QSAR Study on 5-*N*-Substituted-2-(Substituted Benzenesulphonyl) Glutamines as Antitumor Agents through Synthesis and Biological Evaluation: Part III[#]

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Received xxx; Preprint published xxx; Accepted xxx ; Published xxx

Internet Electron. J. Mol. Des. **2003**, *1*, 000–000

Abstract

Motivation. The importance of the non-essential amino acid, glutamine, to the proliferation of human tumour cells was well established. It is one of the two major, if not the only, substrate of cancer. It helps in tumor cell growth by supplying its amide nitrogen atom in the biosynthesis of other amino acids, purine, and pyrimidine bases. Tumor is a "nitrogen trap" as well as "glutamine trap". Hence, the efforts were made to synthesize series of glutamine analogs, evaluate these biologically and QSAR study was performed to explore the substitutional requirements essential for improved anticancer activity.

Method. QSAR study was performed using Log of percentage tumor weight inhibition as dependent parameter and physicochemical parameter, ETSA indices and indicator variable as independent parameters through multiple linear regression analysis.

Results. Some of the compounds showed promising anticancer activity. This study resulted some QSAR models with 86.49, 83.61, 88.52, 88.41 and 88.00% of explained variances. All these models showed more than 80% predicted variance. QSAR study revealed that aliphatic substitution of the glutamine analogs might have played an important role in the hydrophobic/dispersive interaction with the possible glutamine receptor. This study also showed that field effect at R_1 position and resonance effect at R_2 position might increase anticancer activity. Some of the atoms of the general structure were identified as pharmacophore. At least one free hydrogen in amide moiety of glutamine analogs might be essential for the anticancer activity.

Conclusions. This study throws some light in the structural requirements essential for improved anticancer activity and will help to find out substituents for future synthesis of this type of analogs.

Keywords. Glutamine; anticancer agents; synthesis; screening; quantitative structure–activity relationships; physicochemical parameters; ETSA indices.

Abbreviations and notations

QSAR, quantitative structure-activity relationships ETSA, Electrotopological State Atom

1 INTRODUCTION

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 essential and nonessential amino acids [1]. It was observed that tumors assimilate not only the nitrogen from the diet, but also the nitrogen from host proteins, raising the concept of tumors as "nitrogen traps," actively competing with the host for nitrogen compounds [1]. As glutamine is the

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#Part II was published earlier in *Bioorg. Med. Chem.* **2004**, *12*, 1413-1423. This is mentioned in the article as ref. [17].

most abundant amino acid in the body and the main vehicle for circulation of ammonia in a nontoxic form [2], it is considered that tumors behave indeed as "glutamine traps" [3,4]. After glutamine gains access to the cytoplasm, it must be transported into mitochondria. Where it is acted upon by glutaminase, an enzyme requiring high phosphate concentrations to be fully active. The high concentrations of inorganic phosphate found in the mitochondria of tumor cells could explain the high activity of tumor glutaminase *in vivo* [1]. In fact, experimental evidence supports the correlation of glutaminase activity with the extent of malignant proliferation [2,3]. The importance of the non-essential amino acid, glutamine, to the proliferation of human tumor cells was well established [3,5,6]. It is one of the two major, if not the only, substrate of cancer. The other substrate is glucose, the only circulating sugar, which is essential for the growth of normal and neoplastic cells. The presence of a tumor produces great changes in host glutamine metabolism in such a way that host nitrogen metabolism is accommodated to the tumor-enhanced requirements of glutamine [7-10]. Glutamine is also essential for the culture of many cell types. All of the cells studied had a high activity of phosphate-dependent glutaminase and were found to utilize glutamine from the culture medium during long-term culture. The rate of cell proliferation, determined by [6-3H]-thymidine incorporation, was dependent on glutamine concentration [1,11]. Considering the importance of this amino acid in cancer it has prompted us to explore the glutamine analogs for their possible anticancer activity.

In continuation of our previously reported work [12-17] on synthesis, biological evaluation and quantitative structure-activity relationship (QSAR) studies on some derivatives and analogs of glutamine as possible anticancer agents, 32 new 5-*N*-substituted-2-(substituted benzenesulphonyl) glutamines, as shown in **Figure 1,** were synthesized. These compounds were biologically evaluated for anticancer activity. QSAR studies, using percentage inhibition of tumor weight considered as the biological activity parameter, were performed on all thirty-two glutamine analogs. The study was done to explore the substitutional requirements essential for the improved anticancer activity.

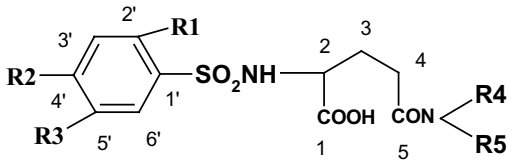


Figure 1. General structure of 5- *N*-substituted-2-(substituted benzenesulphonyl)-glutamines **5-36**

2 MATERIALS AND METHODS

2.1. Synthesis

Thirty-two 5-*N*-substituted-2-(substituted benzenesulphonyl) glutamines were synthesized. All the reagents used for the synthesis were of AR grade and commercially available from SD Fine Chemicals, Fluka, Sigma Aldrich, Rankem.

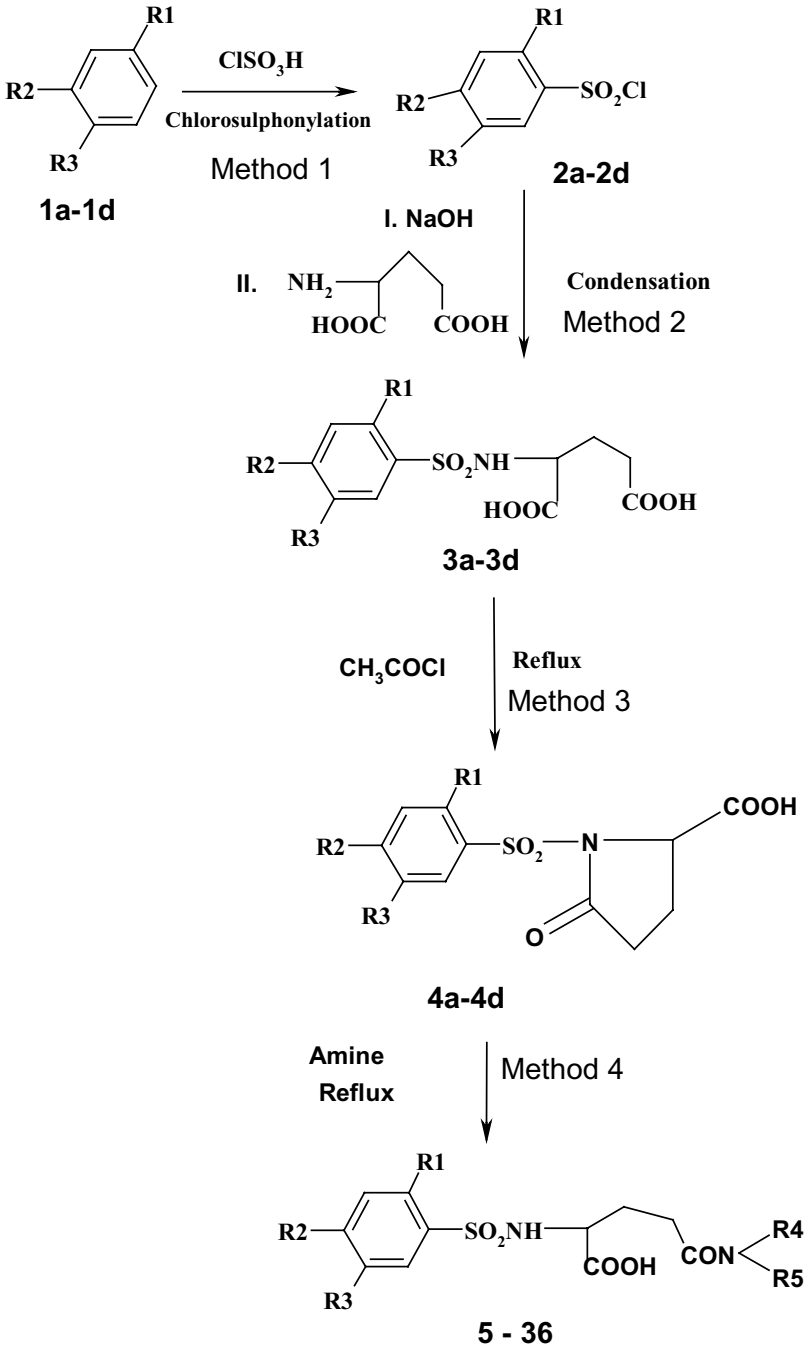
2.1.1. Chemistry

Synthesis of 5- *N*-substituted-2-(substituted benzenesulphonyl)-glutamine analogs were carried out according to **Scheme 1**. Synthesis was started with chlorosulphonylation [18] of substituted benzenes **1** to get corresponding sulphonyl chlorides **2**. This sulphonyl halide **2** proved to be a versatile synthon [13-15, 17] in the subsequent step in the preparation of substituted benzenesulphonyl glutamic acids **3**. With the application of Schotton-Bauman reaction [19], 2-(substituted benzenesulphonyl) glutamic acids **3** were prepared by one-step condensation of with L-glutamic acid. In this reaction alkaline medium was maintained to remove the hydrochloric acid, which was formed during condensation. Reaction of the resulting intermediates **3** with acetyl chloride afforded cyclized acid intermediates 1-(substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acids **4**. Aminolysis [20] of the cyclized acid **4** with various amines afforded the corresponding glutamines **5-36**.

