INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Review Article

A REVIEW ON SYNTHESIS OF SOME N-(p-METHOXY BENZENE SULPHONYL) GLUTAMAMIDE

Banerjee Bhaskar*[1], Banerjee Tanushree[1], Kumar Rajesh[1], Garg Atul Kumar[1], Kumar Avanish[2]
[1]Department of Pharmaceutical Chemistry, RKDF College of Pharmacy, Bhopal, M.P., India
[2]Department of Pharmaceutical Chemistry, TIT Pharmacy, Bhopal, M.P., India

Article Received on: 09/04/2011 Revised on: 20/05/2011 Approved for publication: 08/06/2011

*E mail: rajeshbhurtiya@gmail.com, 2bbhaskar@gmail.com

ABSTRACT
Numerous studies on glutamine metabolism in cancer demonstrate that glutamic acid and glutamine analogues may be developed as possible antitumor agent. Efforts were made to synthesize glutamamide analogues, structure variants of glutamic acid and glutamine contains both the amido groups at position of glutamic acid and derivative of both glutamine and is glutamine. Glutamic acid is a natural dicarboxylic amino acid having, alone or in his derivatives, valuable antimetabolic, antimicrobial and antifungal properties. Also, this compound is considered to be useful for the future treatment of neurological conditions, ulcers, hypoglycemic coma, muscular dystrophy, epilepsy, Parkinson's disease and mental retardation.
Keywords: Glutamamides, antitumor agent; screening, Parkinson's disease

INTRODUCTION

Tumors have been described as nitrogen trap[1,2]. It requires continuous supply of both essential and nonessential amino acid as nitrogen source for increased biosynthesis of nucleic acid and protein- the two most essential components of genomics and proteomics. Glutamine is the most abundant free amino acid in the human body and, therefore, plays a key role in tumor cell growth by supplying its amide nitrogen atom in the biosynthesis of other amino acids, purine and pyrimidine bases[3] via a family comprised of 16 amidotransferases with diversified mechanisms[4]. It is one of the two, if not the only, major substrate of cancer[5]. Thus, tumors indeed behave as glutamine traps. The tumor growth causes a change in host glutamine metabolism so that host nitrogen metabolism is accommodated to the tumor-enhanced requirements of glutamine[6]. To be used in this process, glutamine must reach into mitochondria of tumor cells through plasma membrane and inner mitochondrial membrane transporters. Glutamine also plays an important function in multiple metabolic pathways and an important component in the cell culture media for both carbon and nitrogen source[7]. All of the tumor cells studied so far had a high activity of phosphate dependent glutaminase. These were found to utilized glutamine from the culture medium during long term culture. Rates of cell growth, DNA and protein synthesis as well as thymidine transport were correlated with the glutamine concentration in the culture media[8]. Cell growth is a function of glutamine influx and suggests that glutamine is used to supply glutaminate and cytine perhaps for glutathione synthesis[9]. The reported antagonists of glutamine e.g. Azaserine, 6-diazo-5-oxo-L-norleucin (DON) and Acivicin are potent inhibiters of glutamine dependent amidotransferases[10].

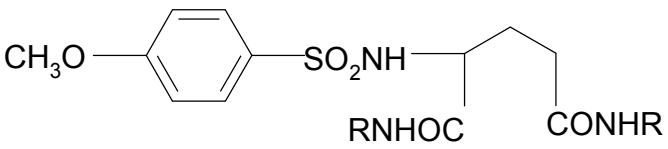
Glutamic acid is a natural dicarboxylic amino acid having, alone or in his derivatives, valuable antimetabolic, antimicrobial and antifungal properties. Also, this compound is considered to be useful for the future treatment of neurological conditions, ulcers, hypoglycemic coma, muscular dystrophy, epilepsy, Parkinson's disease and mental retardation[11].

CHEMISTRY

Synthesis of N-(p-methoxy benzene sulphonyl) glutamamides was carried out according to structure[12]. Neucleophillic displacement of intermediate with amines (amino-dehydroxylation) evolved the corresponding amides.

Synthesis was started with chlorosulphonylation of substituted benzene (p-methoxy benzene) to get corresponding sulphonyl chlorides. These halides prove to be versatile synthon in the subsequent step for the preparation of substituted benzenesulphonyl glutamic acid. P-methoxy benzene sulphonyl-L-glutamic acid was prepared by condensation reaction with L-glutamic acid. In this reaction alkaline medium was maintained to remove the hydrochloric acid, which is formed during condensation. Reaction of resulting intermediates, with

thionyl chloride afforded the acyl chlorides, p-methoxy benzene sulphonyl-L-glutamic acid dichloride[13].



