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QSAR for Analogs of 1,5–*N*,*N*′–Disubstituted–2–(substituted benzenesulphonyl) Glutamamides as Antitumor Agents

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Abstract

Motivation. Cancer is a widespread and life threatening disease for which new and improved drugs are needed. It is well established that the transformation of the normal cells to a cancerous phenotype is often associated with cognate changes in the transport and metabolism of nutrients such as glucose and glutamine. Many tumor cells are particularly avid glutamine consumers. Glutamine also plays a key role in tumor cell energetics, and several tumor cell lines use glutamine as their major respiratory fuel.

Method. Based on our composite program of development of new potential anticancer agents through rational design, 32 analogs of 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl) glutamamide were synthesized, characterized and biologically evaluated against Ehrlich Ascites Carcinoma (EAC) cells in Swiss Albino mice. Tumor cell inhibition was considered as the biological activity parameter. A QSAR study was performed on this data set, showing the importance of ETSA and RTSA indices of several atoms, the energy of HOMO, the energy gap between HOMO and LUMO, as well as the approximate surface area.

Results. The QSAR study highlights the atomic features and molecular descriptors that determine the antitumor activity of these glutamamides analogs. These computational models also illustrate the importance of atomic charge, energy of HOMO, and energy of LUMO for the biological activity.

Keywords. Glutamamides; quantitative structure–activity relationships; QSAR; antitumor activity; topological indices; quantum–chemical descriptors.

Abbreviations and notations

EAC, Ehrlich ascites carcinoma	RTSA, Refractotopological state atom
QSAR, Quantitative structure–activity relationships	E_{HOMO}, Energy of highest occupied molecular orbital
AM1, Austin model 1	E_{LUMO}, Energy of lowest unoccupied molecular orbital
ETSA, Electrotopological state atom	MR, Molar Refractivity

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1 INTRODUCTION

Drugs used in cancer treatment have significant limitations. Neoplastic transformation is accompanied by adaptive increases in nucleotide and protein synthesis. The high rates of protein synthesis in rapidly growing tumors require a continuous supply of both the essential and the nonessential amino acids. Tumors assimilate not only nitrogen from the diet but also nitrogen from the host proteins raising the concept of tumors as the "nitrogen traps" actively competing with the host for nitrogenous compounds. Tumors use the incorporated amino acids for both oxidation and protein synthesis [1]. As glutamine (**1a**), a neutral non–essential amino acid, is the most abundant free α–amino acid in the body. It is the main vehicle for circulation of ammonia in a nontoxic form. It is assumed that tumors behave indeed as "glutamine traps" rather than "nitrogen trap" [2,3]. Glutamine (**1a**) may play a major role in supporting the tumor cell growth and metabolism, in part, through its regulation of key biosynthetic pathways. It also provides multiple contributions to the cellular growth by participating in protein, purine and pyrimidine metabolisms with extensive uses of both its nitrogen and carbon skeleton [4,5] and may be used as a principle respiratory substrate [6]. Studies on experimental and human tumors, looking at changes in enzymic activity and relative mRNA levels of both glutamine synthetase (GS) and glutaminase (GA) revealed a similar pattern in many cases: a knock–down or repression of GS expression along with an over–expression of GA [7–9]. Glutamine (**1a**) uptake of different types of solid tumors (breast, ovarian, colon, and liver) was characterized [10] and the rates of DNA and protein synthesis correlated directly with the concentration of glutamine (**1a**) in the culture media [11]. Neutrophils, lymphocytes, fibroblasts and macrophages use glutamine (**1a**) as a primary metabolic fuel as well as using it for nucleotide synthesis which regulates cellular proliferation. Patients of cancer often develop muscle glutamine (**1a**) depletion due to uptake by tumors and chronic protein catabolism [10]. Cell growth is a function of glutamine (**1a**) influx and suggests that it is used to supply glutamate and cystine perhaps for glutathione synthesis [11].

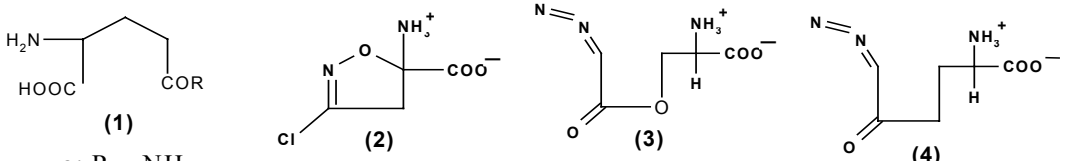

Figure 1. Structure of glutamine (**1**), azaserine (**2**), DON (**3**) and acivicin (**4**).

The reported antagonists of glutamine, *e.g.*, azaserine (**2**), 6–diaza–5–oxo–L–norleucin (DON) (**3**) and acivicin (**4**) (Figure 1) are potent inhibitors of glutamine dependent amidotransferases [12]. On the basis of this, we have already synthesized and reported anticancer activities of some 5–*N*–substituted–2–(substituted benzenesulphonyl) glutamamides earlier [13–17]. Here, we reported

syntheses of some QSAR analogs of these glutamamides, which are the structural variants of glutamine (**1a**) as well as glutamic acid (**1b**), based on our earlier work [13–17]. Glutamine (**1a**) and glutamic acid (**1b**) are biologically interconvertible. Enzymes responsible for this interconvertability are glutaminase and glutamine synthetase. Glutamine (**1a**) played an important role in the tumor cell growth by supplying its amide nitrogen. A glutamamide also contained amide 'N' and may inhibit enzymes glutaminase or glutamine synthetase or both. In keeping all these points in view, it was assumed that the structural variants of glutamine (**1a**) and that of the biotransformation product glutamic acid (**1b**) might possess antitumor activity. Thus, compounds which are analogs of both glutamine (**1a**) and glutamic acid (**1b**) were selected, designed by the QSAR studies of our earlier work [13–17].

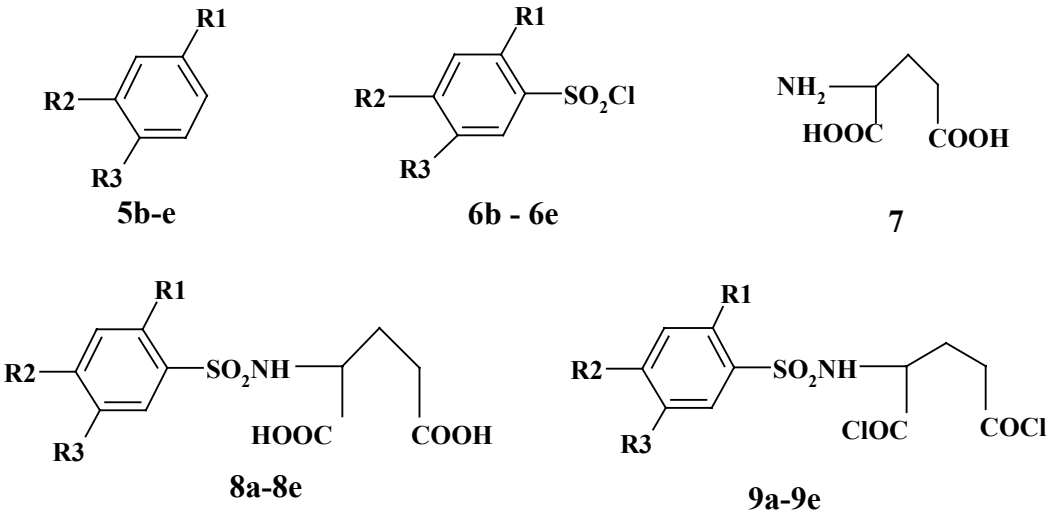

Figure 2. Intermediates and reacting compounds.

In continuation of our composite program of rational drug design [13–43], thirty–two QSAR analogs of 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl)glutamamides were synthesized by preparing substituted benzenesulphonyl chlorides (**6b–e**) from substituted benzenes (**5b–e**), followed by the condensation with glutamic acid (**7**) to 2–(substituted benzenesulphonyl)glutamic acids (**8a–e**), subsequent acid chloride formation to 2–(substituted benzenesulphonyl)glutamoyl dichlorides (**9a–e**). The intermediate and reacting compounds are shown in Figure 2.

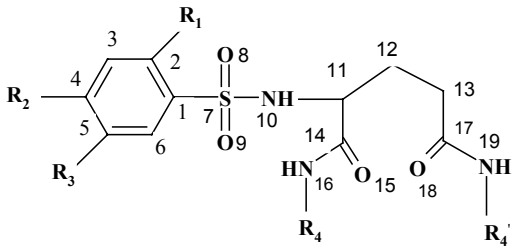

Figure 3. General structure of 1,5–*N*,*N*′–disustituted–2–(substituted benzenesulphonyl) glutamamides (**10–41**) with arbitrary numbers.

The general structure of 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl)glutamamides is shown in Figure 3. The synthesized compounds (**10–41**) were biologically evaluated for their possible anticancer activity against Ehrlich Ascites Carcinoma (EAC) cells in Swiss Albino mice. Percentage inhibition of ascites cells was considered as the biological activity parameter. QSAR studies of these 32 glutamamide were performed using different parameters like physicochemical, topological (ETSA and RTSA indices), geometrical, constitutional and semi–empirical quantum chemical descriptors.

2 MATERIALS AND METHODS

2.1 Chemistry

Thirty two QSAR analogs of 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl) glutamamides (**10**–**41**) were synthesized using 2–(substituted benzenesulphonyl) glutamoyl dichlorides (**9a**–**9e**) according to the method described earlier [13–17]. Compounds **9a**–**9e** were prepared by treating 2–(substituted benzenesulphonyl)glutamic acids (**8a**–**8e**) with thionyl chloride. Chlorosulphonylation of substituted benzenes (**5b**–**5e**) gave the corresponding sulphonyl chlorides (**6b**–**6e**) which when condensed with L–glutamic acid (**7**) yielded 2–(substituted benzenesulphonyl)–glutamic acids **8a**–**8e** (Figure 2) [44–49].

All these compounds were characterized qualitatively and quantitatively by performing both analytical and spectrophotometric analysis. Melting points of all the synthesized compounds were measured on Mel–Temp, a capillary melting point apparatus, and are uncorrected. Elemental analysis (C, H, N) of the final compounds was performed on 2400 Series–II CHN analyzer of Perkin–Elmer. The IR spectra were recorded on FTIR – 8400S Model of SHIMADZU using KBr pellets. Frequencies were expressed in cm^{-1}. ^1H NMR spectra were collected at 25°C in the pulsed Fourier Transformation mode on Bruker DRX 300 MHz spectrophotometers using solvents described and was consistent with the proposed structures. Chemical shifts are reported in δ ppm (parts per million) relative to tetramethyl silane (Me_4Si) as an internal standard for solutions in deuteriorated dimethylsulfoxide (DMSO–d_6). Splitting patterns have been designated as s (singlet), d (doublet), t (triplet), dd (doublet of doublet) and m (multiplet). The position of hydrogen atoms described in the ^1H NMR interpretation are as per the general structure (Figure 2) and substitution at the R_4 position represent by superscript ‘″’ (double dash) and substitution at R_4' position by superscript ‘‴’ (triple dash). The mass spectra (FAB/EI) were recorded on JEOL JMS–SX–102 mass spectrophotometer. m–nitrobenzyl alcohol (MNBA) was used as the matrix (M^+) which showed the M + 1 peak at 154, 2M + 1 peak at 307. Reactions were monitored by the analytical thin layer chromatography performed on silica gel G plates. The spots were located keeping the TLC plates in iodine chamber. Physical data of the intermediates and that of the final compounds are summarized in Table 1 and 2 respectively.