2.1.2. General synthetic procedure

*2.1.2.1. Method 1. Substituted benzenesulphonyl chloride (**2a-2d**)*: To a mixture of substituted benzene (**1a-1d**: 0.1 mole) in chloroform (50 ml) in a 500 ml flask equipped with a dropping funnel, a thermometer and reflux condenser, chlorosulphonic acid (0.25 mole) was added dropwise over a period of 45 min to 60 min. The reaction mixture was mechanically stirred 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. In case of 2, 5-dichloro benzenesulphonyl chloride (**2b**), the temperature was maintained at 90-100^{0}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 on to 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 had been taken for the next step.

Scheme 1


R1
R2
R3
ClSO3H
Chlorosulphonylation
Method 1
SO2Cl
1a-1d
2a-2d
I. NaOH
II. NH2
HOOC
COOH
Condensation
Method 2
SO2NH
3a-3d
CH3COCl
Reflux
Method 3
SO2
N
O
4a-4d
Amine
Reflux
Method 4
CON
R4
R5
5 - 36

*2.1.2.2. Method 2. 2-(Substituted benzenesulphonyl) glutamic acid (**3a-3d**)*: L-glutamic acid (0.1 mole) was taken in a 250-ml conical flask and sodium hydroxide solution (2N) was added slowly till glutamic acid dissolved and the mixture become distinctly alkaline to phenolphthalein. The reaction mixture was stirred on a mechanical stirrer and the temperature was maintained at 70°C using hot water-bath. Substituted benzenesulphonyl chloride (0.11 moles) was added in small portions with constant stirring and sodium hydroxide (2N) was added time-to-time to keep the reaction mixture alkaline. The reaction was continued until a clear homogeneous solution resulted and thin layer chromatography showed the reaction was 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 desired diacid (3a-3d).

*2.1.2.3. Method 3. 1-(Substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid (**4a-4d**)*: 2-(Substituted benzenesulphonyl) glutamic acid (**3a-3d**: 0.01 mole) was taken in 100 ml round bottomed flask, fitted with reflux condenser and calcium chloride guard tube. Acetyl chloride (0.025 mole) was added to it and refluxed for 2 hr on boiling water bath. The completion of the reaction was tested by thin layer chromatography. After the reaction was completed, the reaction mixture was cooled to room temperature and poured onto crushed ice with continuous stirring. The precipitated product was filtered and recrystallized from water with charcoal treatment.

*2.1.2.4. Method 4. 5-N-Substituted 2-(substituted benzenesulphonyl) glutamines (**5-36**)*: In a 50 ml of loosely stoppered conical flask, 1-(substituted benzene sulphonyl)-5-oxopyrrolidine-2-carboxylic acid (**4a-4d**: 0.01 mole) was suspended in 20 ml of water. To this, excess of amines (0.025 mole) were added and allowed to stand overnight. The reaction mixture was concentrated over steam bath to remove excess of amines. It was cooled to room temperature and chilled in an ice bath. The mixture was acidified with 6N hydrochloric acid. The precipitate was filtered and the residue was washed with cold water and finally recrystallized from dilute ethanol with charcoal treatment.

2.1.3. Characterization

Melting points of all the compounds were measured on a capillary melting point apparatus and were uncorrected. All the compounds were characterized qualitatively and quantitatively by performing both analytical and spectrophotometric analysis. The infrared spectra were recorded on BUCK M500 quick scanning Infrared spectrophotometer using KBr pellets. Running the spectrum of 0.05mm polystyrene film did the finer calibration of the machine. The frequencies were expressed in cm^{-1}. Proton Nuclear Magnetic Resonance (^1H NMR) spectra were collected at 25°C in the pulsed Fourier Transformation mode on Bruker DRX 300 MHz spectrophotometers using the solvents described and was consistent with the proposed structures. Chemical shifts are reported in δ ppm (parts per million) relative to Tetramethyl Silane for deuteriorated dimethylsulfoxide (DMSO-d_6). Signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplet). The mass spectra (FAB) were recorded on JEOL-JMS-SX-PNBA (p- nitrobenzyl alcohol) was used as matrix (M^+) which showed M+1 peak at 154, 2M+1 peak at 307. Elemental or microanalysis (C, H, N) of the compounds was performed on 2400 series II CHN analyzer of Perkin-Elmer. Reactions were monitor by 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 intermediate compounds and final compounds are summarized in **Table 1** and **2** respectively. Mass-, IR-, and Proton NMR spectroscopic as well as C,H,N analysis data of the final compounds are shown in **Table 3**.

Table 1. Physical data of intermediate compounds

Cpd[a]	R_1	R_2	R_3	M.P.(^{0}C)	%Yield	Molecular Formula	MW
2a	H	Br	H	73-75	77.90	$C_6H_4O_2SCl\,Br$	255.52
2b	Cl	H	Cl	35-37	80.00	$C_6H_3O_2SCl_3$	245.51
2c	CH_3	CH_3	H	29-31	70.52	$C_8H_9O_2SCl$	204.68
2d	H	*t*-C_4H_9	H	56-58	68.64	$C_{10}H_{13}O_2SCl$	232.73
3a	H	Br	H	148-150	80.84	$C_{11}H_{12}NO_6SBr$	366.19
3b	Cl	H	Cl	188-190	68.56	$C_{11}H_{11}NO_6SCl_2$	356.18
3c	CH_3	CH_3	H	153-155	72.52	$C_{13}H_{17}NO_6S$	315.34
3d	H	*t*-C_4H_9	H	160-164	57.25	$C_{15}H_{21}NO_6S$	343.40
4a	H	Br	H	95-97	64.00	$C_{11}H_{10}NO_5SBr$	348.18
4b	Cl	H	Cl	184-186	74.00	$C_{11}H_9NO_5SCl_2$	338.16
4c	CH_3	CH_3	H	180-182	48.65	$C_{13}H_{15}NO_5S$	297.33
4d	H	*t*-C_4H_9	H	139-141	62.24	$C_{15}H_{19}NO_5S$	325.38

[a]Compound number

Table 2. Physical data of 5- *N*-substituted-2-(substituted benzenesulphonyl)-glutamines **5-36**

Cpd	R_1	R_2	R_3	R_4	R_5	M.P.(^{0}C)	%Yield	Molecular formula	M.W.
5	H	Br	H	*i*-C_3H_7	H	193-195	64.32	$C_{14}H_{19}N_2O_5SBr$	407.28
6	H	Br	H	*c*-C_6H_{11}	H	227-229	56.87	$C_{17}H_{23}N_2O_5SBr$	447.35
7	H	Br	H	$C_6H_5CH_2$	H	198-200	77.42	$C_{18}H_{19}N_2O_5SBr$	455.32
8	H	Br	H	CH_3	CH_3	135-137	58.24	$C_{13}H_{17}N_2O_5SBr$	393.26
9	Cl	H	Cl	CH_3	H	162-164	84.36	$C_{12}H_{14}N_2O_5SCl_2$	369.22
10	Cl	H	Cl	*n*-C_3H_7	H	152-154	68.54	$C_{14}H_{18}N_2O_5SCl_2$	397.28
11	Cl	H	Cl	*i*-C_3H_7	H	195-197	52.14	$C_{14}H_{18}N_2O_5SCl_2$	397.28
12	Cl	H	Cl	*n*-C_4H_9	H	119-121	84.78	$C_{15}H_{20}N_2O_5SCl_2$	411.30
13	Cl	H	Cl	*i*-C_4H_9	H	156-158	56.34	$C_{15}H_{20}N_2O_5SCl_2$	411.30
14	Cl	H	Cl	*n*-C_6H_{13}	H	140-142	74.52	$C_{17}H_{24}N_2O_5SCl_2$	439.35
15	Cl	H	Cl	*c*-C_6H_{11}	H	164-166	67.35	$C_{17}H_{22}N_2O_5SCl_2$	437.34
16	Cl	H	Cl	C_6H_5	H	148-150	65.32	$C_{17}H_{16}N_2O_5SCl_2$	431.29
17	Cl	H	Cl	$C_6H_5CH_2$	H	151-153	58.32	$C_{18}H_{18}N_2O_5SCl_2$	445.32
18	Cl	H	Cl	CH_3	CH_3	118-120	48.32	$C_{13}H_{16}N_2O_5SCl_2$	383.25
19	Cl	H	Cl	*i*-C_3H_7	*i*-C_3H_7	68-70	44.64	$C_{17}H_{24}N_2O_5SCl_2$	439.35
20	CH_3	CH_3	H	H	H	142-144	78.84	$C_{13}H_{18}N_2O_5S$	314.36
21	CH_3	CH_3	H	*n*-C_4H_9	H	120-122	84.56	$C_{17}H_{26}N_2O_5S$	370.47
22	CH_3	CH_3	H	C_2H_5	C_2H_5	153-155	53.32	$C_{17}H_{26}N_2O_5S$	370.47
23	H	*t*-C_4H_9	H	H	H	132-134	68.38	$C_{15}H_{22}N_2O_5S$	342.41
24	H	*t*-C_4H_9	H	CH_3	H	155-157	56.64	$C_{16}H_{24}N_2O_5S$	356.44
25	H	*t*-C_4H_9	H	C_2H_5	H	107-109	58.36	$C_{17}H_{26}N_2O_5S$	370.47
26	H	*t*-C_4H_9	H	*n*-C_3H_7	H	134-136	75.54	$C_{18}H_{28}N_2O_5S$	384.49
27	H	*t*-C_4H_9	H	*i*-C_3H_7	H	134-136	72.25	$C_{18}H_{28}N_2O_5S$	384.49
28	H	*t*-C_4H_9	H	*n*-C_4H_9	H	151-153	89.94	$C_{19}H_{30}N_2O_5S$	398.52
29	H	*t*-C_4H_9	H	*i*-C_4H_9	H	143-145	76.64	$C_{19}H_{30}N_2O_5S$	398.52
30	H	*t*-C_4H_9	H	*n*-C_6H_{13}	H	143-145	84.32	$C_{21}H_{34}N_2O_5S$	426.57
31	H	*t*-C_4H_9	H	*c*-C_6H_{11}	H	170-172	88.34	$C_{21}H_{32}N_2O_5S$	424.56
32	H	*t*-C_4H_9	H	C_6H_5	H	184-186	74.45	$C_{21}H_{26}N_2O_5S$	418.51
33	H	*t*-C_4H_9	H	$C_6H_5CH_2$	H	108-110	90.92	$C_{22}H_{28}N_2O_5S$	432.53
34	H	*t*-C_4H_9	H	CH_3	CH_3	103-105	52.24	$C_{17}H_{26}N_2O_5S$	370.47
35	H	*t*-C_4H_9	H	C_2H_5	C_2H_5	82-84	48.95	$C_{19}H_{30}N_2O_5S$	398.52
36	H	*t*-C_4H_9	H	*i*-C_3H_7	*i*-C_3H_7	130-132	52.36	$C_{21}H_{34}N_2O_5S$	426.57

