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QSAR STUDIES ON SOME AMINO ACID ANALOGUES OF PHTHILIMIDO DERIVATIVES AS ANTICANCER AGENTS

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ABSTRACT

After glucose, amino acids like glutamine, methonine, glycine, alanine, phenyl alanine are a major metabolite necessary synthesizing for the cancer cell. In the synthesis of DNA and RNA, major portions of nitrogen atoms are supplied by amino acids. Structural variants of amino acids may antagonize enzymes involved in DNA and RNA synthesis. A QSAR (quantitative structure–activity relationships) study was performed on some previously synthesized amino acid analogues in order to get insight in the substitution 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. A good QSAR model was obtained considering anticancer activity, *i.e.*, log % of tumor weight inhibition which expresses the biological activity, of three phthilimido derivatives which is a analogues of amino acid as dependent variable and substitution contribution at specific position as independent variable as evidenced by the statistical data (r = 0.8122, s = 0.1196, F = 1.3755).

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KEYWORDS

Amino acids; anti cancer activity; Ehrlich Ascites Carcinoma (EAC), QSAR; quantitative structure–activity relationships; Free Wilson model, Fujita–Ban analysis, *De Novo* model, Hansch method

INTRODUCTION

In the synthesis of DNA and RNA, major portions of nitrogen atoms are supplied by the amino acid like glutamine, methonine, glycine, alanine, phenyl alanine supplies the 3rd and 9th nitrogen atoms of the purine ring, the 2nd aminogroup 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 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], ten analogs of *N*- phthilimido 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 10 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. The Fujita – Ban analysis was used successful in several studies[24-28]

2 MATERIALS AND METHODS

For the QSAR study, the parent structure of N-phthilimido derivative containing was glutamine, glycine and phenyl alanine were used. The anticancer activity, which is % of tumor weight inhibition determined against Ehrlich Ascites Carcinoma (EAC) cells in Swiss albino mice, of some phthilimido substituted amino acid analogs have been collected and considered as biological activity (BA) listed in Table 1. The QSAR study was performed phthilimido on derivatives above mentioned anticancer activities

Structure

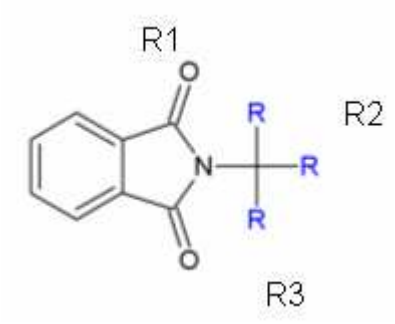

Table 1
Anticancer activities of Phthilimido derivatives

compound	R1	R2	R3	BA[a]	Log BA
1	COOH	$CH_2CH_2SCH_3$	H	42.32	1.6265
2	COOH	$CH_2CH_2CONH_2$	H	59.73	1.7761
3	COOH	H	H	15.21	1.1821
4	COOH	$CH_2C_6H_5$	H	42.28	1.6261
5	COOH	CH_3	H	37.70	1.5763
6	COOH	CH2OH	H	39.05	1.5916
7	COOH	CH2S	H	37.50	1.5740
8	COOH	CH2CH2COOH	H	46.35	1.6660
9	COOH	C6H5CH2OH	H	40.12	1.6033
10	COOH	CH2COOH	H	34.81	1.5417

BA=Biological activity i.e., anticancer activity of compounds

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

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

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 substitute 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:

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

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

RESULTS AND DISCUSSION

Based on these guidelines and using the parent structure **1** and Eq. (2), 12 simultaneous linear equations, Eqs. (3)–(10), were obtained with 5 unknown variables to explore the relationship of the structure of the 5 compounds (1–10) with their biological

activities as shown in Table 1. Representative samples of those Eqs. (3)–(10) are shown below:

$$e\,[i\text{–}CH_2CH_2SCH_3] + \mu = 1.6265 \quad (3)$$

$$e\,[i\text{–}CH_2CH_2CONH_2] + \mu = 1.7761 \quad (4)$$

$$e\,[i\text{–}COOH] + \mu = 1.1821 \quad (5)$$

$$e\,[i\text{–}CH_2C_6H_5] + \mu = 1.16261 \quad (6)$$

$$e\,[i\text{–}CH3] + \mu = 1.5763 \quad (7)$$

$$e\,[i\text{–}CH20H] + \mu = 1.5912 \quad (8)$$

$$e\,[i\text{–}CH2S] + \mu = 1.5740 \quad (9)$$

$$e\,[i\text{–}CH_2CH_2COOH] + \mu = 1.6660 \quad (10)$$

$$e\,[i\text{–}HOCH_2C_6H_5] + \mu = 1.6033 \quad (11)$$

$$e\,[i\text{–}CH2COOH] + \mu = 1.5417 \quad (12)$$

Least square solutions of these 12 equations, Eqs. (3)–(12), 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	$CH_2CH_2SCH_3$	2	-0.1678
2	$CH_2CH_2CONH_2$	2	-0.2681
3	H	2	-0.0045
4	$CH_2C_6H_5$	2	-0.0601
5	CH_3	2	-0.0349

Table 3
Calculated Anticancer activities

C0MPOUND	DeNovo Model	Hansch Analysis	Fujita Ban Analysis
1	42.32	1.5205	1.5741
2	59.73	1.6274	1.7626
3	15.21	1.3350	1.4059
4	42.28	1.7095	1.5552
5	37.70	1.4198	1.5372
6	39.05	1.6435	1.5565
7	37.50	1.5740	1.5328
8	46.35	1.5616	1.6286
9	40.12	1.5865	1.5372
10	34.81	1.4833	1.4960

N–substituted phthalimido derivative of L–glutamine 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.

CONCLUSION

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 N i.e., phthilimido group N positions of C having R2 showed a general decrease of anticancer activity, on the contrary the presence of a alkyl group at the position is correlated positively to the total activity. The anticancer activity was highly increased by a alkylcarbonylamide at R2–position and this substitution had greatest contribution towards the total activity. So far the aliphatic substitutions at the R2–position was concerned, it was observed that all the substitutions were determinal to the anticancer activity. These points should be considered in designing further amino acid analogue of phthilimido derivative. 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 phthilimido glutamine analogue (compound 2) was predicted as more active compound within the series and might be a useful 'lead'. This QSAR model can also predict the anticancer activities of some phthilimido derivative which is amino acid analogues which are not screened for anticancer activity. Abbreviations and notations: :BA- Biological activity, QSAR - quantitative structure activity relationships EAC - Ehrlich ascites carcinoma RDD - rational drug design GLN – glutamine

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