Table 1. Physical Data for the Intermediate Compounds

Cpd.	R_1	R_2	R_3	Mp (°C) [a]	% Yield	Molecular formula	MW [b]
6b	CH_3	H	CH_3	Liquid	69.85	$C_8H_9ClO_2S$	204.68
6c	H	F	H	Liquid	74.60	$C_6H_4ClFO_2S$	194.61
6d	H	*t*–C_4H_9	H	56–58	71.61	$C_{10}H_{13}ClO_2S$	232.73
6e	CH_3	CH_3	H	Liquid	70.20	$C_{8\ 9}ClO_2S$	204.68
8a	H	H	H	145–147	53.08	$C_{11}H_{13}NO_6S$	287.29
8b	CH_3	H	CH_3	102–104	40.61	$C_{13}H_{17}NO_6S$	315.34
8c	H	F	H	125–127	45.65	$C_{11}H_{12}FNO_6S$	305.28
8d	H	*t*– C_4H_9	H	162–164	43.84	$C_{15}H_{21}NO_6S$	343.40
8e	CH_3	CH_3	H	109–111	67.11	$C_{13}H_{17}NO_6S$	315.34

[a] Melting point; [b] Molecular weight

Table 2. Physical Data of Synthesized 1,5–*N*,*N*′–Disustituted–2–(Substituted Benzenesulphonyl) Glutamamides (**10**–**41**)

Cpd.	R_1	R_2	R_3	R_4/ R_4'	Mp (°C) [a]	%Yield	Molecular Formula	MW [b]
10	H	H	H	n–C_5H_{11}	110–112	67.52	$C_{21}H_{35}N_3O_4S$	425.59
11	H	H	H	n–C_6H_{13}	135–137	57.00	$C_{23}H_{39}N_3O_4S$	453.64
12	H	H	H	c–C_6H_{11}	203–205	70.29	$C_{23}H_{35}N_3O_4S$	449.61
13	H	H	H	$C_6H_5CH_2$	188–190	77.13	$C_{25}H_{27}N_3O_4S$	465.57
14	CH_3	H	CH_3	H	141–143	40.25	$C_{13}H_{19}N_3O_4S$	313.37
15	CH_3	H	CH_3	C_2H_5	170–172	21.34	$C_{17}H_{27}N_3O_4S$	369.48
16	CH_3	H	CH_3	n–C_3H_7	124–126	11.90	$C_{19}H_{31}N_3O_4S$	397.53
17	CH_3	H	CH_3	n–C_4H_9	92–94	62.98	$C_{21}H_{35}N_3O_4S$	425.59
18	CH_3	H	CH_3	n–C_5H_{11}	88–90	62.56	$C_{23}H_{39}N_3O_4S$	453.64
19	CH_3	H	CH_3	n–C_6H_{13}	93–95	65.47	$C_{25}H_{43}N_3O_4S$	481.69
20	CH_3	H	CH_3	C_6H_5	120–122	50.80	$C_{25}H_{27}N_3O_4S$	465.57
21	CH_3	H	CH_3	$C_6H_5CH_2$	202–204	31.94	$C_{27}H_{31}N_3O_4S$	493.62
22	CH_3	H	CH_3	i– C_3H_7	165–167	47.59	$C_{19}H_{31}N_3O_4S$	397.53
23	CH_3	H	CH_3	c–C_6H_{11}	185–187	66.02	$C_{25}H_{39}N_3O_4S$	477.66
24	H	F	H	H	91–93	20.13	$C_{11}H_{14}FN_3O_4S$	303.31
25	H	F	H	n–C_3H_7	218–220	51.21	$C_{17}H_{26}FN_3O_4S$	387.47
26	H	F	H	n–C_4H_9	198–200	51.43	$C_{19}H_{30}FN_3O_4S$	415.52
27	H	F	H	n–C_5H_{11}	170–172	61.94	$C_{21}H_{34}FN_3O_4S$	443.58
28	H	F	H	n–C_6H_{13}	186–188	58.26	$C_{23}H_{38}FN_3O_4S$	471.63
29	H	F	H	C_6H_5	188–190	33.57	$C_{23}H_{22}FN_3O_4S$	455.50
30	H	F	H	$C_6H_5CH_2$	222–224	28.41	$C_{25}H_{26}FN_3O_4S$	483.56
31	H	F	H	i–C_3H_7	215–217	43.33	$C_{17}H_{26}FN_3O_4S$	387.47
32	H	F	H	c–C_6H_{11}	235–237	42.44	$C_{23}H_{34}FN_3O_4S$	467.60
33	H	t–C_4H_9	H	i–C_4H_9	75–77	71.91	$C_{23}H_{39}N_3O_4S$	453.64
34	H	t–C_4H_9	H	c–C_6H_{11}	163–165	81.48	$C_{27}H_{43}N_3O_4S$	505.71
35	CH_3	CH_3	H	C_2H_5	164–166	55.48	$C_{17}H_{27}N_3O_4S$	369.48
36	CH_3	CH_3	H	n–C_3H_7	153–155	51.56	$C_{19}H_{31}N_3O_4S$	397.53
37	CH_3	CH_3	H	C_6H_5	226–228	57.57	$C_{25}H_{27}N_3O_4S$	465.57
38	CH_3	CH_3	H	$C_6H_5CH_2$	201–203	44.72	$C_{27}H_{31}N_3O_4S$	493.62
39	CH_3	CH_3	H	i–C_3H_7	200–202	63.46	$C_{19}H_{31}N_3O_4S$	397.53
40	CH_3	CH_3	H	i–C_4H_9	158–160	55.57	$C_{21}H_{35}N_3O_4S$	425.59
41	CH_3	CH_3	H	c–C_6H_{11}	240–242	56.12	$C_{25}H_{39}N_3O_4S$	477.66

[a] Melting point; [b] Molecular weight

Mass–, IR–, and Proton NMR spectroscopic as well as microanalysis data of the final compounds are shown in Table 3.

Table 3. Mass–, IR– and Proton NMR spectroscopic as well as CHN analysis data of the final compounds (**10**–**41**)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO–d_6)	C,H,N: %calcd/found		
				C	H	N
10	M + H^+ peak at m/z 426	3385, 3306 (N–H str. of CONH), 3240 (N–H str of SO_2NH), 3049 (Ar C–H str.), 2950, 2930, 2866 (ali C–H str.), 1640, 1550, 1455 (ali C–H def.), 1323 (S=O str. of SO_2NH, asymmetric), 1157 (S=O str. of SO_2NH, symmetric), 1093, 983, 910, 730 (Ar–C–H def.)	δ 7.91 (s, 1H, H–4'), δ 7.74 (d, 2H, H–3', H–5'), δ 7.49 (m, 2H, H–2', H–6'), δ 3.67 (t, 1H, H–2), δ 2.97 (t, 2H, H–4), δ 2.81 (d, 2H, H–3), δ 2.02 (m, 2H, CH_2 – 1‴), δ 1.70 (m, 2H, CH_2 – 1″), δ 1.30 (m, 12H, CH_2 – 2″, CH_2 – 3″, CH_2 – 4″, CH_2 – 2‴, CH_2 – 3‴, CH_2 – 4‴), δ 0.86 (t, 6H, CH_2 – 5″, CH_2 – 5‴)	59.27 59.01	8.29 8.36	9.87 8.45
11	M + H+ peak at m/z 454	3375, 3304 (N–H str. of CONH), 3236 (N–H str of SO2NH), 3059 (Ar C–H str.), 2955, 2928, 2856 (ali C–H str.), 1641, 1553, 1458 (ali C–H def.), 1323 (S=O str. of SO2NH, asymmetric), 1167 (S=O str. of SO2NH, symmetric), 1094, 984, 910, 729 (Ar–C–H def.)	δ 7.90 (s, 1H, H–4'), δ 7.75 (d, 2H, H–3', H–5'), δ 7.50 (m, 2H, H–2', H–6'), δ 3.65 (t, 1H, H–2), δ 2.98 (t, 2H, H–4), δ 2.80 (d, 2H, H–3), δ 2.00 (m, 2H, CH2 – 1‴), δ1.66 (m, 2H, CH2 – 1″), δ 1.29 (m, 16H, CH2 – 2″, CH2 – 3″, CH2 – 4″, CH2 –5″, CH2 – 2‴, CH2 – 3‴, CH2 – 4‴, CH2 –5‴), δ 0.86 (t, 6H, CH2 – 6″, CH2 – 6‴)	60.90 60.64	8.67 8.74	9.26 7.84
12	M + H^+ peak at m/z 450	3376, 3303 (N–H str. of CONH), 3237 (N–H str of SO_2NH), 3058 (Ar C–H str.), 2954, 2927, 2846 (ali C–H str.), 1642, 1552, 1460 (ali C–H def.), 1324 (S=O str. of SO_2NH, asymmetric), 1166 (S=O str. of SO_2NH, symmetric), 1090, 981, 912, 769 (Ar–C–H def.)	δ 7.95 (s, 1H, H–4'), δ 7.76 (d, 2H, H–3', H–5'), δ 7.51 (m, 2H, H–2', H–6'), δ 3.67 (t, 1H, H–2), δ 3.00 (t, 2H, H–4), δ 2.78 (d, 2H, H–3), δ 3.70 (m, 1H, CH – 1″), δ 3.55 (m, 1H, CH – 1‴), δ 1.50 (m, 20H, cyclohexyl protons)	61.44 61.18	7.85 7.92	9.35 7.93
13	M + H^+ peak at m/z 466	3300 (N–H str. of CONH), 3246 (N–H str of SO_2NH), 3060 (Ar C–H str.), 2925, 2846 (ali C–H str.), 1645, 1550, 1458 (ali C–H def.), 1325 (S=O str. of SO_2NH, asymmetric), 1160 (S=O str. of SO_2NH, symmetric), 1095, 980, 912, 729 (Ar–C–H def.)	δ 7.89 (s, 1H, H–4'), δ 7.72 (d, 2H, H–3', H–5'), δ 7.48 (m, 2H, H–2', H–6'), δ 7.30 (m, 10H, phenyl protons), δ 4.34 (d, 2H, CH_2 –ph– 1″), δ 4.15 (d, 2H, CH_2 –ph– 1‴), δ 3.75 (s, 1H, H–2), δ 2.98 (t, 2H, H–4), δ 2.80 (d, 2H, H–3),	64.50 64.24	5.85 5.92	9.03 7.61
14	M + H+ peak at m/z 313	3325 (N–H str. of CONH), 3260 (N–H str of SO2NH), 3047 (Ar C–H str.), 2986 2878 (ali C–H str.), 1646, 1552, 1441 (ali C–H def.), 1315 (S=O str. of SO2NH, asymmetric), 1153 (S=O str. of SO2NH, symmetric), 1056, 972, 897 (Ar–C–H def.)	δ 7.67 (s, 1H, H–6'), δ 7.30 (d, 1H, H–4'), δ 7.15 (d, 1H, H–3'), δ 3.56 (t, 1H, H–2), δ 3.35 (s, 3H, Ar–CH3 –2'), δ 2.31 (s, 3H, Ar–CH3 –5'), δ 2.03 (m, 2H, H–4), δ 1.69 (d, 2H, H–3)	49.83 50.58	6.11 6.07	13.41 12.92
15	M + H+ peak at m/z 370	3294 (N–H str. of CONH), 3280 (N–H str of SO2NH), 3097 (Ar C–H str.), 2986 293 (ali C–H str.), 1643, 1560, 1491 (ali C–H def.), 1315 (S=O str. of SO2NH, asymmetric), 1153 (S=O str. of SO2NH, symmetric), 1076, 984, 897 (Ar–C–H def.)	δ 7.69 (s, 1H, H–6'), δ 7.27 (d, 1H, H–4'), δ 7.20 (d, 1H, H–3'), δ 3.56 (t, 1H, H–2), δ 3.35 (s, 3H, Ar–CH3 –2'), δ 3.03 (m, 2H, N–CH2 – 1″), δ 2.77 (m, 2H, N–CH2 – 1‴), δ 2.30 (s, 3H, Ar–CH3 –5'), δ 2.05 (m, 2H, H–4), δ 1.71 (d, 2H, H–3), δ 0.99 (t, 3H, CH3 – 2″), δ 0.78 (t, 3H, CH3 – 2‴)	55.26 56.01	7.37 7.33	11.37 10.88