Table 3. Mass-, IR- and Proton NMR spectroscopic as well as CHN analysis data of the final compounds (**5-36**)

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO-d_6)	C,H,N: %calcd/found		
				C	H	N
5	M + H^+ peak at m/z 408	3318, 3114 (N-H str of CONH), 3022 (Ar-C-H str), 2872 (ali C-H str), 1706 (C=O str), 1562, 1442 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 973, 790 & 744 (Ar-C-H def)	12.66 (s, 1H, COOH), 8.46 (d, 1H, SO_2NH), 8.28-7.98 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.74 (m, 1H, CONH), 3.68 (m, 1H, H-2), 2.92 (m, 1H, N-CH-1″), 2.00 (m, 2H, H_2-4), 1.86 (m, 1H, H_A-3), 1.68 (m, 1H, H_B-3), 1.12-0.96 (m, 6H, CH_3-2″, CH_3-3″)	41.29 41.20	4.70 4.68	6.88 6.71
6	M + H^+ peak at m/z 448	3314, 3104 (N-H str of CONH), 3028 (Ar-C-H str), 2874 (ali C-H str), 1705 (C=O str), 1564, 1445 (ali C-H def), 1336 & 1162 (S=O str of SO_2NH), 967, 794 & 748 (Ar-C-H def)	12.74 (s, 1H, COOH), 8.40 (d, 1H, SO_2NH), 8.12-7.88 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.58 (m, 1H, CONH), 3.72 (m, 1H, H-2), 2.10 (m, 2H, H_2-4), 1.82 (m, 1H, H_A-3), 1.62 (m, 1H, H_B-3), 1.42-1.12 (m, 11H, cyclohexyl protons)	45.64 45.60	5.18 5.08	6.26 6.18
7	M + H^+ peak at m/z 456	3322, 3112 (N-H str of CONH), 3032 (Ar-C-H str), 2868 (ali C-H str), 1694 (C=O str), 1560, 1444 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 975, 798 & 756 (Ar-C-H def)	12.72 (s, 1H, COOH), 8.48 (d, 1H, SO_2NH), 8.20-7.94 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.78 (m, 1H, CONH), 7.64-7.48 (5H, Phenyl protons), 4.24 (m, 2H, CH_2-Ph), 3.78 (m, 1H, H-2), 2.10 (m, 2H, H_2-4), 1.86 (m, 1H, H_A-3), 1.70 (m, 1H, H_B-3)	47.48 47.52	4.21 4.26	6.15 6.12
8	M + H^+ peak at m/z 394	3028 (Ar-C-H str), 2836 (ali C-H str), 1706 (C=O str), 1565, 1448 (ali C-H def), 1326 & 1160 (S=O str of SO_2NH), 978, 796 & 750 (Ar-C-H def)	12.64 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.22-7.96 (m, 4H, H-2′, H-3′, H-5′, H-6′), 3.74 (m, 1H, H-2), 3.18-3.00 (m, 6H, CH_3-1″, CH_3-2″), 2.08 (m, 2H, H_2-4), 1.88 (m, 1H, H_A-3), 1.62 (m, 1H, H_B-3)	39.70 39.58	4.36 4.32	7.12 7.06
9	M + H^+ peak at m/z 370	3310, 3108 (N-H str of CONH), 3032 (Ar-C-H str), 2882 (ali C-H str), 1695 (C=O str), 1562, 1442 (ali C-H def), 1336 & 1164 (S=O str of SO_2NH), 974, 796 & 752 (Ar-C-H def)	12.68 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.26-8.16 (m, 2H, H-3′, H-6′), 7.85 (m, 1H, H-4′), 7.78 (m, 1H, CONH), 3.74m, 1H, H-2), 3.02 (m, 3H, CH_3-1″), 2.02 (m, 2H, H_2-4), 1.84 (m, 1H, H_A-3), 1.65 (m, 1H, H_B-3)	39.04 38.96	3.82 3.76	7.59 7.52
10	M + H^+ peak at m/z 398	3320, 3118 (N-H str of CONH), 3024 (Ar-C-H str), 2882 (ali C-H str), 1700 (C=O str), 1552, 1440 (ali C-H def), 1338 & 1164 (S=O str of SO_2NH), 975, 798 & 752 (Ar-C-H def)	12.72 (s, 1H, COOH), 8.40 (d, 1H, SO_2NH), 8.12-8.04 (m, 2H, H-3′, H-6′), 7.74 (m, 1H, H-4′), 7.60 (m, 1H, CONH), 3.76 (m, 1H, H-2), 3.00 (m, 2H, N-CH_2-1″), 2.18 (m, 2H, H_2-4), 1.88 (m, 1H, H_A-3), 1.68 (m, 1H, H_B-3), 1.32 (m, 2H, CH_2-2″), 0.90 (m, 3H, CH_3-3″)	42.33 42.18	4.57 4.52	7.05 6.98
11	M + H^+ peak at m/z 398	3312, 3100 (N-H str of CONH), 3022 (Ar-C-H str), 2876 (ali C-H str), 1695 (C=O str), 1562, 1436 (ali C-H def), 1334 & 1162 (S=O str of SO_2NH), 976, 790 & 746 (Ar-C-H def)	12.70 (s, 1H, COOH), 8.44 (d, 1H, SO_2NH), 8.16-8.04 (m, 2H, H-3′, H-6′), 7.80 (m, 1H, H-4′), 7.68 (m, 1H, CONH), 3.74 (m, 1H, H-2), 3.04 (m, 1H, N-CH-1″), 2.04 (m, 2H, H_2-4), 1.82 (m, 1H, H_A-3), 1.64 (m, 1H, H_B-3), 0.95-0.88 (m, 6H, CH_3-2″, CH_3-3″)	42.33 42.22	4.57 4.48	7.05 6.96
12	M + H^+ peak at m/z 412	3320, 3100 (N-H str of CONH), 3016 (Ar-C-H str), 2880 (ali C-H str), 1700 (C=O str), 1556, 1440 (ali C-H def), 1332 & 1164 (S=O str of SO_2NH), 975, 793 & 750 (Ar-C-H def)	12.66 (s, 1H, COOH), 8.40 (d, 1H, SO_2NH), 8.16-8.06 (m, 2H, H-3′, H-6′), 7.78 (m, 1H, H-4′), 7.64(m, 1H, CONH), 3.70 (m, 1H, H-2), 3.04 (m, 2H, N-CH_2-1″), 2.18 (m, 2H, H_2-4), 1.92 (m, 1H, H_A-3), 1.72 (m, 1H, H_B-3), 1.42-1.24 (m, 4H, CH_2-2″, CH_2-3″), 0.98 (m, 3H, CH_3-4″)	43.80 43.70	4.90 4.84	6.81 6.75
13	M + H^+ peak at m/z 412	3314, 3112 (N-H str of CONH), 3020 (Ar-C-H str), 2872 (ali C-H str), 1705 (C=O str), 1558, 1438 (ali C-H def), 1334 & 1162 (S=O str of SO_2NH), 975, 798 & 752 (Ar-C-H def)	12.66 (s, 1H, COOH), 8.48 (d, 1H, SO_2NH), 8.22-8.12 (m, 2H, H-3′, H-6′), 7.84 (m, 1H, H-4′), 7.70 (m, 1H, CONH), 3.84 (m, 1H, H-2), 3.06 (m, 2H, N-CH_2-1″), 2.12 (m, 2H, H_2-4), 1.86 (m, 1H, H_A-3), 1.72 (m, 1H, H_B-3), 1.42 (m, 1H, CH-2″), 1.15-0.98 (m, 6H, CH_3-3″, CH_3-4″)	43.80 43.65	4.90 4.80	6.81 6.78

