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QSAR Study on Some Substituted Glutamine Analogs as Anticancer Agents[#]

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Abstract

Motivation. After glucose, glutamine is a major substrate for the cancer cell. In the synthesis of DNA and RNA, major portions of nitrogen atoms are supplied by glutamine (GLN). Structural variants of glutamine may antagonize enzymes involved in DNA and RNA synthesis. A QSAR (quantitative structure–activity relationships) study was performed on some previously synthesized glutamine analogs in order to get insight in the substitutional requirements for their anticancer activity as well as to overcome the symmetry restriction of *De Novo* model and time consuming determination of partition coefficients of Hansch analysis.

Method. The QSAR study was performed using the Fujita Ban model.

Results. A good QSAR model was obtained considering anticancer activity, *i.e*., log % of tumor weight inhibition which expresses the biological activity, of thirty 5–*N*–substituted–2–(substituted benzenesulphonyl)–L–glutamines as dependent variable and substitutional contribution at specific position as independent variable as evidenced by the statistical data (r = 0.8122, s = 0.1196, F = 1.3755).

Conclusions. Substituent at the 3' and 5'– positions of the phenyl ring lead to a general decreased anticancer activity, but a Br at the 4'–position and a Cl at the 2'–position were positively correlated to the total activity.

Keywords. Glutamine; anticancer activity; QSAR; quantitative structure–activity relationships; Fujita Ban model; Free Wilson model.

Abbreviations and notations

BA, Biological activity	QSAR, quantitative structure–activity relationships
EAC, Ehrlich ascites carcinoma	RDD, rational drug design
GLN, glutamine	

1 INTRODUCTION

In the synthesis of DNA and RNA, major portions of nitrogen atoms are supplied by the amino acid glutamine (GLN). GLN supplies the 3rd and 9th nitrogen atoms of the purine ring, the 2nd amino group of guanine and the 3rd nitrogen atom and amino group of cytosine [1]. It also acts as the major respiratory fuel in the tumor cell [2]. Some cancer cells need this amino acid more in comparison

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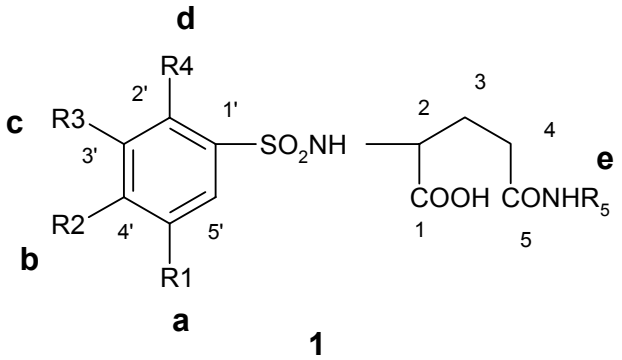
with normal cell [3]. The only circulatory sugar D–glucose and the non–essential amino acid L–glutamine are two major substrates for cancer [3]. Since all living cells, both normal and cancerous, need D–glucose for survival, L–glutamine may be the major substrate for cancer. Moreover, GLN is responsible for almost all physiological functions [4] and cancer cases. At most of the physiological systems, tissues and cells as well as this amino acid is essential for maintaining artificial culture of cell lines [5] which show mutations after a certain period of time. On the basis of these, structural variants of glutamine may antagonize enzymes involved for their possible anticancer activity in the way of competitive inhibition of the amino acid glutamine.

QSAR (quantitative structure–activity relationship) models are important tools in the area of drug design. Some recent articles on QSAR are the evidence of that. Hiroshima *et al.* [6], Hadjipavlou–Latina *et al.* [7], Garcia–Domenech and coworkers [8] performed QSAR studies on sex–pheromone production inhibitors, lypoxygenase inhibitors and anti–fungal activity, respectively. Some recent papers of QSAR studies performed by us on glutamine and its derivatives are good efforts towards recent research. Srikanth *et al*. reported the synthesis, biological evaluation and QSAR study on glutamamides [9] and glutamines [10]. Debnath *et al*. worked on synthesis, anticancer evaluation and QSAR study on some glutamamides [11].