Table 3. (Continued)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO–d_6)	C,H,N: %calcd/found		
				C	H	N
16	M + H+ peak at m/z 398	3300 (N–H str. of CONH), 3250 (N–H str of SO2NH), 3067 (Ar C–H str.), 2976 2832 (ali C–H str.), 1645, 1562, 1490 (ali C–H def.), 1315 (S=O str. of SO2NH, asymmetric), 1153 (S=O str. of SO2NH, symmetric), 1075, 986, 890 (Ar–C–H def.)	δ 7.70 (s, 1H, H–6'), δ 7.29 (d, 1H, H–4'), δ 7.22 (d, 1H, H–3'), δ 3.70 (t, 1H, H–2), δ 3.45 (s, 3H, Ar–CH3 –2'), δ 3.25 (m, 2H, N–CH2 – 1"), δ 2.83 (m, 2H, N–CH2 – 1'"), δ 2.35 (s, 3H, Ar–CH3 –5'), δ 2.10 (m, 2H, H–4), δ 1.77 (d, 2H, H–3), δ 1.55 (m, 2H, CH2 – 2"), δ 1.35 (m, 2H, CH2 – 2'"), δ 0.96 (t, 3H, CH3 – 3"), δ 0.79 (t, 3H, CH3 – 3'")	57.40 58.15	7.86 7.82	10.57 10.08
17	M + H^+ peak at m/z 426	3322 (N–H str. of CONH), 3270 (N–H str of SO_2NH), 3020 (Ar C–H str.), 2986 2874 (ali C–H str.), 1643, 1552, 1444 (ali C–H def.), 1320 (S=O str. of SO_2NH, asymmetric), 1150 (S=O str. of SO_2NH, symmetric), 1076, 974, 896 (Ar–C–H def.)	δ 7.68 (s, 1H, H–6'), δ 7.27 (d, 1H, H–4'), δ 7.17 (d, 1H, H–3'), δ 3.72 (t, 1H, H–2), δ 3.41 (s, 3H, Ar–CH_3 –2'), δ 3.01 (m, 2H, N–CH_2 – 1"), δ 2.72 (m, 2H, N–CH_2 – 1'"), δ 2.30 (s, 3H, Ar–CH_3 –5'), δ 2.15 (m, 2H, H–4), δ 1.61 (d, 2H, H–3), δ 1.53–1.20 (m, 8H, CH_2 – 2", CH_2 – 3" CH_2 – 2'", CH_2 – 3'"), δ 0.94–0.80 (m, 6H, CH_3 – 4", CH_3 – 4'")	59.27 60.02	8.29 8.25	9.87 9.38
18	M + H^+ peak at m/z 454	3320 (N–H str. of CONH), 3277 (N–H str of SO_2NH), 3058 (Ar C–H str.), 2954, 2927 (ali C–H str.), 1642, 1562, 1490 (ali C–H def.), 1316 (S=O str. of SO_2NH, asymmetric), 1154 (S=O str. of SO_2NH, symmetric), 1070, 981, 912, 769 (Ar–C–H def.)	δ 7.67 (s, 1H, H–6'), δ 7.22 (d, 1H, H–4'), δ 7.19 (d, 1H, H–3'), δ 3.69 (t, 1H, H–2), δ 3.38 (s, 3H, Ar–CH_3 –2'), δ 2.98 (m, 2H, N–CH_2 – 1"), δ 2.68 (m, 2H, N–CH_2 – 1'"), δ 2.30 (s, 3H, Ar–CH_3 –5'), δ 2.14 (m, 2H, H–4), δ 1.58 (d, 2H, H–3), δ 1.50–1.12 (m, 12H, CH_2 – 2", CH_2 – 3", CH_2 – 4", CH_2 – 2'", CH_2 –3'" CH_2 – 4'"), δ 0.92–0.81 (m, 6H, CH_3 – 5", CH_3 – 5'")	60.90 61.65	8.67 8.63	9.26 8.77
19	M + H+ peak at m/z 482	3300 (N–H str. of CONH), 3246 (N–H str of SO2NH), 3060 (Ar C–H str.), 2925, 2846 (ali C–H str.), 1645, 1550, 1458 (ali C–H def.), 1325 (S=O str. of SO2NH, asymmetric), 1155 (S=O str. of SO2NH, symmetric), 1095, 980, 912 (Ar–C–H def.)	δ 7.68 (s, 1H, H–6'), δ 7.24 (d, 1H, H–4'), δ 7.21 (d, 1H, H–3'), δ 3.70 (t, 1H, H–2), δ 3.36 (s, 3H, Ar–CH3 –2'), δ 2.95 (m, 2H, N–CH2 – 1"), δ 2.64 (m, 2H, N–CH2 – 1'"), δ 2.32 (s, 3H, Ar–CH3 –5'), δ 2.16 (m, 2H, H–4), δ 1.60 (d, 2H, H–3), δ 1.32 (m, 16H, CH2 – 2", CH2 – 3", CH2 – 4", CH2 –5", CH2 – 2'", CH2 – 3'", CH2 – 4'", CH2 –5'"), δ 0.88 (t, 6H, CH2 – 6", CH2 – 6'")	62.34 63.09	9.00 9.04	8.72 8.23
20	M + H^+ peak at m/z 398	3394 (N–H str. of CONH), 3280 (N–H str of SO_2NH), 3067 (Ar C–H str.), 2956, 2832 (ali C–H str.), 1643, 1560, 1490 (ali C–H def.), 1315 (S=O str. of SO_2NH, asymmetric), 1153 (S=O str. of SO_2NH, symmetric), 1086, 984, 890 (Ar–C–H def.),	δ 7.92 (s, 1H, H–6'), δ 7.67 (d, 1H, H–4'), δ 7.53 (d, 1H, H–3'), 7.43–7.20 (d, 10H, phenyl protons), δ 3.69 (t, 1H, H–2), δ 3.42 (s, 3H, Ar–CH_3 –2'), δ 2.36 (s, 3H, Ar–CH_3 –5'), δ 2.20 (m, 2H, H–4), δ 1.68 (d, 2H, H–3)	57.40 58.15	7.86 7.82	10.57 10.08

Table 3. (Continued)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO–d_6)	C,H,N: %calcd/found		
				C	H	N
21	M + H^+ peak at m/z 478	3487 (N–H str. of CONH), 3285 (N–H str of SO_2NH), 3069 (Ar C–H str.), 2924, 2866 (ali C–H str.), 1645, 1551, 1493 (ali C–H def.), 1315 (S=O str. of SO_2NH, asymmetric), 1153 (S=O str. of SO_2NH, symmetric), 1094, 1028, 905 (Ar–C–H def.)	δ 7.72 (s, 1H, H–6'), δ 7.37 (d, 1H, H–4'), δ 7.23 (d, 1H, H–3'), δ 7.20 – 7.12 (m, 10H, phenyl protons), δ 4.34 (d, 2H, CH_2 –ph– 1"), δ 4.15 (d, 2H, CH_2 –ph– 1"'), δ 3.66 (t, 1H, H–2), δ 3.40 (s, 3H, Ar–CH_3 –2'), δ 2.36 (s, 3H, Ar–CH_3 –5'), δ 2.10 (m, 2H, H–4), δ 1.79 (d, 2H, H–3)	62.86 63.60	8.23 8.19	8.80 8.30
22	M + H^+ peak at m/z 466	3486 (N–H str. of CONH), 3284 (N–H str. of SO_2NH), 3066 (Ar C–H str.), 2923, 2860 (ali C–H str.), 1645, 1550, 1492 (ali C–H def.), 1315 (S=O str. of SO_2NH, asymmetric), 1153 (S=O str. of SO_2NH, symmetric), 1090, 1027, 904 (Ar–C–H def.)	δ 7.71 (s, 1H, H–6'), δ 7.30 (d, 1H, H–4'), δ 7.24 (d, 1H, H–3'), δ 3.72 (t, 1H, H–2), δ 3.43 (s, 3H, Ar–CH_3 –2'), δ 3.25 (m, 2H, N–CH_2 – 1"), δ 2.83 (m, 2H, N–CH_2 – 1"'), δ 2.35 (s, 3H, Ar–CH_3 –5'), δ 2.10 (m, 2H, H–4), δ 2.03 (m, 2H, N–CH – 1", N–CH – 1"'), δ 1.75 (d, 2H, H–3), δ 0.91 (m, 12H, CH_3 – 2", CH_3 – 3", CH_3 – 2"', CH_3 – 3"')	64.50 65.25	5.85 5.80	9.03 8.54
23	M + H^+ peak at m/z 494	3487 (N–H str. of CONH), 3285 (N–H str of SO_2NH), 3069 (Ar C–H str.), 2924, 2866 (ali C–H str.), 1645, 1551, 1493 (ali C–H def.), 1315 (S=O str. of SO_2NH, asymmetric), 1153 (S=O str. of SO_2NH, symmetric), 1094, 1028, 905 (Ar–C–H def.)	δ 7.63 (s, 1H, H–3'), δ 7.50 (d, 1H, H–6'), δ 7.12 (d, 1H, H–5'), δ 3.60 (t, 1H, H–2), δ 3.42 (s, 3H, Ar–CH_3 –2'), δ 2.45 (m, 2H, H–4), δ 2.30 (s, 3H, Ar–CH_3 –4'), δ 1.94 (d, 2H, H–3), δ 1.56–1.24 (m, 20 H,cyclohexyl protons)	65.70 66.45	6.33 6.29	8.51 8.02
24	M + H+ peak at m/z 303	3351 (N–H str. of CONH), 3240 (N–H str. of SO2NH), 3068 (Ar C–H str.), 2942 (ali C–H str.), 1640, 1567, 1473 (ali C–H def.), 1333 (S=O str. of SO2NH, asymmetric), 1178 (S=O str. of SO2NH, symmetric), 1060, 984, 905 (Ar–C–H def.)	δ 7.87 (t, 2H, H–3', H–5'), δ 7.77 (t, 2H, H–2', H–6'), δ 3.82 (t, 1H, H–2), δ 3.34 (s, 2H, H–4), δ 1.95 (d, 2H, H–3)	43.56 43.64	4.65 4.76	13.85 13.68
25	M + H^+ peak at m/z 388	3316 (N–H str of CONH), 3247 (N–H str of SO_2NH), 3062 (Ar C–H str.), 2972 (ali C–H str.), 1647, 1597, 1540, 1493 (ali C–H def.), 1332 (S=O str of SO_2NH, asymmetric), 1168 (S=O str of SO_2NH, symmetric), 1091, 1060, 981, 906 (Ar–C–H def.)	δ 7.97 (t, 2H, H–3', H–5'), δ 7.83 (t, 2H, H–2', H–6'), δ 3.82 (t, 1H, H–2), δ 3.65 (m, 2H, N–CH_2 – 1"), δ 3.23 (m, 2H, N–CH_2 – 1"'), δ 2.81 (m, 2H, H–4), δ 2.05 (d, 2H, H–3), δ 1.35 (m, 2H, CH_2 – 2"), δ 1.26 (m, 2H, CH_2 – 2"'), δ 1.06 (t, 3H, CH_3 – 3"), δ 0.80 (t, 3H, CH_3 – 3"')	52.70 52.78	6.76 6.87	10.84 10.07
26	M + H^+ peak at m/z 416	3375, 3310 (N–H str of CONH), 3238 (N–H str of SO_2NH), 3101 (Ar C–H str.), 2959, 2934, 2870 (ali C–H str.), 1639, 1593, 1553, 1495 (ali C–H def.), 1325 (S=O str of SO_2NH, asymmetric), 1167 (S=O str of SO_2NH, symmetric), 1092, 1068, 984, 903 (Ar–C–H def.)	δ 7.93 (t, 2H, H–3', H–5'), δ 7.79 (t, 2H, H–2', H–6'), δ 3.80 (t, 1H, H–2), δ 3.61 (m, 2H, N–CH_2 – 1"), δ 3.20 (m, 2H, N–CH_2 – 1"'), δ 2.58 (m, 2H, H–4), δ 1.99 (d, 2H, H–3), δ 1.40–1.08 (m, 8H, CH_2 – 2", CH_2 – 3" CH_2 – 2"', CH_2 – 3"'), δ 0.95–0.82 (m, 6H, CH_3 – 4", CH_3 – 4"')	54.92 55.01	7.28 7.39	10.11 9.94