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO-d_6)	C,H,N: %calcd/found		
				C	H	N
14	M + H^+ peak at m/z 440	3318, 3105 (N-H str of CONH), 3012 (Ar-C-H str), 2876 (ali C-H str), 1705 (C=O str), 1556, 1444 (ali C-H def), 1334 & 1162 (S=O str of SO_2NH), 970, 790 & 748 (Ar-C-H def)	12.62 (s, 1H, COOH), 8.46 (d, 1H, SO_2NH), 8.12-8.02 (m, 2H, H-3′, H-6′), 7.72 (m, 1H, H-4′), 7.60 (m, 1H, CONH), 3.68 (m, 1H, H-2), 3.00 (m, 2H, N-CH_2-1″), 2.12 (m, 2H, H_2-4), 1.90 (m, 1H, H_A-3), 1.68 (m, 1H, H_B-3), 1.40-1.16 (m, 8H, CH_2-2″, CH_2-3″, CH_2-4″, CH_2-5″), 0.90 (m, 3H, CH_3-6″)	46.47 46.32	5.51 5.43	6.38 6.29
15	M + H^+ peak at m/z 438	3308, 3102 (N-H str of CONH), 3028 (Ar-C-H str), 2878 (ali C-H str), 1698 (C=O str), 1560, 1440 (ali C-H def), 1336 & 1162 (S=O str of SO_2NH), 972, 794 & 750 (Ar-C-H def)	12.62 (s, 1H, COOH), 8.48 (d, 1H, SO_2NH), 8.22-8.12 (m, 2H, H-3′, H-6′), 7.82 (m, 1H, H-4′), 7.68 (m, 1H, CONH), 3.74m, 1H, H-2), 2.12 (m, 2H, H_2-4), 1.80 (m, 1H, H_A-3), 1.62 (m, 1H, H_B-3) 1.38-1.10 (m, 11H, cyclohexyl protons)	46.69 46.58	5.07 5.02	6.41 6.54
16	M + H^+ peak at m/z 432	3322, 3116 (N-H str of CONH), 3020 (Ar-C-H str), 2878 (ali C-H str), 1702 (C=O str), 1548, 1442 (ali C-H def), 1336 & 1160 (S=O str of SO_2NH), 972, 796 & 748 (Ar-C-H def)	12.62 (s, 1H, COOH), 8.38 (d, 1H, SO_2NH), 8.10-8.02 (m, 2H, H-3′, H-6′), 7.84 (m, 5H, ph.-protons), 7.70 (m, 1H, H-4′), 7.58 (m, 1H, CONH), 3.74 (m, 1H, H-2), 2.12 (m, 2H, H_2-4), 1.86 (m, 1H, H_A-3), 1.72 (m, 1H, H_B-3)	47.34 47.13	3.74 3.68	6.50 6.56
17	M + H^+ peak at m/z 446	3316, 3106 (N-H str of CONH), 3012 (Ar-C-H str), 2876 (ali C-H str), 1700 (C=O str), 1556, 1440 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 977, 798 & 748 (Ar-C-H def)	12.66 (s, 1H, COOH), 8.46 (d, 1H, SO_2NH), 8.20-8.08 (m, 2H, H-3′, H-6′), 7.88-7.76 (m, 6H, H-4′, ph.-protons), 7.72 (m, 1H, CONH), 4.22 (m, 2H, CH_2-ph), 3.76 (m, 1H, H-2), 2.70 (s, 3H, Ar-CH_3), 2.10 (m, 2H, H_2-4), 1.92 (m, 1H, H_A-3), 1.66 (m, 1H, H_B-3)	48.55 48.69	4.07 4.17	6.29 6.32
18	M + H^+ peak at m/z 484	3028 (Ar-C-H str), 2836 (ali C-H str), 1706 (C=O str), 1565, 1448 (ali C-H def), 1326 & 1160 (S=O str of SO_2NH), 978, 796 & 754 (Ar-C-H def)	12.64 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.22-7.96 (m, 3H, H-3′, H-4′, H-6′), 3.74 (m, 1H, H-2), 3.18-3.00 (m, 6H, CH_3-1″, CH_3-2″), 2.08 (m, 2H, H_2-4), 1.88 (m, 1H, H_A-3), 1.62 (m, 1H, H_B-3)	40.74 40.58	4.25 4.21	7.31 7.42
19	M + H^+ peak at m/z 440	3024 (Ar-C-H str), 2830 (ali C-H str), 1700 (C=O str), 1562, 1440 (ali C-H def), 1328 & 1164 (S=O str of SO_2NH), 976, 794 & 748 (Ar-C-H def)	12.70 (s, 1H, COOH), 8.56 (d, 1H, SO_2NH), 8.26-7.16 (m, 3H, H-3′, H-4′, H-6′), 3.68 (m, 1H, H-2), 3.16 (m, 2H, N-CH-1″, N-CH-2″), 2.18 (m, 2H, H_2-4), 1.96 (m, 1H, H_A-3), 1.72 (m, 1H, H_B-3), 1.54-1.32 (m, 12H, CH_3-3″, CH_3-4″, CH_3-5″, CH_3-6″)	46.47 46.45	5.51 5.48	6.38 6.32
20	M + H^+ peak at m/z 315	3320, 3106 (N-H str of CONH), 3022 (Ar-C-H str), 2878 (ali C-H str), 1702 (C=O str), 1552, 1440 (ali C-H def), 1336 & 1164 (S=O str of SO_2NH), 972, 794 & 750 (Ar-C-H def)	12.70 (s, 1H, COOH), 8.46 (d, 1H, SO_2NH), 8.20-8.12 (m, 3H, H-3′, H-5′, H-6′), 7.70 (m, 2H, $CONH_2$), 3.76 (m, 1H, H-2), 2.70-2.62 (m, 6H, Ar-CH_3-2′, Ar-CH_3-4′), 2.12 (m, 2H, H_2-4), 1.88 (m, 1H, H_A-3), 1.72 (m, 1H, H_B-3)	49.56 49.67	5.77 5.72	8.91 8.83
21	M + H^+ peak at m/z 371	3322, 3110 (N-H str of CONH), 3018 (Ar-C-H str), 2874 (ali C-H str), 1705 (C=O str), 1552, 1444 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 974, 796 & 752 (Ar-C-H def)	12.66 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.22-8.16 (m, 3H, H-3′, H-5′, H-6′), 7.64 (m, 1H, CONH), 3.72 (m, 1H, H-2), 2.70-2.60 (m, 6H, Ar-CH_3-2′, Ar-CH_3-4′), 2.14 (m, 2H, H_2-4), 1.86 (m, 1H, H_A-3), 1.70 (m, 1H, H_B-3)	55.12 55.02	7.07 6.98	7.56 7.62
22	M + H^+ peak at m/z 371	3016 (Ar-C-H str), 2872 (ali C-H str), 1700 (C=O str), 1554, 1446 (ali C-H def), 1330 & 1162 (S=O str of SO_2NH), 976, 798 & 750 (Ar-C-H def)	12.72 (s, 1H, COOH), 8.48 (d, 1H, SO_2NH), 8.18-8.10 (m, 3H, H-3′, H-5′, H-6′), 3.70 (m, 1H, H-2), 3.16-3.04 (m, 4H, N-CH_2-1″, N-CH_2-2″), 2.68-2.56 (m, 6H, Ar-CH_3-2′, Ar-CH_3-4′), 2.12 (m, 2H, H_2-4), 1.80 (m, 1H, H_A-3), 1.73 (m, 1H, H_B-3), 1.60-1.46 (m, 6H, CH_3-3″, CH_3-4″)	55.12 54.98	7.07 7.02	7.56 7.48
23	M + H^+ peak at m/z 343	3322, 3118 (N-H str of CONH), 3026 (Ar-C-H str), 2868 (ali C-H str), 1705 (C=O str), 1564, 1444 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 975, 794 & 750 (Ar-C-H def)	12.64 (s, 1H, COOH), 8.46 (d, 1H, SO_2NH), 8.28-7.98 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.68 (m, 2H, $CONH_2$), 3.66 (m, 1H, H-2), 2.16 (m, 2H, H_2-4), 2.08-1.92 (m, 9H, three CH_3 of *t*-Butyl), 1.82 (m, 1H, H_A-3), 1.70 (m, 1H, H_B-3)	52.62 52.57	6.48 6.37	8.18 8.10