In this present study, which is a part of our composite program of Rational Drug Design (RDD) [9–20], thirty analogs of 5–*N*–substituted–2–(substituted benzenesulphonyl)–L–glutamine (**1**) were selected. These compound were synthesized and biologically evaluated for their inhibitory activity against Ehrlich Ascites Carcinoma (EAC) cells in Swiss Albino mice [12–14] and QSAR models were obtained through the *De Novo* model [14] as well as the Hansch method [16] earlier. These 30 compounds were used in a QSAR study through Fujita–Ban analysis [21], which is a modification of *De Novo* model [22] developed to relate non–parabolic Hansch method [23] to overcome the symmetry restrictions of *De Novo* model as well as time consuming determination of partition coefficients of Hansch model. This Fujita–Ban analysis was used successfully in several studies [24–28].

2 MATERIALS AND METHODS

For the QSAR study, the parent structure of 5–*N*–substituted–2– (substituted benzenesulphonyl)–L–glutamines **1** was used. The anticancer activity, which is % of tumor weight inhibition determined against Ehrlich Ascites Carcinoma (EAC) cells in Swiss albino mice, of some substituted glutamine analogs have been collected from our previous research articles [12–14] and considered as biological activity (BA) listed in Table 1. The QSAR study was performed using the Fujita Ban model [21] for structure **1** and the above–mentioned anticancer activities of glutamines.



1

2: $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = i\text{–}C_3H_7$
3–11: $R_1 = R_3 = R_4 = H$; $R_2 = Cl$; $R_5 = H, CH_3, C_2H_5, n\text{–}C_3H_7, n\text{–}C_4H_9, n\text{–}C_6H_{13}, c\text{–}C_6H_{11}, C_6H_5, C_6H_5CH_2$
12–14: $R_1 = R_3 = R_4 = H$; $R_2 = Br$; $R_5 = H, CH_3, C_2H_5$
15–16: $R_1 = R_3 = R_4 = H$; $R_2 = NO_2$; $R_5 = H, C_2H_5$
17–25: $R_1 = R_4 = H$; $R_2 = R_3 = Cl$; $R_5 = H, CH_3, C_2H_5, n\text{–}C_3H_7, n\text{–}C_4H_9, n\text{–}C_6H_{13}, c\text{–}C_6H_{11}, C_6H_5, C_6H_5CH_2$
26–27: $R_1 = R_4 = Cl$; $R_2 = R_3 = H$; $R_5 = H, C_2H_5$
28–31: $R_1 = Cl$; $R_2 = R_3 = H$; $R_4 = CH_3$; $R_5 = H, CH_3, C_2H_5, i\text{–}C_3H_7$

Table 1. Anticancer activities of 5–*N*–substituted–2–(substituted benzenesulphonyl)–L–glutamines **1**

Cpd	Substituent Type					BA [a]	log BA
	R1	R2	R3	R4	R5		
2	H	H	H	H	$i\text{–}C_3H_7$	64.29	1.8081
3	H	Cl	H	H	H	84.62	1.9275
4	H	Cl	H	H	CH_3	53.85	1.7312
5	H	Cl	H	H	C_2H_5	28.88	1.7312
6	H	Cl	H	H	$n\text{–}C_3H_7$	24.81	1.3946
7	H	Cl	H	H	$n\text{–}C_4H_9$	10.00	1.0000
8	H	Cl	H	H	$n\text{–}C_6H_{13}$	66.66	1.8239
9	H	Cl	H	H	$c\text{–}C_6H_{11}$	61.33	1.7879
10	H	Cl	H	H	C_6H_5	43.60	1.6395
11	H	Cl	H	H	$C_6H_5CH_2$	10.00	1.0000
12	H	Br	H	H	H	55.56	1.7448
13	H	Br	H	H	CH_3	77.78	1.8908
14	H	Br	H	H	C_2H_5	50.00	1.6990
15	H	NO_2	H	H	H	18.75	1.2730
16	H	NO_2	H	H	C_2H_5	50.00	1.6990
17	H	Cl	Cl	H	H	53.01	1.7274
18	H	Cl	Cl	H	CH_3	29.70	1.4728
19	H	Cl	Cl	H	C_2H_5	20.31	1.3077
20	H	Cl	Cl	H	$n\text{–}C_3H_7$	37.5	1.5740
21	H	Cl	Cl	H	$n\text{–}C_4H_9$	15.00	1.1761
22	H	Cl	Cl	H	$n\text{–}C_6H_{13}$	25.00	1.3979
23	H	Cl	Cl	H	$c\text{–}C_6H_{11}$	25.00	1.3979
24	H	Cl	Cl	H	C_6H_5	19.00	1.2788
25	H	Cl	Cl	H	$C_6H_5CH_2$	30.00	1.4771
26	Cl	H	H	Cl	H	72.23	1.8587
27	Cl	H	H	Cl	C_2H_5	53.71	1.7301
28	Cl	H	H	CH_3	H	37.50	1.5740
29	Cl	H	H	CH_3	CH_3	37.50	1.5740
30	Cl	H	H	CH_3	C_2H_5	23.92	1.3788
31	Cl	H	H	CH_3	$i\text{–}C_3H_7$	34.79	1.5414