Table 3. (Continued)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO–d_6)	C,H,N: %calcd/found		
				C	H	N
27	M + H+ peak at m/z 444	3377, 3309 (N–H str. of CONH), 3238 (N–H str. of SO2NH), 3103 (Ar C–H str.), 2956, 2935, 2868 (ali C–H str.), 1640, 1593, 1553, 1494 (ali C–H def.), 13251 (S=O str of SO2NH, asymmetric), 1166 (S=O str. of SO2NH, symmetric), 1093, 1069, 987, 904 (Ar–C–H def.)	δ 7.85 (t, 2H, H–3', H–5'), δ 7.76 (t, 2H, H–2', H–6'), δ 3.90 (t, 1H, H–2), δ 3.51 (m, 2H, N–CH2 – 1"), δ 3.18 (m, 2H, N–CH2 – 1'"), δ 2.55 (m, 2H, H–4), δ 1.96 (d, 2H, H–3), δ 1.45–1.10 (m, 12H, CH2 – 2", CH2 – 3", CH2 – 4", CH2 – 2'", CH2 –3'" CH2 – 4'"), δ 0.90–0.78 (m, 6H, CH3 – 5", CH3 – 5'")	56.86 56.94	7.73 7.84	9.47 9.30
28	M + H+ peak at m/z 472	3316 (N–H str. of CONH), 3247 (N–H str. of SO2NH), 3065 (Ar C–H str.), 2962 (ali C–H str.), 1647, 1590, 1539, 1485 (ali C–H def.), 1332 (S=O str. of SO2NH, asymmetric), 1168 (S=O str. of SO2NH, symmetric), 1095, 1062, 989, 905 (Ar–C–H def.)	δ 7.82 (t, 2H, H–3', H–5'), δ 7.71 (t, 2H, H–2', H–6'), δ 3.87 (t, 1H, H–2), δ 3.49 (m, 2H, N–CH2 – 1"), δ 3.16 (m, 2H, N–CH2 – 1'"), δ 2.35 (m, 2H, H–4), δ 1.94 (d, 2H, H–3), δ 1.40 (m, 16H, CH2 – 2", CH2 – 3", CH2 – 4", CH2 –5", CH2 – 2'", CH2 – 3'", CH2 – 4'", CH2 –5'"), δ 1.07–0.94 (t, 6H, CH2 – 6", CH2 – 6'")	58.57 58.65	8.12 8.23	8.91 8.74
29	M + H+ peak at m/z 456	3358 (N–H str. of CONH), 3240 (N–H str. of SO2NH), 3093 (Ar C–H str.), 2938 (ali C–H str.), 1640, 1562, 1495 (ali C–H def.), 1335 (S=O str. of SO2NH, asymmetric), 1170 (S=O str. of SO2NH, symmetric), 1020, 989, 895 (Ar–C–H def.)	δ 7.90 (t, 2H, H–3', H–5'), δ 7.81 (t, 2H, H–2', H–6'), 7.60–7.24 (d, 10H,phenyl protons), δ 3.88 (t, 1H, H–2), δ 3.44 (s, 2H, H–4), δ 2.15 (d, 2H, H–3)	60.65 60.73	4.87 4.98	9.23 9.06
30	M + H+ peak at m/z 484	3312 (N–H str. of CONH), 3248 (N–H str. of SO2NH), 3065 (Ar C–H str.), 2922, 2866 (ali C–H str.), 1645, 1550, 1495 (ali C–H def.), 1333 (S=O str. of SO2NH, asymmetric), 1169 (S=O str. of SO2NH, symmetric), 1093, 1031, 979, 912 (Ar–C–H def.)	δ 7.92 (t, 2H, H–3', H–5'), δ 7.78 (t, 2H, H–2', H–6'), δ 7.42 – 7.27 (m, 10H, phenyl protons), δ 4.26 (d, 2H, CH2 –ph– 1"), δ 4.17 (d, 2H, CH2 –ph– 1'"), δ 3.86 (t, 1H, H–2), δ 3.42 (s, 2H, H–4), δ 2.18 (d, 2H, H–3)	62.10 62.18	5.42 5.53	8.69 8.52
31	M + H^+ peak at m/z 388	3315 (N–H str. of CONH), 3248 (N–H str. of SO_2NH), 3063 (Ar C–H str.), 2972 (ali C–H str.), 1645, 1593, 1539, 1495 (ali C–H def.), 1333 (S=O str. of SO_2NH, asymmetric), 1169 (S=O str. of SO_2NH, symmetric), 1090, 1061, 989, 906 (Ar–C–H def.)	δ 7.81 (t, 2H, H–3', H–5'), δ 7.67 (t, 2H, H–2', H–6'), δ 3.80 (t, 1H, H–2), δ 3.37 (s, 2H, H–4), δ 2.01 (m, 2H, N–CH – 1", N–CH – 1'"), δ 1.65 (d, 2H, H–3), δ 0.92 (m, 12H, CH_3 – 2", CH_3 – 3", CH_3 – 2'", CH_3 – 3'")	52.70 52.78	6.76 6.87	10.84 10.67
32	M + H^+ peak at m/z 466	3365 (N–H str of CONH), 3248 (N–H str of SO_2NH), 3093 (Ar C–H str.), 2947 (ali C–H str.), 1640, 1560, 1485 (ali C–H def.), 1334 (S=O str of SO_2NH, asymmetric), 1172 (S=O str of SO_2NH, symmetric), 1060, 974, 896 (Ar–C–H def.)	δ 7.85 (t, 2H, H–3', H–5'), δ 7.69 (t, 2H, H–2', H–6'), δ 3.82 (t, 1H, H–2), δ 3.60 (m, 2H, CH – 1", CH – 1'"), δ 3.36 (s, 2H, H–4), δ 1.65 (d, 2H, H–3), δ 1.44–1.05 (m, 20 H,cyclohexyl protons)	59.08 59.16	7.33 7.44	8.99 8.62