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO-d_6)	C,H,N: %calcd/found		
				C	H	N
24	M + H^+ peak at m/z 357	3316, 3112 (N-H str of CONH), 3022 (Ar-C-H str), 2856 (ali C-H str), 1695 (C=O str), 1558, 1440 (ali C-H def), 1330 & 1163 (S=O str of SO_2NH), 973, 797 & 754 (Ar-C-H def)	12.68 (s, 1H, COOH), 8.50 (d, 1H, SO_2NH), 8.26-8.05 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.62 (m, 1H, CONH), 3.69 (m, 1H, H-2), 3.12 (m, 3H, CH_3-1″), 2.16 (m, 2H, H_2-4), 2.08-1.94 (m, 9H, three CH_3 of *t*-Butyl), 1.82 (m, 1H, H_A-3), 1.68 (m, 1H, H_B-3)	53.91 53.93	6.79 6.78	7.86 7.82
25	M + H^+ peak at m/z 371	3320, 3115 (N-H str of CONH), 3025 (Ar-C-H str), 2856 (ali C-H str), 1698(C=O str), 1560, 1445 (ali C-H def), 1335 & 1168 (S=O str of SO_2NH), 975, 801 & 757 (Ar-C-H def)	12.71 (s, 1H, COOH), 8.55 (d, 1H, SO_2NH), 8.24-8.10 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.67(m, 1H, CONH), 3.73 (m, 1H, H-2), 3.16 (m, 2H, N-CH_2-1″), 2.19 (m, 2H, H_2-4), 2.10-1.96 (m, 9H, three CH_3 of *t*-Butyl),1.85 (m, 1H, H_A-3), 1.72 (m, 1H, H_B-3), 1.64 (m, 3H, CH_3-2″)	55.12 55.20	7.07 7.16	7.56 7.68
26	M + H^+ peak at m/z 385	3327, 3119 (N-H str of CONH), 3029 (Ar-C-H str), 2858 (ali C-H str), 1700 (C=O str), 1566, 1449 (ali C-H def), 1339 & 1170 (S=O str of SO_2NH), 978, 796 & 758 (Ar-C-H def)	12.75 (s, 1H, COOH), 8.60 (d, 1H, SO_2NH), 8.27-8.15 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.70(m, 1H, CONH), 3.78 (m, 1H, H-2), 3.20 (m, 2H, N-CH_2-1″), 2.26 (m, 2H, H_2-4), 2.14-1.98 (m, 9H, three CH_3 of *t*-Butyl),1.89(m, 1H, H_A-3), 1.75 (m, 1H, H_B-3), 1.66 (m, 3H, CH_3-2″)	56.23 56.65	7.34 7.23	7.29 7.33
27	M + H^+ peak at m/z 385	3319, 3112 (N-H str of CONH), 3028 (Ar-C-H str), 2855 (ali C-H str), 1695(C=O str), 1562, 1448 (ali C-H def), 1340 & 1170(S=O str of SO_2NH), 975, 799 & 754 (Ar-C-H def)	12.68 (s, 1H, COOH), 8.58 (d, 1H, SO_2NH), 8.23-8.11 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.68(m, 1H, CONH), 3.75 (m, 1H, H-2), 3.18 (m, 1H, N-CH-1″), 2.20 (m, 2H, H_2-4), 2.10-1.96 (m, 9H, three CH_3 of *t*-Butyl), 1.88 (m, 1H, H_A-3), 1.77 (m, 1H, H_B-3), 1.63-1.50 (m, 6H, CH_3-2″, CH_3-3″)	56.23 56.27	7.34 7.38	7.29 7.12
28	M + H^+ peak at m/z 399	3324, 3109 (N-H str of CONH), 3029 (Ar-C-H str), 2853 (ali C-H str), 1692 (C=O str), 1564, 1451 (ali C-H def), 1343 & 1169 (S=O str of SO_2NH), 972, 802 & 749 (Ar-C-H def)	12.65 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.20-8.13 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.72 (m, 1H, CONH), 3.77(m, 1H, H-2), 3.15 (m, 2H, N-CH_2-1″), 2.32 (m, 2H, H_2-4), 2.16-2.02 (m, 9H, three CH_3 of *t*-Butyl), 1.92 (m, 1H, H_A-3), 1.82 (m, 1H, H_B-3), 1.72-1.52 (m, 7H, CH_2-2″, CH_2-3″, CH_3-4″)	57.26 57.12	7.59 7.53	7.03 6.95
29	M + H^+ peak at m/z 399	3324, 3112 (N-H str of CONH), 3025 (Ar-C-H str), 2850 (ali C-H str), 1698 (C=O str), 1568, 1448 (ali C-H def), 1340 & 1164 (S=O str of SO_2NH), 971, 798 & 752 (Ar-C-H def)	12.72 (s, 1H, COOH), 8.56 (d, 1H, SO_2NH), 8.18-8.09 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.78 (m, 1H, CONH), 3.80 (m, 1H, H-2), 3.17 (m, 2H, N-CH_2-1″), 2.35 (m, 2H, H_2-4), 2.16-1.98 (m, 9H, three CH_3 of *t*-Butyl), 1.89 (m, 1H, H_A-3), 1.78 (m, 1H, H_B-3), 1.68-1.52 (m, 7H, CH-2″, CH_3-3″, CH_3-4″)	57.26 57.06	7.59 7.50	7.03 6.98
30	M + H^+ peak at m/z 427	3320, 3114 (N-H str of CONH), 3022 (Ar-C-H str), 2856 (ali C-H str), 1705 (C=O str), 1556, 1442 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 973, 794 & 748 (Ar-C-H def)	12.66 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.14-8.06 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.81 (m, 1H, CONH), 3.78 (m, 1H, H-2), 3.12 (m, 2H, N-CH_2-1″), 2.38 (m, 2H, H_2-4), 2.18-2.06 (m, 9H, three CH_3 of *t*-Butyl), 1.92 (m, 1H, H_A-3), 1.82 (m, 1H, H_B-3), 1.74-1.48 (m, 11H, CH_2-2″, CH_2-3″, CH_2-4″, CH_2-5″, CH_3-6″)	59.13 58.96	8.03 7.92	6.57 6.48
31	M + H^+ peak at m/z 425	3321, 3115 (N-H str of CONH), 3027 (Ar-C-H str), 2855 (ali C-H str), 1701 (C=O str), 1558, 1440 (ali C-H def), 1336 & 1164 (S=O str of SO_2NH), 976, 797 & 752 (Ar-C-H def)	12.72 (s, 1H, COOH), 8.56 (d, 1H, SO_2NH), 8.18-8.06 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.85 (m, 1H, CONH), 3.82 (m, 1H, H-2), 2.44 (m, 2H, H_2-4), 2.22-2.12 (m, 9H, three CH_3 of *t*-Butyl), 1.96 (m, 1H, H_A-3), 1.86 (m, 1H, H_B-3), 1.52-1.26 (m, 11H, cyclohexyl protons)	59.41 59.28	7.60 7.54	6.60 6.62

Cpd	Mass (FAB)	IR (KBr, cm^{-1})	^{1}HNMR (300 MHz, DMSO-d_6)	C,H,N: %calcd/found		
				C	H	N
32	M + H^+ peak at m/z 419	3319, 3114 (N-H str of CONH), 3023 (Ar-C-H str), 2857 (ali C-H str), 1699 (C=O str), 1559, 1445 (ali C-H def), 1337 & 1165 (S=O str of SO_2NH), 977, 798 & 753 (Ar-C-H def)	12.64 (s, 1H, COOH), 8.46 (d, 1H, SO_2NH), 8.12-8.02 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.88 (m, 1H, CONH), 7.72 (m, 5H, ph.-protons), 3.86 (m, 1H, H-2), 2.44 (m, 2H, H_2-4), 2.22-2.08 (m, 9H, three CH_3 of *t*-Butyl), 1.94 (m, 1H, H_A-3), 1.88 (m, 1H, H_B-3)	60.27 60.08	6.26 6.14	6.69 6.54
33	M + H^+ peak at m/z 433	3324, 3118 (N-H str of CONH), 3028 (Ar-C-H str), 2855 (ali C-H str), 1703 (C=O str), 1556, 1442 (ali C-H def), 1332 & 1162 (S=O str of SO_2NH), 975, 794 & 750 (Ar-C-H def)	12.68 (s, 1H, COOH), 8.52 (d, 1H, SO_2NH), 8.18-8.08 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.92 (m, 1H, CONH), 7.74-7.66 (m, 5H, ph.-protons), 4.28 (m, 2H, CH_2-ph), 3.84 (m, 1H, H-2), 2.46 (m, 2H, H_2-4), 2.20-2.12 (m, 9H, three CH_3 of *t*-Butyl), 2.02 (m, 1H, H_A-3), 1.94 (m, 1H, H_B-3)	61.09 60.92	6.52 6.42	6.48 6.36
34	M + H^+ peak at m/z 371	3025 (Ar-C-H str), 2858 (ali C-H str), 1706 (C=O str), 1548, 1440 (ali C-H def), 1336 & 1164 (S=O str of SO_2NH), 977, 796 & 754 (Ar-C-H def)	12.62 (s, 1H, COOH), 8.55 (d, 1H, SO_2NH), 8.14-8.06 (m, 4H, H-2′, H-3′, H-5′, H-6′), 3.80 (m, 1H, H-2), 3.24-3.12 (m, 6H, CH_3-1″, CH_3-2″), 2.40 (m, 2H, H_2-4), 2.10-1.98 (m, 9H, three CH_3 of *t*-Butyl), 1.92 (m, 1H, H_A-3), 1.82 (m, 1H, H_B-3)	55.12 54.98	7.07 6.99	7.56 7.48
35	M + H^+ peak at m/z 399	3025 (Ar-C-H str), 2858 (ali C-H str), 1706 (C=O str), 1548, 1440 (ali C-H def), 1336 & 1164 (S=O str of SO_2NH), 977, 796 & 754 (Ar-C-H def)	12.68 (s, 1H, COOH), 8.50 (d, 1H, SO_2NH), 8.10-8.02 (m, 4H, H-2′, H-3′, H-5′, H-6′), 3.74 (m, 1H, H-2), 3.22-3.08 (m, 4H, CH_2-1″, CH_2-2″), 2.44 (m, 2H, H_2-4), 2.18-2.04 (m, 9H, three CH_3 of *t*-Butyl), 1.98 (m, 1H, H_A-3), 1.80 (m, 1H, H_B-3), 1.72-1.56 (m, 6H, CH_3-3″, CH_3-4″)	57.26 57.22	7.59 7.49	7.03 6.98
36	M + H^+ peak at m/z 427	3020 (Ar-C-H str), 2852 (ali C-H str), 1700 (C=O str), 1552, 1444 (ali C-H def), 1332 & 1160 (S=O str of SO_2NH), 975, 794 & 752 (Ar-C-H def)	12.62 (s, 1H, COOH), 8.56 (d, 1H, SO_2NH), 8.14-8.08 (m, 4H, H-2′, H-3′, H-5′, H-6′), 3.78 (m, 1H, H-2), 3.20-3.12 (m, 2H, N-CH-1″, N-CH-2″), 2.42 (m, 2H, H_2-4), 2.22-2.08 (m, 9H, three CH_3 of *t*-Butyl), 2.02 (m, 1H, H_A-3), 1.94 (m, 1H, H_B-3), 1.74-1.62 (m, 12H, CH_3-3″, CH_3-4″, CH_3-5″, CH_3-6″)	59.13 59.02	8.03 7.92	6.57 6.62

2.2. Biological Activity

The title compounds were evaluated for their possible anticancer activity *in vivo* against Ehrlich Ascites Carcinoma (EAC) cell in Swiss Albino mice as per the standard procedure [13-15, 17] using percentage of tumor weight inhibition (% TWI) as the biological activity data.

2.2.1. Tumor cells

EAC 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 title compounds.

2.2.2. Animals

Swiss albino mice (either sex) of 10 weeks old with an average body weight of 18-20 grams were used. All mice were kept on basal metabolic diet with water *ad libitum*.