[a] BA= Biological activity, *i.e.* anticancer activity of the compounds

The mathematical model of the Fujita Ban analysis can be represented as:

$$\log 1/C = \sum a_i.x_i + \mu \quad (1)$$

where C = concentration of the test substance, x_i = group contribution of the i^{th} substituent, a_i = coefficient of x_i at i^{th} position which is = 1 if the substituent is present, or = 0, if there is no substitution (*i.e.* for H), and μ = log 1/C calculated for the unsubstituted compound. Symmetric equations of Free–Wilson's *De Novo* model are totally neglected in Fujita Ban analysis [21]. The alternate form of Eq. (1) is:

$$\log BA = \sum a_i.x_i + \mu \quad (2)$$

which has been used in this work, where BA = biological activity and μ = log BA, calculated for the unsubstituted compound, *i.e.*, parent compound.

3 RESULTS AND DISCUSSION

Based on these guidelines and using the parent structure **1** and Eq. (2), 30 simultaneous linear equations, Eqs. (3)–(32), were obtained with 17 unknown variables to explore the relationship of the structure of the 30 compounds (**2**–**31**) with their biological activities as shown in Table 1. Representative samples of those Eqs. (3)–(32) are shown below:

$$e\,[i\text{–}C_3H_7] + \mu = 1.8081 \quad (3)$$

$$b\,[Cl] + \mu = 1.8081 \quad (4)$$

$$b\,[Cl] + e\,[CH_3] + \mu = 1.7312 \quad (5)$$

$$b\,[Cl] + e\,[C_2H_5] + \mu = 1.7312 \quad (6)$$

…….. (..)

$$a\,[Cl] + d\,[CH_3] + \mu = 1.5740 \quad (29)$$

$$a\,[Cl] + d\,[CH_3] + e\,[CH_3] + \mu = 1.5740 \quad (30)$$

$$a\,[Cl] + d\,[CH_3] + e\,[C_2H_5] + \mu = 1.3788 \quad (31)$$

$$a\,[Cl] + d\,[CH_3] + e\,[i\text{–}C_3H_7] + \mu = 1.5414 \quad (32)$$

Least square solutions of these 30 equations, Eqs. (3)–(32), obtained with the help of a Minicomp computer (Model 40x) gave individual contribution of each substituent group and that of the parent moiety μ. These are recorded in Table 2. The regression analysis also gave calculated anticancer activities of each compound. Calculated anticancer activities by Fujita Ban analysis as well as that of earlier studied *De Novo* model [14] and Hansch method [16] are recorded in Table 3 for comparison of the results of the three type of analysis.