Table 3. (Continued)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO–d_6)	C,H,N: %calcd/found		
				C	H	N
33	M + H^+ peak at m/z 454	3299 (N–H str. of CONH), 3257 (N–H str. of SO_2NH), 3092 (Ar C–H str.), 2930, 2855 (ali C–H str.), 1625, 1552, 1457 (ali C–H def.), 1340 (S=O str. of SO_2NH, asymmetric), 1166 (S=O str. of SO_2NH, symmetric), 1029, 995, 890 (Ar–C–H def.)	δ 7.90 (d, 2H, H–2', H–6'), δ 7.66 (d, 2H, H–3', H–5'), δ 3.81 (t, 1H, H–2), δ 3.27 (m, 4H, N–CH_2 – 1", N–CH_2 – 1'''), δ 2.37 (m, 2H, H–4), δ 2.20 (m, 9H, three CH_3 of t– Butyl), δ 2.05 (m, 2H, CH – 2", CH –2'''), δ 1.85 (d, 2H, H–3), δ 1.64–1.50 (m, 12 H, CH_3 – 3", CH_3 – 4", CH_3 – 3''', CH_3 – 4''')	60.90 61.30	8.67 8.60	9.26 9.20
34	M + H^+ peak at m/z 506	3300 (N–H str. of CONH), 3094 (Ar C–H str.), 2934, 2856 (ali C–H str.), 1624, 1553, 1450 (ali C–H def.), 1342 (S=O str. of SO_2NH, asymmetric), 1167 (S=O str. of SO_2NH, symmetric), 1028, 995, 891 (Ar–C–H def.)	δ 7.93 (d, 2H, H–2', H–6'), δ 7.68 (d, 2H, H–3', H–5'), δ 3.84 (t, 1H, H–2), δ 2.45 (m, 2H, H–4), δ 2.14 (m, 9H, three CH_3 of t– Butyl), δ 1.90 (d, 2H, H–3), δ 1.54–1.25 (m, 20 H,cyclohexyl protons)	64.12 65.03	8.57 8.32	8.31 7.99
35	M + H^+ peak at m/z 370	3299 (N–H str. of CONH), 3249 (N–H str. of SO_2NH), 3018 (Ar C–H str.), 2923, 2872 (ali C–H str.), 1541, 1446 (ali C–H def.), 1323 (S=O str of SO_2NH, asymmetric), 1155 (S=O str. of SO_2NH, symmetric), 1027, 976, 912 (Ar–C–H def.)	δ 7.60 (s, 1H, H–3'), δ 7.52 (d, 1H, H–6'), δ 7.14 (d, 1H, H–5'), δ 3.74 (t, 1H, H–2), δ 3.37 (s, 3H, Ar–CH_3 –2'), δ 3.04 (m, 2H, N–CH_2 – 1"), δ 2.77 (m, 2H, N–CH_2 – 1'''), δ 2.28 (s, 3H, Ar–CH_3 –4'), δ 2.15 (m, 2H, H–4), δ 1.76 (d, 2H, H–3), δ 0.97 (t, 3H, CH_3 – 2"), δ 0.76 (t, 3H, CH_3 – 2''')	55.26 54.74	7.37 7.56	11.37 11.30
36	M + H^+ peak at m/z 398	3310 (N–H str. of CONH), 3249 (N–H str of SO_2NH), 3018 (Ar C–H str.), 2874 (ali C–H str.), 1551, 1444 (ali C–H def.), 1323 (S=O str of SO_2NH, asymmetric), 1155 (S=O str of SO_2NH, symmetric), 1028, 974, 911 (Ar–C–H def.)	δ 7.59 (s, 1H, H–3'), δ 7.51 (d, 1H, H–6'), δ 7.15 (d, 1H, H–5'), δ 3.74 (t, 1H, H–2), δ 3.37 (s, 3H, Ar–CH_3 –2'), δ 3.06 (m, 2H, N–CH_2 – 1"), δ 2.79 (m, 2H, N–CH_2 – 1'''), δ 2.28 (s, 3H, Ar–CH_3 –4'), δ 2.15 (m, 2H, H–4), δ 1.76 (d, 2H, H–3), δ 1.56 (m, 2H, CH_2 – 2"), δ 1.38 (m, 2H, CH_2 – 2'''), δ 0.98 (t, 3H, CH_3 – 2"), δ 0.77 (t, 3H, CH_3 – 2''')	57.40 56.68	7.86 7.93	10.57 10.50
37	M + H^+ peak at m/z 466	3360, 3308 (N–H str. of CONH), 3238 (N–H str of SO_2NH), 3055 (Ar C–H str.), 2939 (ali C–H str.), 1602, 1547, 1520, 1500 (ali C–H def.), 1319 (S=O str of SO_2NH, asymmetric), 1155 (S=O str of SO_2NH, symmetric), 1090, 1028, 980, 910 (Ar–C–H def.)	δ 8.60 (s, 1H, H–3'), δ 8.32 (d, 1H, H–6'), δ 8.14 (d, 1H, H–5'),7.55–7.20 (d, 10H,phenyl protons), δ 3.64 (t, 1H, H–2), δ 3.40 (s, 3H, Ar–CH_3 –2'), δ 2.28 (s, 3H, Ar–CH_3 –4'), δ 2.15 (m, 2H, H–4), δ 1.76 (d, 2H, H–3)	64.50 63.58	5.85 6.04	9.03 8.96
38	M + H^+ peak at m/z 494	3300 (N–H str. of CONH), 3248 (N–H str of SO_2NH), 3028 (Ar C–H str.), 2924, 2868 (ali C–H str.), 1641, 1539, 1497 (ali C–H def.), 1323 (S=O str. of SO_2NH, asymmetric), 1155 (S=O str. of SO_2NH, symmetric), 1092, 1028, 972, 912 (Ar–C–H def.)	δ 7.57 (s, 1H, H–3'), δ 7.50 (d, 1H, H–6'), δ 7.32 – 7.25 (m, 10H, phenyl protons), δ 7.11 (d, 1H, H–5'), δ 4.24 (d, 2H, CH_2 –ph– 1"), δ 4.10 (d, 2H, CH_2 –ph– 1'''), δ 3.76 (s, 1H, H–2), δ 3.37 (s, 3H, Ar–CH_3 –2"), δ 2.28 (d, 3H, Ar–CH_3 –4'), δ 2.14 (m, 2H, H–4), δ 1.78 (m, 2H, H–3)	65.70 65.18	6.33 6.52	8.51 7.84

Table 3. (Continued)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO–d_6)	C,H,N: %calcd/found		
				C	H	N
39	$M + H^+$ peak at m/z 398	3310 (N–H str. of CONH), 3247 (N–H str. of SO_2NH), 3028 (Ar C–H str.), 2933, 2855 (ali C–H str.), 1540, 1445 (ali C–H def.), 1323 (S=O str. of SO_2NH, asymmetric), 1155 (S=O str. of SO_2NH, symmetric), 1028, 966, 910 (Ar–C–H def.)	δ 7.61 (s, 1H, H–3'), δ 7.49 (d, 1H, H–6'), δ 7.16 (d, 1H, H–5'), δ 3.64 (t, 1H, H–2), δ 3.38 (s, 3H, Ar–CH_3 –2'), δ 2.28 (s, 3H, Ar–CH_3 –4'), δ 2.16 (m, 2H, H–4), δ 2.03 (m, 2H, N–CH – 1", N–CH – 1"'), δ 1.67 (d, 2H, H–3), δ 0.96 (m, 12H, CH_3 – 2", CH_3 – 3", CH_3 – 2"', CH_3 – 3"')	57.40 56.68	7.86 8.05	10.57 10.50
40	$M + H^+$ peak at m/z 426.	3362, 3307 (N–H str. of CONH), 3236 (N–H str. of SO_2NH), 3065 (Ar C–H str.), 2948 (ali C–H str.), 1607, 1548, 1482 (ali C–H def.), 1323 (S=O str. of SO_2NH, asymmetric), 1156 (S=O str. of SO_2NH, symmetric), 1028, 987, 910 (Ar–C–H def.)	δ 7.64 (s, 1H, H–3'), δ 7.52 (d, 1H, H–6'), δ 7.17 (d, 1H, H–5'), δ 3.63 (t, 1H, H–2), δ 3.40 (s, 3H, Ar–CH_3 –2'), δ 3.37 (m, 4H, N–CH_2 – 1", N–CH_2 – 1"'), δ 2.40 (m, 2H, H–4), δ 2.28 (s, 3H, Ar–CH_3 –4'), δ 2.03 (m, 2H, CH – 2", CH –2"'), δ 1.65 (d, 2H, H–3), δ 1.50 (m, 12 H, CH_3 – 3", CH_3 – 4", CH_3 – 3"', CH_3 – 4"')	59.27 58.75	8.29 8.48	9.87 9.80
41	$M + H^+$ peak at m/z 478	3359, 3307 (N–H str. of CONH), 3236 (N–H str of SO_2NH), 3053 (Ar C–H str.), 2940 (ali C–H str.), 1604, 1546, 1519, 1502 (ali C–H def.), 1312 (S=O str. of SO_2NH, asymmetric), 1156 (S=O str. of SO_2NH, symmetric), 1087, 1027, 979, 914 (Ar–C–H def.)	δ 7.63 (s, 1H, H–3'), δ 7.50 (d, 1H, H–6'), δ 7.12 (d, 1H, H–5'), δ 3.60 (t, 1H, H–2), δ 3.42 (s, 3H, Ar–CH_3 –2'), δ 2.45 (m, 2H, H–4), δ 2.30 (s, 3H, Ar–CH_3 –4'), δ 1.94 (d, 2H, H–3), δ 1.56–1.24 (m, 20 H, cyclohexyl protons)	62.86 62.34	8.23 8.42	8.80 8.73

Table 4. Antitumor activities of the 1,5–*N*,*N'*–disubstituted–2–(substituted benzenesulphonyl) glutamamides (**10**–**41**)

Cpd	% TCI	Log (BA)
10	28.84	1.460
11	25.14	1.400
12	49.20	1.692
13	24.22	1.384
14	53.37	1.727
15	25.57	1.408
16	27.59	1.441
17	23.56	1.372
18	20.54	1.313
19	27.09	1.433
20	45.32	1.656
21	42.77	1.631
22	59.67	1.776
23	52.82	1.723
24	34.72	1.541
25	31.77	1.502
26	21.48	1.332
27	20.56	1.313
28	20.46	1.311
29	28.03	1.448
30	23.38	1.369
31	17.24	1.237
32	24.56	1.390
33	36.18	1.558
34	23.50	1.371
35	21.92	1.341
36	21.00	1.322
37	79.57	1.901
38	30.30	1.481
39	33.15	1.520
40	47.15	1.673
41	53.17	1.726
Mitomycin (**42**)	100.00	2.000
Azaserine (**2**)	100.00	2.000
Don (**3**)	100.00	2.000

2.2 Biological Activity

The antitumor activity of all final compounds (**10–41**) was evaluated in vivo against Ehrlich Ascites Carcinoma (EAC) cells in Swiss Albino mice according to the earlier reported method [13–17]. Mitomycin C (**42**) was used as the universal standard while azaserine (**2**) and DON (**3**) were

used as the specific standards. The antitumor activity was expressed in terms of the percentage inhibition of the cell count. Standards showed 100% inhibitions. Results are shown in Table 4.

2.3 QSAR Study

QSAR studies of 32 synthesized QSAR analogs of 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl)glutamamides (**10–41**) were performed using different parameters like physicochemical, topological (ETSA and RTSA indices), geometrical, constitutional, semi–emperical quantum chemical descriptors as well as indicators parameters. Electrotopological state atom (ETSA) index [50–52] is an atom level topological descriptor encoding both electronic and topological information. 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 ΔI_j, shown in Eq. (1). The atom intrinsic value includes both electronic and topological information. The perturbation effect ΔI_j stands for influence of information field on the intrinsic atom value I_i.

$$S_i = I_i + \Delta I_j \tag{1}$$

The intrinsic state value of atom i is expressed as

$$I_i = [((2/N)^2\ \delta^v + 1)/\delta] \tag{2}$$

where N = principle quantum number of valence electrons, δ^v = number of valence electrons – number of hydrogen atom attached, and δ = number of sigma electrons – number of hydrogen atom attached.

The expression for the perturbation effect is as follows:

$$\Delta I_j = \Sigma(I_i - I_j)/\ r_{ij}^2 \tag{3}$$

where r_{ij} is the graph distance.

The refractotopological state atom (RTSA) index [53–54] is a novel atom level topological descriptor used in QSAR study. The R–state index $\Re_i$ of an atom i in a molecule is composed of an intrinsic refractivity AR_i and the perturbation effect ΔAR_i, as shown in Eq. (4).

$$\Re_i = AR_i + \Delta AR_i \tag{4}$$

The perturbation term is defined as:

$$\Delta AR_i = \Sigma(AR_i - \Delta AR_i)/\ r_{ij}^2 \tag{5}$$

where r_{ij} is the graph distance.

The RTSA index is based on the atomic refractivity and the topological environment of the atom. Sum of the atomic refractivity, that is, molar refractivity is directly proportional to the polarizability of a substance which determines London force/dispersive force between nonpolar molecules. Therefore, R–state indices are important for modeling the dispersive/van der Waals interactions with the receptors. The logarithm of percentage tumor cell inhibition (Log BA) was used as the

biological activity parameter and is listed in Table 4.