2.2.3. Procedure

Two groups of Swiss Albino Mice, each containing 5 healthy animal of the same sex, approximately of the same age and body weight, were selected at random and kept in two different cages under identical conditions. One of these two groups served as control while the other as test. Ehrlich Ascites Carcinoma (EAC) cells were collected from the donor mice and were suspended in sterile isotonic solution (0.9% w/v NaCl). A definite number (about $2X10^6$ cells/0.2 ml) of these living viable cells was injected or implanted into the peritoneal cavity of each mouse. A day of incubation was allowed to establish the disease in the body before the start of the drug administration. From the second day of transplantation up to the eighth day, a suitable challenge dose (0.2 mili mole/kg body weight) of the drug solution/suspension in sterile phosphate buffer (pH 7.2) was injected intraperitoneally to each mouse in the test group at 24 hr interval. Thus, seven doses of the drug were administered to each mouse in the test group. On the ninth day, food and water was withheld 18 hr before the start of the testing operation. The weights of all the animals were recorded before they were sacrificed. The peritoneal cavity was dissected and by a syringe, the ascitic fluid was withdrawn to a suitable volume, collected in sterile ice-cold saline and preserved in ice bath. The fluid was sucked by adsorbent cotton. The weight of the 5 mice after sacrifice was recorded. The evaluation of the test drug was made by comparing the tumor weight of the test with that of the control.

2.3. QSAR Methodology

2.3.1. Dataset and Parameter

Antitumor activities of thirty-two 5-*N*-substituted-2-(substituted benzenesulphonyl) glutamines of the general structure shown in **Figure 1** were used to develop QSAR models separately. Percentage tumor weight inhibition (%TWI) has been considered as biological activity parameters for QSAR studies. All these activities are calibrated to the logarithmic value.

2.3.2. Physicochemical Parameters

The physicochemical parameters like, hydrophobic constant π, electronic parameters σ (Hammett constant), ℜ (resonance effect) & ℑ (field effect), MR (Molar Refractivity), steric parameter E_s, sterimol parameters like L, B_1, B_5 were collected from the literature [21, 22] and are listed in **Table 5**. σ, ℜ, ℑ all these parameters describe the influence of a certain group or substituent on electron density distribution. MR is largely a measure of volume with a small correction for polarizability. MR values were scaled by a factor 0.1. Es is the classical Taft parameter derived from the rate of hydrolysis of aliphatic esters.

2.3.3. Electrotopological state atom (ETSA) indices

The ESTA index of each atom explained electronic and topological information of all other atoms within the structure [23, 24]. ETSA indices were calculated using the computer programme 'Mouse' [25] developed in our laboratory. For calculation of E-state index, arbitrary numbering was used and these are shown in **Figure 2**.

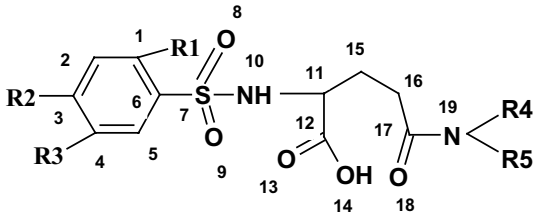


Figure 2. General Structure of 5-*N*-substituted-2-(substituted benzenesulphonyl) glutamines (**5-36**) with arbitrary numbers used for ETSA calculations

2.3.4. Statistical Analysis

2.3.4.1. Correlation Analysis

Correlation analysis [26] of biological activity, ETSA indices and physicochemical parameters was carried out. Inter-correlated parameters were eliminated stepwise depending on their individual correlation with the biological activity. All possible combinations of parameters were considered for multiple regression analysis.

5.3.4.2. Multiple Regression Analysis

Multiple regression analysis [26-29] was carried out by 'Multi Regress' [30], a programme developed in our laboratory. The statistical quality of the regression equation were justified by parameters like correlation coefficient (R), percentage of explained variance (%EV), adjusted R^2 (R^2_A), variance ratio (F), standard error of estimate (s). All the final equations have significant regression coefficients, intercepts and variance ratio (F) and that are more than 95% level. Use of more than one variable in the multivariate equation was justified by autocorrelation study.

2.3.4.3. Cross Validation

The predictive powers of the equation were validated by Leave-One-Out (LOO-) cross validation method [31]. Predicted residual sum of square (PRESS), total sum of squares (SSY), cross-validated R^2 (R^2_{CV}), standard error of PRESS (S_{PRESS}) and predictive standard error of prediction (S_{DEP}) for the QSAR equations were considered for the validation of the models.

3 RESULTS AND DISCUSSION

3.1. Synthesis

32 new 5-*N*-substituted-2-(substituted benzenesulphonyl) glutamines were synthesized. There were four types of substitutions at aromatic ring whereas the aliphatic side chain contains thirteen substitutions. Percentage of yields of the final compounds was ranging from 45 to 92% as shown in **Table 2**.

3.2. Screening

All the final compounds were screened for their possible anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell as per standard method [13-15, 17]. Compounds were dissolved or suspended in PBS with 2% Tween 80 (whenever necessary) separately. The solution or suspension of the test compounds was administered at a dose level of 2 mmol/kg/day intraperitonially (i.p.) for 7 consecutive days. % Inhibition of tumor weight was considered as the biological activity parameter for QSAR study and thus, all the activity data are converted into logarithmic scale. **Table 4** shows the anticancer activity of all the compounds.

Table 4. Anticancer activities of 5-*N*-Substituted-2-(substituted benzenesulphonyl) glutamines **5-36**

Cpd	R_1	R_2	R_3	R_4	R_5	%TWI	Log (TWI)
5	H	Br	H	*i*-C_3H_7	H	46.51	1.668
6	H	Br	H	*c*-C_6H_{11}	H	63.24	1.801
7	H	Br	H	$C_6H_5CH_2$	H	34.39	1.536
8	H	Br	H	CH_3	CH_3	26.56	1.424
9	Cl	H	Cl	CH_3	H	40.28	1.605
10	Cl	H	Cl	*n*-C_3H_7	H	40.00	1.602
11	Cl	H	Cl	i-C_3H_7	H	52.15	1.717
12	Cl	H	Cl	*n*-C_4H_9	H	47.67	1.678
13	Cl	H	Cl	*i*-C_4H_9	H	48.21	1.683
14	Cl	H	Cl	*n*-C_6H_{13}	H	56.36	1.751
15	Cl	H	Cl	*c*-C_6H_{11}	H	56.09	1.749
16	Cl	H	Cl	C_6H_5	H	48.19	1.683
17	Cl	H	Cl	$C_6H_5CH_2$	H	42.76	1.631
18	Cl	H	Cl	CH_3	CH_3	22.28	1.348
19	Cl	H	Cl	*i*-C_3H_7	*i*-C_3H_7	44.23	1.646
20	CH_3	CH_3	H	H	H	23.23	1.366
21	CH_3	CH_3	H	*n*-C_4H_9	H	35.55	1.551
22	CH_3	CH_3	H	C_2H_5	C_2H_5	21.86	1.340
23	H	*t*-C_4H_9	H	H	H	55.01	1.300
24	H	*t*-C_4H_9	H	CH_3	H	40.01	1.602
25	H	*t*-C_4H_9	H	C_2H_5	H	32.38	1.510
26	H	*t*-C_4H_9	H	*n*-C_3H_7	H	32.81	1.516
27	H	*t*-C_4H_9	H	*i*-C_3H_7	H	45.68	1.660
28	H	*t*-C_4H_9	H	*n*-C_4H_9	H	45.16	1.655
29	H	*t*-C_4H_9	H	*i*-C_4H_9	H	38.55	1.586
30	H	*t*-C_4H_9	H	*n*-C_6H_{13}	H	50.82	1.706
31	H	*t*-C_4H_9	H	*c*-C_6H_{11}	H	61.42	1.788
32	H	*t*-C_4H_9	H	C_6H_5	H	67.85	1.832
33	H	*t*-C_4H_9	H	$C_6H_5CH_2$	H	33.93	1.531
34	H	*t*-C_4H_9	H	CH_3	CH_3	23.57	1.372
35	H	*t*-C_4H_9	H	C_2H_5	C_2H_5	22.79	1.358
36	H	*t*-C_4H_9	H	*i*-C_3H_7	*i*-C_3H_7	28.74	1.458

3.3. QSAR Study

To identify the chemical structural features required for antitumor activity of 5-*N*-substituted-2-(substituted benzenesulphonyl) glutamines, Quantitative Structure-Activity Relationship (QSAR) studies were performed as a part of our composite programme of rational drug design [12-17, 31-39]. The physicochemical parameters and ETSA indices were used to develop QSAR models. Important physicochemical parameters and ETSA indices are shown in **Table 5**. Correlation analysis was performed using Log (TWI) as the dependent variable and physicochemical and ETSA indices as independent parameter. The result of this analysis is shown in **Table 6**.

