcinoma) cells were maintained in vivo in Swiss albino mice, by passaging every 10 days. EAC cells of 9 day old were used for the screening of the entire target compounds 6–41. Female Swiss albino mice of 10 weeks old with an average body weight of 18–20 g were used. All mice were kept on basal metabolic diet with water *ad libitum*.

Two groups of five mice each were kept in separate cages under identical conditions. One of these groups was served as control and other as test. Compounds were dissolved or suspended (where and when necessary with two percent Tween 80) in phosphate buffered saline (PBS: pH 7.2). EAC cells were collected from the donor mouse and were suspended in sterile isotonic saline. The viable EAC cells were counted (Trypan blue indicator) under the microscope and were adjusted at 10×10^6 cells/mL. 0.1 mL of EAC cells per 10 g body weight of the animals was injected (ip) on day zero. A day of incubation was allowed for multiplication of the cells. Seven doses of compound (0.2 mmol/kg, 0.1 mL per 10 g body weight) and mitomycin-C (1 mg/kg) were injected ip from the first day up to the seventh day with 24-h intervals. Control animals received only vehicle. Food and water were withheld 6 h before sacrificing the animals. On day 8, all the animals were sacrificed. All the fluid in the peritoneal cavity was wiped off with absorbent cotton, weight of animals were taken before sacrificing and after removing the fluid from the peritoneal cavity. The difference in weight was considered as tumor weight. Mitomycin C at a dose level of 1 mg per kg body weight was used as standard, which showed 100% inhibition at all times which is shown in Table 3.

QSAR methodology

Data set and parameters. QSAR studies of 36 newly synthesized 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides (Fig. 1) were performed

using Hansch analysis[8] against EAC. Percentage inhibition of tumor weight was used as the biological activity (BA) parameter. All these activities were calibrated to their logarithmic values (log BA) and are listed in Table 3. Being limited substitution on the phenyl ring, predictor descriptors were taken as sum of all the substituents on the phenyl ring for a particular compound.

Physicochemical parameters for the substituents like Hansch–Fujita's substituent constant characterizing hydrophobicity (π), Hammett's electronic constant (σ) characterizing electron withdrawing power of the substituent, steric parameter (Es), molar refractivity (MR), field effect ($\mathcal{F}$), resonance effect ($\mathcal{R}$) were collected from the literature.[12] Structural descriptor of the molecules, molecular volume (MV) was calculated using MMP-MAP program of Chem SW Inc. USA (www.chemsw.com). All the parameters are tabulated in Tables 4 and 5. Antitumor activities of the compounds were subjected to multiple regression analyses on different physicochemical parameters.

Due to similar chemical reactive groups at the R_5 and R_5' and R_6 and R_6' positions for a particular compound, parameters were considered as sum of two positions, the R_5 and R_5' positions or R_6 and R_6' positions for the convenience of regression analysis, which otherwise resulting in statistical error due to non-variance in independent variables.[13] Comparatively the substitution on the R_6 and R_6' positions are limited, hence the indicator variable I_1 was used which takes the value of '1' for the presence of any substituent at the R_6 and R_6' positions and '0' for the absence of any substituent or for the presence of hydrogen.

Correlation analysis

Correlation analysis on all independent descriptors was performed and the resultant correlation matrix is presented in Table 6. Intercorrelated parameters (parameters with the intercorrelation of more than 0.6) were eliminated one by one depending on their individual correlation with the biological activity. All possible combinations of parameters were considered.

Multiple regression analysis

Regression analysis was carried out on different possible combinations of parameters. Statistical quality of the equations[13] were justified by parameters like c*orrelation coefficient* (r or R), s*tandard error of the estimate* (SEE), v*ariance ratio* (F) at specified degrees of freedom (df) and constant terms of regression equations: regression coefficients and intercepts. Significance of the regression coefficients was justified by t-test. QSAR equations were cross-validated by LOO prediction[9] and cross-validated R^2,[14] representing the predictive power of the equation. q^2 should be more than 0.3 for a model to be valid. Compounds **36**, **34** and **15** (deleted compounds, DC) were behaving as outliers (predicted activities were much higher than the observed ones), were excluded step by step to get best statistical quality equations.

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