Table 5. ETSA indices, RTSA indices, physicochemical (steric), semi–empirical quantum descriptors and some other parameters of glutamamide analogs along with indicator parameters

Cpd	S_3	R_3	R_{16}	$R_4/R_4'B_5$	qC_{13}	E_{HOMO}	GAP	SA	nHAcc	I_1	I_2
10	1.623	4.809	3.993	4.940	–0.182	–9.810	–8.916	0.816	7.000	0.000	0.000
11	1.628	4.808	3.981	5.960	–0.182	–9.802	–8.915	0.886	7.000	0.000	0.000
12	1.642	4.833	4.151	3.490	–0.177	–9.755	–8.872	0.582	7.000	0.000	1.000
13	1.607	4.846	4.139	6.020	–0.184	–9.771	–9.094	0.645	7.000	0.000	0.000
14	1.673	4.945	6.163	1.000	–0.178	–9.940	–8.919	0.462	7.000	0.000	0.000
15	1.722	4.944	4.011	3.170	–0.185	–9.791	–8.978	0.654	7.000	0.000	0.000
16	1.730	4.944	4.005	3.490	–0.185	–9.786	–8.903	0.721	7.000	0.000	0.000
17	1.737	4.943	3.993	4.540	–0.184	–9.771	–9.004	0.807	7.000	0.000	0.000
18	1.743	4.942	3.980	4.940	–0.184	–9.779	–8.964	0.867	7.000	0.000	0.000
19	1.749	4.941	3.969	5.960	–0.182	–9.785	–8.969	0.940	7.000	0.000	0.000
20	1.718	4.987	4.295	3.110	–0.186	–8.760	–7.901	0.685	7.000	0.000	0.000
21	1.727	4.979	4.126	6.020	–0.181	–9.399	–8.505	0.714	7.000	0.000	0.000
22	1.725	4.944	4.052	3.170	–0.183	–9.785	–8.957	0.702	7.000	0.000	0.000
23	1.762	4.966	4.139	3.490	–0.177	–9.717	–8.966	0.653	7.000	0.000	1.000
24	0.969	5.414	6.199	1.000	–0.179	–10.211	–8.850	0.416	8.000	0.000	0.000
25	1.027	5.413	4.058	3.490	–0.183	–9.872	–8.716	0.679	8.000	0.000	0.000
26	1.034	5.412	4.045	4.540	–0.182	–9.844	–8.693	0.756	8.000	0.000	0.000
27	1.040	5.411	4.033	4.940	–0.182	–9.861	–8.714	0.820	8.000	0.000	0.000
28	1.045	5.411	4.021	5.960	–0.182	–9.860	–8.716	0.890	8.000	0.000	0.000
29	1.015	5.456	4.348	3.110	–0.186	–8.777	–7.522	0.632	8.000	0.000	0.000
30	1.024	5.448	4.179	6.020	–0.183	–9.625	–8.470	0.703	8.000	0.000	0.000
31	1.022	5.413	4.105	3.170	–0.184	–9.941	–8.796	0.654	8.000	0.000	0.000
32	1.059	5.435	4.191	3.490	–0.175	–9.620	–8.429	0.575	8.000	0.000	0.000
33	1.779	5.004	3.994	4.450	–0.182	–9.756	–8.933	0.857	7.000	0.000	0.000
34	1.809	5.027	4.133	3.490	–0.188	–9.635	–8.831	0.719	7.000	1.000	1.000
35	1.768	5.016	4.012	3.170	–0.184	–9.858	–9.003	0.643	7.000	1.000	0.000
36	1.776	5.015	4.006	3.490	–0.184	–9.831	–8.985	0.719	7.000	0.000	0.000
37	1.765	5.059	4.296	3.110	–0.187	–8.738	–7.800	0.683	7.000	0.000	0.000
38	1.774	5.051	4.127	6.020	–0.182	–9.693	–9.021	0.761	7.000	0.000	0.000
39	1.771	5.016	4.053	3.170	–0.184	–9.861	–9.007	0.705	7.000	0.000	0.000
40	1.779	5.015	4.000	4.450	–0.184	–9.800	–8.979	0.776	7.000	0.000	0.000
41	1.809	5.038	4.139	3.490	–0.182	–9.660	–8.862	0.641	7.000	0.000	1.000

The physicochemical parameters like, hydrophobic constant (π), molar refractivity (MR), steric parameter (E_s), Verloop STERIMOL parameters like L, B_1, B_5 were collected from the literature [18,55–56]. Topological indices like ETSA indices and RTSA indices were calculated using programme 'Mouse' developed in our laboratory [57]. Semi–empirical quantum chemical descriptors like atomic charges, E_{HOMO}, E_{LUMO}, the HOMO–LUMO energy gap (GAP) and different QSAR properties like surface area (approx.), surface area (grid), volume, hydration energy, log P, refractivity, polarizability and mass were calculated using Hyperchem Release 7.0 Pro Package [58]. 2D structure of compounds were drawn and converted to 3D structure. Geometry optimization was done by a semi–empirical method [59–61] – Austin Model 1 (AM1) using Polack-Ribiere (conjugate gradient) algorithm with RMS gradient of 0.1 kcal/Å mol (1 cal = 4.184 J). Molecular mechanics (MM+) force field was applied for the preliminary structure optimization to shorten the total time required for the energy minimization by AM1 method. Various descriptors such as

geometrical and constitutional descriptors, functional groups, properties, and empirical descriptors were calculated by a software 'DRAGON' ver 3, 2003 [62]. Besides these, indicator parameters were also used in order to find out the role of the specific substituent at the specific position towards the biological activity. The selected parameters used to develop QSAR models are listed in Table 5.

Correlation analysis was performed on a data matrix containing all the predictor parameters and response variable. Intercorreleted parameters were eliminated. The correlation matrix is shown in Table 6. Remaining data matrix was subjected to multiple regression analysis [63] to build QSAR models using a computer program "multi regress" [64] developed in our laboratory.

Table 6. Correlation matrix of important variables and the biological activity

	R_3	R_{16}	$R_4/R_4'B_5$	qC_{13}	E_{LUMO}	GAP	SA	nHAcc	I_1	I_2	Log (BA)
S_3	–0.91	–0.21	0.03	–0.22	0.10	–0.35	0.19	–0.99	0.21	0.26	0.41
R_3	1.00	0.16	–0.11	0.08	0.01	0.42	–0.19	0.96	–0.08	–0.22	–0.34
R_{16}		1.00	–0.63	0.34	–0.15	0.06	–0.70	0.17	–0.07	–0.06	0.29
$R_4/R_4'B_5$			1.00	–0.07	–0.01	–0.14	0.76	–0.04	–0.14	–0.16	–0.36
qC_{13}				1.00	–0.40	–0.25	–0.30	0.18	–0.31	0.22	0.16
E_{LUMO}					1.00	0.88	–0.01	–0.08	–0.04	–0.00	0.37
GAP						1.00	–0.17	0.36	–0.11	–0.13	0.22
SA							1.00	–0.17	–0.07	–0.21	–0.34
nHAcc								1.00	–0.16	–0.24	–0.42
I_1									1.00	0.29	–0.21
I_2										1.00	0.31

Statistical qualities of the regression equation were justified by parameters like *R*, %*EV*, R^2_A, *F*, *p* and *SEE*. The predictive powers of QSAR equation are validated by leave–one–out (LOO–) cross–validation method. Parameters like *PRESS*, *SSY*, R^2_{cv}, S_{PRESS} and *PSE* are considered for validation of the models.

3 RESULTS AND DISCUSSION

Thirty two 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl)glutamamides (**10**–**41**) were synthesized on the basis of our earlier QSAR studies. These glutamamides were biologically evaluated for anticancer activity against Erlich Ascite Carcinoma (EAC) cells in Swiss Albino mice. The synthesized compounds contain four types of substitutions in the aromatic ring whereas the aliphatic side chain contains eleven different substitutions. Physical data of intermediates and final compounds are listed in Table 1 and 2 respectively. Antitumor activity in terms of percentage of tumor cell inhibition (%TCI) is presented in Table 4.

For the QSAR study, logarithm of %TCI (log BA) of these glutamamides analogs was computed and is presented in Table 4. Correlation analysis and k–mean cluster analysis were performed to reduce the number of predictor variables for the study. The selected variables are listed in Table 5. All possible combinations of predictor variables were considered to develop QSAR models by

multiple linear regression analysis. The best QSAR model was obtained as follows:

$$\begin{gathered}\text{Log (BA)} = 4.439\ (\pm 0.871) - 0.273\ (\pm 0.108)\ R_3 + 0.136\ (\pm 0.045)\ R_{16} + 0.221\ (\pm 0.070)\ E_{\text{HOMO}} \\ + 0.128\ (\pm 0.070)\ I_2 \\ n = 32\ R = 0.699\ \%EV = 48.88\ R^2_A = 0.413\ F_{(4,27)} = 6.454\ p<0.0009\ SEE = 0.128\ PRESS = \\ 0.640\ SSY = 0.868\ R^2_{\text{cv}} = 0.263\ S_{PRESS} = 0.154\ PSE = 0.141\end{gathered} \quad (6)$$

Where n is the number of data point. R, R^2_a, F, p, SEE, PRESS, SSY, R^2_{cv}, PSE, S_{PRESS} are correlation coefficient, adjusted R^2 , variance ratio, probability factor related to F–ratio, standard error of estimate, predicted residual sum of square, total sum of squares, cross–validated R^2, standard deviation error of prediction and Standard error of PRESS respectively. R_3 and R_{16} are the R–state indices of atoms 3 and 16 respectively, E_{HOMO} is the energy of the highest occupied molecular orbital and I_2 is the indicator variable for the presence of cyclohexyl group at R_4/R_4' position of glutamamide analogs. Eq. (6) explains up to 48.88 % of variances in the activity data. Negative coefficient of R_3 in the above model suggests that the higher value of R_3 is detrimental to the activity whereas the higher value of R_{16} may increase the antitumor activity as evidenced by the positive regression coefficients. The positive coefficient of E_{HOMO} in the equation showed the positive contribution of E_{HOMO} towards the activity. The equation suggests that the presence of cyclohexyl group at R_4/R_4' position of glutamamide analogs may favor the antitumor activity as demonstrated by the positive regression coefficient of I_2. However, deletion of compounds **20**, **22**, **29**, **34**, and **40** yielded the following models.

$$\begin{gathered}\text{Log (BA)} = 5.554\ (\pm 0.618) - 0.145\ (\pm 0.065)\ R_3 + 0.169\ (\pm 0.026)\ R_{16} + 0.418\ (\pm 0.60)\ E_{\text{HOMO}} \\ + 0.240\ (\pm 0.045)\ I_2 \\ n = 27\ \textbf{DC} = \textbf{20}, \textbf{22}, \textbf{29}, \textbf{34}, \text{and } \textbf{40}\ R = 0.916\ \%EV = 83.85\ R^2_A = 0.809\ F_{(4,22)} = 28.548 \\ p<0.0001\ SEE = 0.072\ PRESS = 0.143\ SSY = 0.703\ R^2_{\text{cv}} = 0.797\ S_{\text{PRESS}} = 0.081\ PSE = 0.073\end{gathered} \quad (7)$$

where DC refers to the deleted compounds which behave as outliers possibly by working with a different mechanism of action. Eq. (7) explains up to 83.85 % of variances in the antitumor activity.