Table 5. Physicochemical parameters and ETSA indices of glutamine analogs **5-36**

Cpd	$\Im R_1$	$\Re R_2$	πR_4	MRR_4	LR_4	B_1R_4	S_2	S_3	S_4	S_5	S_6	S_7	S_{AV}
5	0.000	-0.170	0.870	1.287	4.110	1.900	1.542	0.706	1.542	1.358	-0.042	-3.975	0.226
6	0.000	-0.170	2.070	2.497	6.170	1.910	1.557	0.714	1.557	1.376	-0.028	-3.979	0.239
7	0.000	-0.170	2.060	2.867	4.620	1.520	1.543	0.701	1.543	1.359	-0.050	-4.007	0.218
8	0.000	-0.170	0.040	0.357	2.870	1.520	1.541	0.707	1.541	1.357	-0.040	-3.965	0.228
9	0.410	0.000	0.040	0.357	2.870	1.520	1.290	1.406	0.142	1.115	-0.325	-4.190	-0.112
10	0.410	0.000	1.090	1.290	4.920	1.520	1.298	1.412	0.145	1.124	-0.320	-4.201	-0.108
11	0.410	0.000	0.870	1.287	4.110	1.900	1.296	1.41	0.142	1.121	-0.340	-4.207	-0.116
12	0.410	0.000	1.620	1.747	6.170	1.520	1.301	1.415	0.146	1.127	-0.318	-4.205	-0.107
13	0.410	0.000	1.490	1.747	4.920	1.520	1.299	1.413	0.144	1.125	-0.321	-4.209	-0.110
14	0.410	0.000	2.680	2.677	8.220	1.520	1.306	1.419	0.148	1.133	-0.316	-4.211	-0.104
15	0.410	0.000	2.070	2.497	6.170	1.910	1.311	1.424	0.152	1.140	-0.310	-4.211	-0.099
16	0.410	0.000	2.270	2.277	6.280	1.520	1.293	1.408	0.134	1.118	-0.336	-4.243	-0.125
17	0.410	0.000	2.060	2.867	4.620	1.520	1.297	1.411	0.137	1.122	-0.331	-4.239	-0.121
18	0.410	0.000	0.040	0.357	2.870	1.520	1.295	1.41	0.144	1.121	-0.322	-4.197	-0.110
19	0.410	0.000	0.870	1.287	4.110	1.900	1.306	1.419	0.146	1.134	-0.318	-4.239	-0.110
20	-0.040	-0.130	0.000	0.103	2.060	1.000	1.688	0.899	1.626	1.416	0.013	-3.982	0.332
21	-0.040	-0.130	1.620	1.747	6.170	1.520	1.714	0.913	1.651	1.448	0.039	-3.982	0.357
22	-0.040	-0.130	0.560	0.817	4.110	1.520	1.716	0.96	1.654	1.451	0.034	-3.999	0.363
23	0.000	-0.130	0.000	0.103	2.060	1.000	1.688	0.959	1.688	1.426	-0.031	-3.997	0.347
24	0.000	-0.130	0.040	0.357	2.870	1.520	1.703	0.969	1.703	1.445	-0.011	-3.983	0.365
25	0.000	-0.130	0.560	0.817	4.110	1.520	1.707	0.971	1.707	1.450	-0.009	-3.989	0.367
26	0.000	-0.130	1.090	1.290	4.920	1.520	1.711	0.972	1.712	1.454	-0.006	-3.993	0.370
27	0.000	-0.130	0.870	1.287	4.110	1.900	1.709	0.97	1.709	1.452	-0.010	-3.999	0.366
28	0.000	-0.130	1.620	1.747	6.170	1.520	1.714	0.973	1.714	1.457	-0.005	-3.997	0.371
29	0.000	-0.130	1.490	1.747	4.920	1.520	1.712	0.971	1.712	1.455	-0.007	-4.002	0.368
30	0.000	-0.130	2.680	2.677	8.220	1.520	1.718	0.975	1.718	1.463	-0.002	-4.004	0.374
31	0.000	-0.130	2.070	2.497	6.170	1.910	1.724	0.978	1.724	1.470	-0.004	-4.003	0.378
32	0.000	-0.130	2.270	2.277	6.280	1.710	1.706	0.963	1.706	1.448	-0.022	-4.035	0.353
33	0.000	-0.130	2.060	2.867	4.620	1.520	1.710	0.965	1.71	1.453	-0.017	-4.032	0.358
34	0.000	-0.130	0.040	0.357	2.870	1.520	1.708	0.971	1.708	1.451	-0.008	-3.990	0.368
35	0.000	-0.130	0.560	0.817	4.110	1.520	1.716	0.974	1.716	1.461	-0.002	-4.001	0.373
36	0.000	-0.130	0.870	1.287	4.110	1.900	1.719	0.972	1.719	1.464	-0.005	-4.022	0.369

Table 6. Correlation matrix for the anticancer activity, physicochemical parameters, ETSA indices and indicator parameter

	$\Im R_1$	$\Re R_2$	πR_4	MRR_4	LR_4	B_1R_4	S_2	S_3	S_4	S_5
$\Im R_1$	1.00	0.98	0.15	0.15	0.15	0.13	-0.96	0.94	-0.99	-0.98
$\Re R_2$		1.00	0.13	0.11	0.15	0.06	-0.89	0.99	-0.97	-0.93
πR_4			1.00	0.97	0.91	0.30	-0.13	0.13	-0.14	-0.12
MRR_4				1.00	0.81	0.37	-0.15	0.10	-0.14	-0.12
LR_4					1.00	0.33	-0.10	0.16	-0.13	-0.09
B_1R_4						1.00	-0.15	0.06	-0.12	-0.11
S_2							1.00	-0.82	0.98	0.99
S_3								1.00	-0.92	-0.86
S_4									1.00	0.99
S_5										1.00

	S_6	S_7	S_{AV}	I	Log (TWI)
$\Im R_1$	-0.99	-0.99	-0.98	-0.07	0.32
$\Re R_2$	-0.99	-0.98	-0.92	-0.07	0.27
πR_4	-0.15	-0.22	-0.14	-0.48	0.72
MRR_4	-0.15	-0.22	-0.15	-0.45	0.69
LR_4	-0.12	-0.19	-0.12	-0.39	0.72
B_1R_4	-0.13	-0.14	-0.14	0.09	0.60
S_2	0.98	0.93	0.99	0.07	-0.32
S_3	-0.91	-0.95	-0.86	-0.06	0.26
S_4	0.99	0.98	0.99	0.06	-0.30
S_5	0.99	0.95	0.99	0.07	-0.30
S_6	1.00	0.98	0.99	0.08	-0.32
S_7		1.00	0.95	0.06	-0.33
S_{AV}			1.00	0.07	-0.32
I				1.00	-0.58
Log (TWI)					1.00

Multiple regression analysis using the combination of physicochemical parameters πR_4 (hydrophobicity of the R_4 substituent), B_1R_4 (sterimol parameter for minimum width of R_4 substituent) developed the following QSAR model as shown bellow:

$$\text{Log (TWI)} = 1.024\ (\pm 0.111) + 0.103\ (\pm 0.019)\ \pi R_4 + 0.274\ (\pm 0.072)\ B_1R_4 \qquad (1)$$

n = 32; R = 0.824; %EV = 67.90; $R^2_A = 0.657$; $F_{(2,29)} = 30.664$; $p<0.001$; s = 0.087; SSY = 0.688; PRESS = 0.264; $R^2_{CV} = 0.616$; $S_{PRESS} = 0.095$; $S_{DEP} = 0.091$

where n is the number of data points, R, %EV, F, p, s are the correlation coefficient, percentage of explained variance, ratio between the variances of observed and calculated activities, probability

factor related to the F-ratio, standard error of estimate respectively. SSY, PRESS, R^2_{CV}, S_{PRESS}, S_{DEP} are total sum of squares, predicted residual sum of square, cross-validated R^2, standard error of PRESS and standard deviation error of prediction respectively. This model explains 67.90 % of the variances in the activity data. Equation (1) suggests the importance of B_1R_4 and πR_4 in tumor weight inhibition of the glutamine analogs. Positive coefficients of B_1R_4 and πR_4 indicate that these are conducive to the activity.

Analysis of the correlation matrix reveals that ETSA indices like S_2, S_3, S_4, S_5, S_6, and S_7 have almost equal important contribution to the activity. But these indices are highly inter-correlated with each other and cannot be used in a single equation. Hence an average of these (S_{AV}) is considered as single best variable and incorporation of this index along with physicochemical parameters of equation (1) yielded equation (2) as shown bellow:

$$\text{Log (TWI)} = 1.070\ (\pm 0.111) + 0.099\ (\pm 0.018)\ \pi R_4 + 0.262\ (\pm 0.071)\ B_1R_4 - 0.121(\pm 0.070)\ S_{AV} \quad (2)$$

n = 32; R = 0.843; %EV = 71.06; $R^2_A = 0.679$; $F_{(3,28)} = 22.852$; $p<0.001$; s = 0.084; SSY = 0.688; PRESS = 0.258; $R^2_{CV} = 0.625$; $S_{PRESS} = 0.096$; $S_{DEP} = 0.090$

The explained variance and predicted variance of the equation (2) are 71.06% and 62.50% respectively. Negative coefficient of the S_{AV} indicates that the lower value of this index corresponds to higher anticancer activity. Inclusion of indicator parameter I for the presence of disubstitution at aliphatic side chain improve the statistical quality of the relationship as:

$$\text{Log (TWI)} = 1.030\ (\pm 0.077) + 0.054\ (\pm 0.015)\ \pi R_4 + 0.343\ (\pm 0.051)\ B_1R_4 - 0.113\ (\pm 0.048)\ S_{AV} - 0.167(\pm 0.030)\ I \quad (3)$$

n = 32; R= 0.930; %EV = 86.49; $R^2_A = 0.846$; $F_{(4,27)} = 43.512$; $p<0.001$; s = 0.059; SSY = 0.688; PRESS = 0.127; $R^2_{CV} = 0.815$; $S_{PRESS} = 0.069$; $S_{DEP} = 0.063$

Equation (3) explains 86.49% of the variances in the activity data. Negative coefficient of the 'I' also indicates that presence of disubstitution at R_4/R_5 position is disadvantageous to the activity.
Another models with near statistical quality of equation (3) were developed using MRR_4 (molar refractivity of the R_4 substituent) and LR_4 (sterimol parameter for length of the R_4 substituent) instead of πR_4 respectively as shown in equation (4) and (5):

Log (TWI) = 1.029 (±0.086) + 0.038 (±0.016) MRR_4 + 0.351 (±0.058) B_1R_4 - 0.116 (±0.053) S_{AV} - 0.184 (±0.033) I (4)

n = 32; R= 0.914; %EV = 83.61; R^2_A = 0.812; $F_{(4,27)}$ = 34.443; p<.001; s = 0.065; SSY = 0.688; PRESS = 0.156; R^2_{CV} = 0.773; S_{PRESS} = 0.076; S_{DEP} = 0.070

Log (TWI) = 0.962 (±0 .071) + 0.032 (±0.007) LR_4 + 0.333 (±0.047) B_1R_4 - 0.117 (±0.045) S_{AV} - 0.173 (±0.026) I (5)

n = 32; R= 0.941; %EV = 88.52; R^2_A = 0.868; $F_{(4,27)}$ = 52.041; p<0.001; s = 0.054; SSY = 0.688; PRESS = 0.107; R^2_{CV} = 0.844; S_{PRESS} = 0.063; S_{DEP} = 0.058

This equation (4) and (5) explain 83.61% and 88.52% of the variances in the activity data. Significant values of R^2_{CV} (0.773 and 0.844 respectively) confirm the validity of these models. Lower values of S_{PRESS} suggest that optimum number of variables were taken to relate the antitumor activity (%TWI) of the structure of those analogs.