Table 2. Substituent and parent moiety contributions in Eq. (1)

Sl. No.	Substituent	Position	Contribution to BA
1	Cl	5'	–0.3016
2	Cl	4'	–0.0562
3	Br	4'	0.0026
4	NO_2	4'	–0.2681
5	Cl	3'	–0.2298
6	Cl	2'	0.3419
7	CH_3	2'	0.0349
8	CH_3	5	–0.0045
9	C_2H_5	5	–0.1384
10	*n*–C_3H_7	5	–0.1678
11	*n*–C_4H9	5	–0.3611
12	*n*–C_6H_{13}	5	–0.0412
13	*c*–C_6H_{11}	5	–0.0592
14	C_6H_5	5	–0.1930
15	$C_6H_5CH_2$	5	–0.0601
16	*i*–C_3H_7	5	–0.0151
17	μ	5	1.8232

Table 3. Calculated anticancer activities

Cpd	De Novo Model [a]	Hansch Analysis [b]	Fujita Ban Analysis
	BA	log BA	log BA
2	64.29	1.6254	1.8081
3	62.15	1.7946	1.7671
4	59.73	1.6274	1.7626
5	46.35	1.5616	1.6286
6	42.17	1.6591	1.5993
7	15.21	1.3350	1.4059
8	56.84	1.6909	1.7258
9	54.18	1.7403	1.7078
10	42.32	1.5205	1.5741
11	18.74	1.6923	1.7069
12	67.19	1.9639	1.8258
13	64.77	1.7967	1.8213
14	51.38	1.7309	1.6874
15	42.28	1.7095	1.5552
16	26.47	1.4759	1.4168
17	40.12	1.5865	1.5372
18	37.70	1.4198	1.5328
19	24.31	1.3539	1.3989
20	20.14	1.4515	1.3694
21	15.00	1.1980	1.1761
22	34.81	1.4833	1.4960
23	32.15	1.5327	1.4780
24	20.28	1.3129	1.3442
25	30.00	1.4566	1.4771
26	70.87	1.8036	1.8636
27	55.76	1.5706	1.7252
28	39.05	1.6435	1.5565
29	36.63	1.4763	1.5521
30	23.24	1.4104	1.4182
31	34.79	1.7473	1.5414

[a] Ref. [14]; [b] Ref. [16]

This work has been undertaken with the objective of rational drug design of anticancer 5–*N*–substituted–2–(substituted benzenesulphonyl)–L–glutamine **1** analogs to find and use another easy method of QSAR study for optimization and in order to find out a new lead compound. Log of % tumor weight inhibition is the % of tumor weight inhibition in logarithmic scale and is the parameter that expresses the biological activity. Appreciable correlation (correlation coefficient r = 0.8122) was obtained with log of % tumor weight inhibition as evidenced by statistical data, *i.e*. n = 30, s = 0.1196, F = 1.3755.

4 CONCLUSIONS

The work upholds the additivity model of Fujita Ban analysis and can be used as a good model as shown by earlier report of *De Novo* model [14] having limitations of symmetry restriction and time consuming determination of partition coefficient in Hansch model [16]. An inspection of individual contribution of substituents at positions 3' and 5' of the phenyl ring showed a general decrease of anticancer activity, on the contrary the presence of a Br at 4'–position is correlated positively to the total activity. The anticancer activity was highly increased by a Cl at 2'–position and this substitution had greatest contribution towards the total activity. So far the aliphatic substitutions at the 5–position was concerned, it was observed that all the substitutions were detrimental to the anticancer activity. These points should be considered in designing further glutamines. On the basis of this analysis, calculated anticancer activities showed that these are not very different from those of *De Novo* model [14] and Hansch method [16]. Using this analysis one can avoid limitations and problems correlated to these two methods. This work substantiates and extends support to the earlier finding of the usefulness of Fujita Ban analysis [24–28]. Using the RDD approach the 2–(4′–chlorobenzenesulphonyl)–L–glutamine (compound **3**) was predicted as the most active compound within the series and might be a useful "lead". This QSAR model can also predict the anticancer activities of some 5–*N*–substituted–2–(substituted benzenesulphonyl)–L–glutamines, *e.g*., 2–(4'–bromobenzenesulphonyl)–L–glutamine and 2–(2'–chloro–4'–bromobenzenesulphonyl)–L–glutamine which are not synthesized yet but having higher activities than the most active compound **3**.

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