Combination of qC_{13} (the atomic charge of atom 13), GAP (the energy difference between HOMO–LUMO), SA (approximate surface area of the whole molecule) and nHAcc [number of acceptor atoms for H– bonds (N, O, F) of these compounds] produced a model for antitumor activity of glutamamide analogs as shown in Eq. (8).

$$\begin{gathered}\text{Log (BA)} = 9.335\ (\pm 2.064) + 20.015\ (\pm 8.879)\ qC_{13} + 0.230(\pm 0.068)\ \text{GAP} \\ - 0.393\ (\pm 0.201)\ \text{SA} - 0.260\ (\pm 0.053)\ \text{nHAcc} \\ n = 32\ R = 0.744\ \%EV = 55.36\ R^2_A = 0.487\ F_{(4,27)} = 8.371\ p<0.0002\ SEE = 0.120 \\ PRESS = 0.569\ SSY = 0.868\ R^2_{\text{cv}} = 0.344\ S_{\text{PRESS}} = 0.145\ PSE = 0.133\end{gathered} \quad (8)$$

Eq. (8) explains up to 55.36 % of variances in the activity data. The positive coefficient of qC_{13} indicates that increasing the atomic charge on the carbon atom 13 is favorable for the activity. The equation reveals that the HOMO–LUMO energy gap plays an important role in the stability of these compounds. The negative coefficient of the approximate surface area implies that lower values of

the whole molecular surface area correspond to higher antitumor activity of these glutamamides. The equation suggests that the number of acceptor atoms for hydrogen bonds plays an important role in the antitumor activity. Higher number of acceptor atoms for hydrogen bonds may decrease the antitumor activity of these glutamamides as indicated by the negative coefficient of nHAcc. Stepwise deletions of the outliers **22**, **40**, **32**, **29**, and **20** yielded statistically significant Eq. (9).

$$\begin{gathered}\text{Log (BA)} = 13.331\ (\pm1.510) + 32.584\ (\pm6.465)\ qC_{13} + 0.440(\pm0.063)\ \text{GAP} - 0.412\ (\pm0.128)\\ \text{SA} - 0.238\ (\pm0.035)\ \text{nHAcc}\\ n = 27\ \textbf{DC} = \textbf{22}, \textbf{40}, \textbf{32}, \textbf{29}, \text{and } \textbf{20}\ R = 0.907\ \%EV = 82.18\ R^2_A = 0.789\ F_{(4,22)} = 25.357\\ p<0.0001\ SEE = 0.076\ PRESS = 0.202\ SSY = 0.707\ R^2_{cv} = 0.714\ S_{\text{PRESS}} = 0.096;\ PSE = 0.086\end{gathered} \quad (9)$$

Eq. [9] explains up to 82.18 % of the variances in the activity data. The equation has significant statistical predictivity as revealed by its R^2_{cv} value (>0.7).

Another QSAR model was developed by taking S_3 (E–state index of atom 3), $R_4/R_4'B_5$ (maximum width Verloop STERIMOL parameter of R_4/R_4' substituent), E_{HOMO} (the energy of highest occupied molecular orbital) and an indicator parameter I_1 (indicate the presence of tert–butyl group at R_3 position of the phenyl ring) and shown in Eq. (10).

$$\begin{gathered}\text{Log (BA)} = 2.825\ (\pm0.669) + 0.241(\pm0.069)\ S_3 - 0.052\ (\pm0.016)\ R_4/R_4'B_5\\ + 0.152\ (\pm0.067)\ E_{\text{HOMO}} - 0.243\ (\pm0.092)\ I_1\\ n = 32\ R = 0.732\ \%EV = 53.66\ R^2_A = 0.468\ F_{(4,27)} = 7.815\ p<0.0003\ SEE = 0.122\\ PRESS = 0.540\ SSY = 0.868\ R^2_{cv} = 0.378\ S_{\text{PRESS}} = 0.141\ PSE = 0.130\end{gathered} \quad (10)$$

Eq. [10] explains up to 53.66 % of variances in the activity data. The model suggests that higher value of S_3 increases the antitumor activity of these glutamamide analogs as evidenced by the positive regression coefficient of S_3. The equation revealed that the width of substituents at R_4/R_4' position of glutamamide analogs plays an important role in the intermolecular interactions with the glutamine receptors. The negative coefficient of $R_4/R_4'B_5$ indicates that the lower value of $R_4/R_4'B_5$ may elevate the antitumor activity. The model also signifies that the presence of tert–butyl group at R_3 position of the phenyl ring will hamper the antitumor activity of these analogs as indicated by the negative coefficient I_1. The QSAR model from Eq. (11) was developed by stepwise deleting the compounds **36**, **18**, **15**, **17**, and **16**.

$$\begin{gathered}\text{Log (BA)} = 2.252\ (\pm0.495) + 0.339(\pm0.053)\ S_3 - 0.059\ (\pm0.012)\ R_4/R_4'B5\\ + 0.101\ (\pm0.049)\ E_{\text{HOMO}} - 0.319\ (\pm0.068)\ I_1\\ n = 27\ \textbf{DC} = \textbf{15}, \textbf{16}, \textbf{17}, \textbf{18}\ \text{and } \textbf{36}\ R = 0.881\ \%EV = 77.68\ R^2_A = 0.736\ F_{(4,22)} = 19.145\\ p<0.0000\ SEE = 0.088\ PRESS = 0.258\ SSY = 0.769\ R^2_{cv} = 0.664\ S_{\text{PRESS}} = 0.108\ PSE = 0.098\end{gathered} \quad (11)$$

The Eq. [11] explains up to 77.68 % of variances in the activity data. Correlation matrix for the biological activity and selected parameters is shown in Table 6. All these equations are significant at more than 95% confidence intervals as supported by the *t*–statistics and *p*–values and are shown in Table 7.

Table 7. *t*–Values and *p*– values of all QSAR models

Eqn No	Intercept/ Parameters	t–values	p–values	Eqn No	Intercept/ Parameters	t–values	p–values
[6]	Intercept	5.094	0.0000	[9]	Intercept	8.831	0.0000
	R_3	–2.533	0.0174		qC_{13}	5.040	0.0000
	R_{16}	3.026	0.0053		GAP	6.940	0.0000
	E_{HOMO}	3.144	0.0040		SA	–3.216	0.0040
	I_2	1.829	0.0784*		nHAcc	–6.751	0.0000
[7]	Intercept	8.991	0.0000	[10]	Intercept	4.224	0.0002
	R_3	–2.241	0.0355		S_3	3.484	0.0017
	R_{16}	6.492	0.0000		$R_4/R_4'B_5$	–3.208	0.0034
	E_{HOMO}	6.929	0.0000		E_{HOMO}	2.280	0.0307
	I_2	5.308	0.0000		I_1	–2.629	0.0140
						4.224	0.0002
[8]	Intercept	4.522	0.0001	[11]	Intercept	4.547	0.0002
	qC_{13}	2.254	0.0325		S_3	6.358	0.0000
	GAP	3.389	0.0022		$R_4/R_4'B_5$	–4.837	0.0001
	SA	–1.950	0.0617*		E_{HOMO}	2.061	0.0513
	nHAcc	–4.901	0.0000		I_1	–4.663	0.0001

Table 8. Observed (Obs.), calculated (Calc.), residual (Res.), LOO–predicted (LOO Pred.) and predicted residual (Pres) activities of final eqs [7], [9], and [11].

Cpd	Obs	Eq. (7)				Eq. (9)				Eq. (11)			
		Calc	Res	Pred	Pres	Calc	Res	Pred	Pres	Calc	Res	Pred	Pres
10	1.460	1.426	0.034	1.422	0.038	1.475	–0.015	1.476	–0.016	1.518	–0.058	1.522	–0.062
11	1.400	1.428	–0.027	1.432	–0.031	1.446	–0.046	1.453	–0.053	1.460	–0.060	1.468	–0.068
12	1.692	1.713	–0.021	1.724	–0.032	1.753	–0.061	1.776	–0.084	1.615	0.077	1.609	0.083
13	1.384	1.462	–0.078	1.470	–0.086	1.401	–0.017	1.404	–0.020	1.453	–0.069	1.462	–0.077
14	1.727	1.718	0.009	1.708	0.020	1.736	–0.008	1.739	–0.011	1.752	–0.025	1.763	–0.035
15	1.408	1.418	–0.010	1.418	–0.011	1.415	–0.008	1.417	–0.009	–	–	–	–
16	1.441	1.419	0.022	1.417	0.024	1.432	0.009	1.431	0.009	–	–	–	–
17	1.372	1.423	–0.051	1.427	–0.055	1.385	–0.012	1.386	–0.014	–	–	–	–
18	1.313	1.418	–0.105	1.426	–0.113	1.383	–0.071	1.392	–0.079	–	–	–	–
19	1.433	1.414	0.019	1.412	0.021	1.414	0.019	1.409	0.023	1.503	–0.070	1.514	–0.081
20	1.656	–	–	–	–	–	–	–	–	1.764	–0.107	1.812	–0.155
21	1.631	1.596	0.035	1.591	0.041	1.724	–0.090	1.741	–0.110	1.531	0.100	1.515	0.116
22	1.776	–	–	–	–	–	–	–	–	1.659	0.117	1.646	0.129
23	1.723	1.707	0.016	1.699	0.023	1.688	0.035	1.676	0.047	1.659	0.064	1.653	0.069
24	1.541	1.543	–0.002	1.546	–0.005	1.526	0.015	1.517	0.024	1.486	0.054	1.455	0.085
25	1.502	1.324	0.178	1.297	0.205	1.352	0.150	1.326	0.176	1.394	0.108	1.380	0.122
26	1.332	1.333	–0.001	1.333	–0.001	1.365	–0.033	1.371	–0.039	1.338	–0.006	1.339	–0.007
27	1.313	1.324	–0.011	1.326	–0.012	1.318	–0.005	1.319	–0.006	1.315	–0.002	1.315	–0.002
28	1.311	1.323	–0.012	1.324	–0.013	1.284	0.027	1.275	0.036	1.257	0.054	1.245	0.066
29	1.448	–	–	–	–	–	–	–	–	1.524	–0.076	1.577	–0.130
30	1.369	1.442	–0.073	1.456	–0.087	1.453	–0.084	1.471	–0.102	1.270	0.099	1.246	0.123
31	1.237	1.303	–0.066	1.313	–0.077	1.306	–0.069	1.321	–0.085	1.404	–0.168	1.431	–0.194
32	1.390	1.448	–0.058	1.458	–0.068	–	–	–	–	1.431	–0.041	1.436	–0.045
33	1.558	1.421	0.138	1.412	0.146	1.442	0.116	1.429	0.130	1.605	–0.046	1.609	–0.050
34	1.371	–	–	–	–	1.372	–0.001	1.373	–0.002	1.365	0.006	1.358	0.013
35	1.341	1.379	–0.039	1.382	–0.041	1.433	–0.093	1.446	–0.106	1.347	–0.006	1.353	–0.013
36	1.322	1.390	–0.068	1.394	–0.072	1.403	–0.081	1.411	–0.089	–	–	–	–
37	1.901	1.889	0.011	1.849	0.052	1.863	0.038	1.707	0.194	1.782	0.119	1.724	0.176
38	1.481	1.463	0.019	1.462	0.020	1.460	0.022	1.458	0.023	1.517	–0.036	1.523	–0.041
39	1.520	1.385	0.135	1.376	0.145	1.427	0.094	1.419	0.102	1.666	–0.146	1.685	–0.165
40	1.673	–	–	–	–	–	–	–	–	1.600	0.073	1.594	0.080
41	1.726	1.721	0.005	1.718	0.008	1.555	0.171	1.542	0.183	1.681	0.045	1.676	0.049

The predictive power of the final Eqs. (7), (9), and (11) was evaluated by the leave–one–out cross–validation (LOO) method. In this method, each compound was left out of the model and the prediction of activity of that compound was done. The observed (Obs), calculated (Calc), residual (Res), LOO– predicted (Pred) and predicted residual (Pres) values of the final Eqs. (7), (9), and (11) are shown in Table 8.