Another two models (eqs. 6 and 7) were developed using $\Im R_1$ (field effect of the substituents at R_1 position) and $\Re R_2$ (resonance effect of the substituent at R_2 position) instead of S_{AV} as shown bellow:

Log (TWI) = 0.923 (±0.069) + 0.127 (±0.049) $\Im R_1$+ 0.031 (±0.007) LR_4 + 0.335 (±0.047) B_1R_4 - 0.173 (±0.026) I (6)

n = 32; R= 0.940; %EV = 88.41; R^2_A = 0.866; $F_{(4,27)}$ = 51.495; p<0.001; s = 0.054; SSY = 0.688; PRESS = 0.093; R^2_{CV} = 0.865; S_{PRESS} = 0.059; S_{DEP} = 0.054

Log (TWI) = 0.958 (±0.073) + 0.345(±0.149) $\Re R_2$ + 0.031 (±0.008) LR_4 + 0.344 (±0.048) B_1R_4 - 0.176 (±0.027) I (7)

n = 32; R= 0.938; %EV = 88.00; R^2_A= 0.862; $F_{(4,27)}$ = 49.372; p<.001; s = 0.055; SSY = 0.688; PRESS = 0.113; R^2_{CV} = 0.840; S_{PRESS} = 0.065; S_{DEP} = 0.059

Equation (6) and (7) explain 88.41% and 88.00% variances of the activity data. Equation (6) suggests that $\Im R_1$ is conducive to the activity. Probably electron-donating group at R_1 position

increases the field effect at this position. Equation (7) indicates that $\Re R_2$ is advantageous to the anticancer activity. These equations are also significantly predictive (R^2_{CV} = 0.865 and 0.840 respectively) in nature.

Confidence intervals of the final equations (3), (4), (5), (6), (7) are more than 95% level as suggested by the *p*- and *t*-values shown in the **Table 7**.

Table 7. t-statistic and p-values of QSAR equation 1-7

Eqn.	Parameter/ Intercept	t-value	p-value	Eqn.	Parameter/ Intercept	t-value	p-value
1	Intercept	9.201	0.000	2	Intercept	9.653	0.000
	πR_4	5.404	0.000		πR_4	5.365	0.000
	B_1R_4	3.784	0.001		B_1R_4	3.724	0.001
					S_{AV}	-1.732	0.094
3	Intercept	13.355	0.000				
	πR_4	3.556	0.001	4	Intercept	12.020	0.000
	B_1R_4	6.749	0.000		MRR_4	2.344	0.027
	S_{AV}	-2.341	0.027		B_1R_4	6.032	0.000
	I	-5.595	0.000		S_{AV}	-2.178	0.038
					I	-5.639	0.000
5	Intercept	13.477	0.000				
	LR_4	4.402	0.000	6	Intercept	13.283	0.000
	B_1R_4	7.067	0.000		$\Im R_1$	2.570	0.016
	S_{AV}	-2.631	0.014		LR_4	4.270	0.000
	I	-6.651	0.000		B_1R_4	7.099	0.000
					I	-6.673	0.000
7	Intercept	13.096	0.000				
	$\Re R_2$	2.320	0.028				
	LR_4	4.132	0.000				
	B_1R_4	7.195	0.000				
	I	-6.612	0.000				

The observed, calculated and LOO-predicted activities of the equations (3), (4), (5), (6), (7) are listed in the **Table 8**.

Table 8. Observed (Obs), Calculated (Calc) and LOO-predicted (Pred) activities of Eqs. 3-7

Cpd	Obs	Eqn 3		Eqn 4		Eqn 5		Eqn 6		Eqn 7	
		Calc	Pred	Calc	Pred	Calc	Pred	Calc	Pred	Calc	Pred
5	1.668	1.703	1.711	1.719	1.729	1.699	1.706	1.689	1.693	1.682	1.686
6	1.801	1.770	1.765	1.767	1.762	1.768	1.763	1.757	1.750	1.750	1.739
7	1.536	1.638	1.646	1.647	1.666	1.591	1.593	1.577	1.580	1.567	1.570
8	1.424	1.361	1.349	1.366	1.355	1.360	1.348	1.348	1.333	1.337	1.317
9	1.605	1.566	1.555	1.589	1.585	1.573	1.566	1.574	1.567	1.571	1.563
10	1.602	1.622	1.625	1.624	1.627	1.638	1.642	1.639	1.643	1.635	1.639
11	1.717	1.742	1.749	1.758	1.770	1.740	1.745	1.741	1.747	1.741	1.747
12	1.678	1.651	1.648	1.642	1.638	1.679	1.679	1.678	1.678	1.674	1.673
13	1.683	1.644	1.640	1.642	1.637	1.639	1.634	1.639	1.634	1.635	1.630
14	1.751	1.706	1.696	1.677	1.663	1.744	1.742	1.743	1.739	1.738	1.733
15	1.749	1.808	1.818	1.806	1.816	1.807	1.817	1.809	1.819	1.808	1.819
16	1.683	1.688	1.689	1.664	1.661	1.684	1.684	1.682	1.681	1.677	1.676
17	1.631	1.676	1.683	1.686	1.700	1.630	1.630	1.629	1.629	1.626	1.625
18	1.348	1.399	1.415	1.405	1.422	1.400	1.415	1.400	1.416	1.395	1.410
19	1.646	1.574	1.551	1.574	1.551	1.566	1.540	1.566	1.540	1.565	1.537
20	1.366	1.336	1.324	1.345	1.337	1.322	1.303	1.317	1.297	1.322	1.304
21	1.551	1.598	1.602	1.588	1.590	1.624	1.632	1.621	1.629	1.629	1.637
22	1.340	1.374	1.381	1.367	1.373	1.384	1.394	1.382	1.391	1.389	1.399
23	1.300	1.334	1.347	1.343	1.361	1.320	1.328	1.323	1.332	1.322	1.331
24	1.602	1.512	1.494	1.534	1.520	1.517	1.503	1.522	1.511	1.526	1.516
25	1.510	1.540	1.543	1.551	1.556	1.557	1.560	1.561	1.565	1.565	1.569
26	1.516	1.568	1.572	1.569	1.573	1.582	1.587	1.587	1.591	1.590	1.594
27	1.660	1.687	1.694	1.702	1.713	1.683	1.689	1.689	1.695	1.696	1.703
28	1.655	1.597	1.592	1.586	1.581	1.623	1.619	1.626	1.623	1.629	1.627
29	1.586	1.590	1.590	1.587	1.587	1.583	1.582	1.587	1.587	1.590	1.590
30	1.706	1.654	1.641	1.622	1.607	1.688	1.682	1.691	1.685	1.693	1.688
31	1.788	1.754	1.748	1.751	1.744	1.751	1.745	1.758	1.752	1.763	1.760
32	1.832	1.699	1.682	1.675	1.660	1.691	1.677	1.693	1.679	1.698	1.686
33	1.531	1.622	1.632	1.631	1.651	1.574	1.577	1.577	1.580	1.581	1.584
34	1.372	1.345	1.340	1.349	1.345	1.344	1.338	1.348	1.343	1.351	1.347
35	1.358	1.373	1.376	1.366	1.368	1.383	1.388	1.387	1.393	1.389	1.396
36	1.458	1.520	1.537	1.518	1.535	1.510	1.524	1.514	1.529	1.520	1.535

4 CONCLUSIONS

The QSAR study suggested that the length and width of the aliphatic substituent must be higher for the possible receptor ligand interaction through hydrophobic or dispersive force. The study also revealed that atoms 2, 3, 4, 5, 6, 7 are of great importance for anticancer activity of the glutamine analogs. Field effect of the R_1 substitutions possibly helps in electronic interaction with the substrate. In this case, electron-donating group may contribute in the binding with the electron deficient receptor site. Resonance effects of the R_2 substitution also might take part in the electronic interaction with the substrate. The presence of disubstitution at aliphatic side chain (R_4 and R_5) of glutamine analogs may not conducive to the activity. At least one free hydrogen atom in amide moiety may be essential for anticancer activity. This will help to select substituents for future synthesis of this type of compounds.

Acknowledgment

Authors are thankful to the University Grants Commission (UGC), New Delhi and All India Council for Technical Education (AICTE), New Delhi for providing financial assistance. Two of the authors BD and SS are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi and University Grants Commission (UGC), New Delhi for providing Senior Research Fellowship (SRF) and Junior Research Fellowship (JRF) respectively. Authors are also grateful to the authority of Jadavpur University for their help and encouragement.

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