4 CONCLUSIONS

All synthesized glutamamides were evaluated for their possible anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell in Swiss Albino mice. The result was expressed in terms of percentage of tumor cell inhibition. The QSAR study performed on 32 synthesized glutamamides analogs showed that RTSA indices of atom numbers 3 and 16, ETSA index of atom number 3, atomic charge on atom number 13, the energy of HOMO, the energy difference between HOMO and LUMO and indicator parameters are important for antitumor activity. RTSA indices are related to atomic refractivity as well as to molecular connectivity and are the measure of dispersive/van der Waals force between two nonpolar molecules, thus atom 3 and 16 may be involved in dispersive/van der Waals interactions with glutamine receptor(s). The study also showed that ETSA index of atom number 3 is favorable for the antitumor activity. As ETSA indices are the measure of the availability of the π and/or lone pair electrons on the atoms it is evident that atom 3 may involved in electronic interaction with glutamine receptor(s). The atomic charge on atom number 13 is favorable for the antitumor activity. From the QSAR model, it is found that the energy of the highest occupied molecular orbital (E_{HOMO}) of these compounds has significant electronic contribution to the activity. As the energy of the HOMO is directly related to the ionization potential and characterizes the susceptibility of the molecule towards the attack by electrophiles, the QSAR equations reveal that these glutamamide analogs have higher susceptibility to lose a pair of electrons to an electrophile and these compounds are soft nucleophiles. It is also revealed that the HOMO–LUMO energy gap has a significant role in antitumor activity. The HOMO–LUMO energy gap, i.e. the difference in energy between the HOMO and the LUMO is an important stability index. As these glutamamide analogs have high HOMO–LUMO energy gap, these compounds are strong stable compounds for interactions and have lowest excitation energy. The study also revealed that the numbers of the acceptor atoms for hydrogen bonds (nHAcc) are of importance for the antitumor activity. The study also showed that the smaller molecular volume and the smaller width of substituents at at R_4/R_4' position is required for the activity. Presence of cyclohexyl group at R_4/R_4' position of glutamamide analogs is favorable for the antitumor activity while the presence of *tert*–butyl group at R_3 position of the phenyl ring is detrimental for the activity. The results of QSAR study which may help in further tailoring was shown in Figure 4. Our prediction is supported by the 3D isosurface electrostatic potential maps of compounds 37 and 34 obtained by AM1 calculations and shown in Figures 5 and 6 respectively.

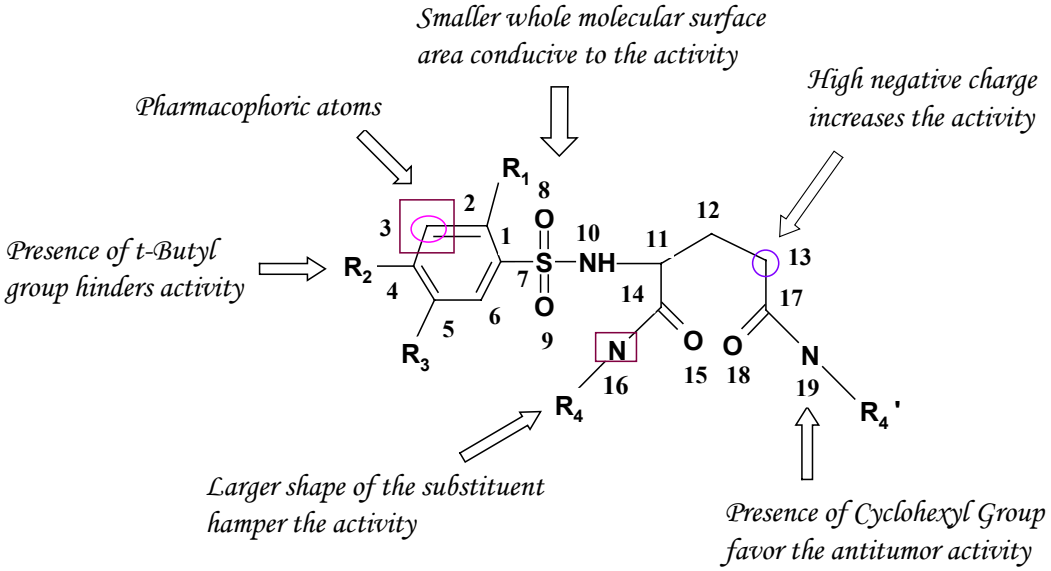

Figure 4. Requirements of glutamamide analogs for the antitumor activity: atoms bounded by brown rectangle are important for dispersive interaction with the receptor(s) and atom bounded by magenta circle is important for electronic interaction with the receptor(s)

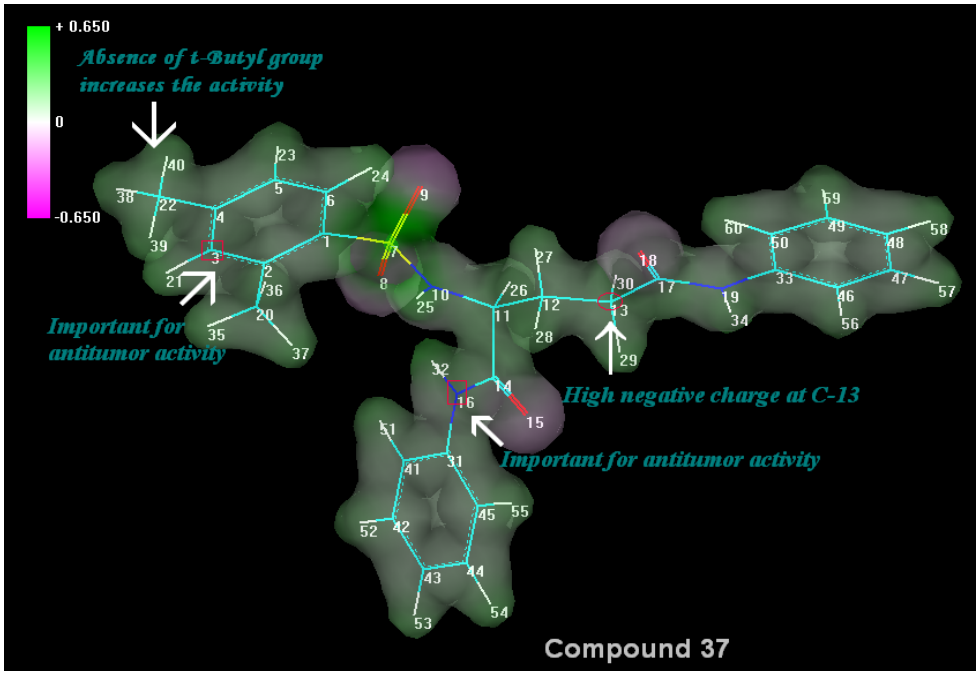

Figure 5. 3D Iso–surface electrostatic potential map of compound **37**.

From the comparison between these two Figures (Figures 5 and 6), it was found that the compound 37 has high negative charge at atom number 13 and the antitumor activity is higher whereas the compound 34 has low antitumor activity although it has high negative charge on the atom no. 13 and also contains cyclohexyl group at R_4/R_4' positions. It may be due to the presence of tert–butyl group at R_3 position of the phenyl ring and the effect of higher whole molecular surface area of this compound.

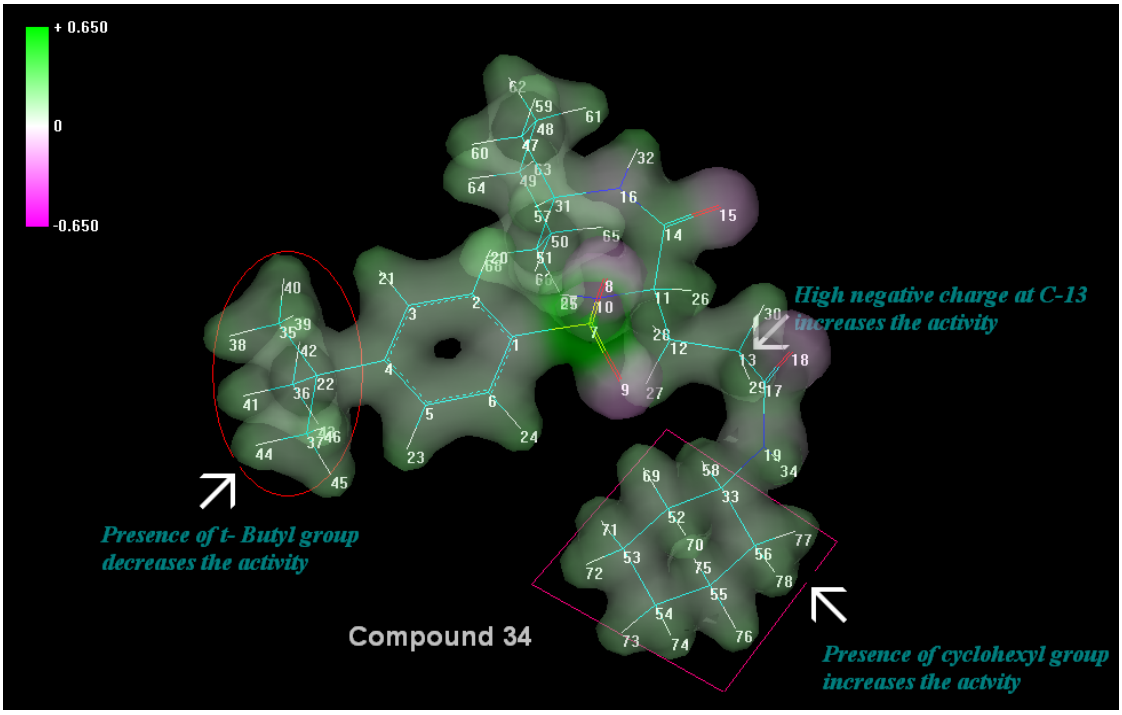

Figure 6. 3D Iso–surface electrostatic potential map of compound **34**.

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