QSAR STUDY

Quantitative Structure-Activity Relationship has been performed on the anticancer activity of 1, 5-N, N'-disubstituted-2-(substituted benzenesulphonyl) glutamamides using electro topological state atom (E-state) indices, refract topological state atom (R-state) indices [13-14].

PHARMACOLOGY

Anti cancer activity

The 1, 5-N, N'-disubstituted-2-(substituted benzenesulphonyl) glutamamides were biologically screened for their possible anticancer activity against Ehrlich Ascites Carcinoma (EAC) cell in Swiss Albino mice.

Ehrlich Ascites carcinoma (EAC) cell were originated from human breast carcinoma. EAC cell were maintained *in vivo* in Swiss Albino mice, by passaging every 10 days. EAC cell of 9 days old were used for the screening of the compounds[13].

The 1, 5-N, N'-disubstituted-2-(substituted benzenesulphonyl) glutamamides were synthesized, as tools for further elucidation of the structure requirement for antitumor activity. All the synthesis compounds were tested for antitumor activity against Ehrlich Ascites Carcinoma (EAC) in Swiss albino mice using tumor weight as inhibitory paramrter[14].

The study also shows that the increasing molar volumes of these analogues have advantageous effect to antitumor activity[15-16].

FUJITA- BAN ANALYSIS

In the QSAR study using Fujita-Ban model, the structure of 1, 5-N, N'-disubstituted-2-(substituted benzenesulphonyl) glutamamides was used. Biological activities along with the substituent types of the glutamamide analogs are given. The method used in this study is a modification of the Free-Wilson technique. Here, the log of activity is considered to be a free energy related parameter which is additive in nature. Fujita and Ban in 1971 derived a linear equation for a set of substituent, in the form equation which is as follows: [17]

$$\text{Log BA} = \sum GiXi + \mu$$

CONCLUSION

The above compounds have been synthesized, characterized and evaluated. The designing of the compounds synthesized for this research work was based on biochemical rationale, now the most active molecule of the series will be predicted and its QSAR study is done. Based on regression analysis, substituents in different compounds are chosen, which suggest that glutamamide derivative have excellent scope for further development as commercial anticancer agent. The present work upholds the additive nature of Fajita –Ban analysis and can be used as a good model by overcoming limitations.

REFERENCES

1. Medina M. Glutamine and cancer. J. Nutr. 2001; 131: 2539S-2542S.

2. Klimberg VS, McClellan JL. Glutamine cancer and its therapy. Am. J. Surg. 1996; 172: 418-424.

3. Costa C, Huneau JF, Tome D. Characteristics of L-glutamine transport during Caco-2 cell differentiation. Biochem. Biophys. Acta/Biomemb. 2000; 1509: 95-102.

4. Zalkin H, Smith JL. Enzymes utilizing glutamine as an amide donor. Adv. Enzymol. Relat. Areas. Mol. Biol. Sci. 1998; 72: 87-144.

5. Kallinowski L, Runkel S, Fortmeyer HP, Forster H, Vaupel P. L-glutamine: a major substrate for tumor cell in vivo? Cancer Res. Clin. Oncol. 1987; 113: 209-215.

6. Ollenschager G, Simmel A, Roth E. Availability of glutamine from peptides and acetylglutamine for human tumor-cell cultures. Metabolism. 1989; 38: 40-42.

7. Collins CL, Wasa M, Sauba WW, Abcouwer SF. Determinants of glutamine dependence and utilization by normal and tumor-derived breast cell line. J. Cell. Ptysiol. 1998; 176: 166-178.

8. Colquhonn A, Newsholme EA. Aspects of glutamine metabolism in human tumor cell. Biochem. Mol. Biol. Int. 1997; 41: 583-596.

9. Wasa M, Bode BP, Abcouwer SF, Collins CL, Tanabe KK, Souba WW. Glutamine as a regulator of DNA and protein biosynthesis in human solid tumor cell line, Ann. Surg. 1996; 224: 189-197.

10. Lyons SD, Sant ME, Christopherson RI. Cytotoxic mechanism of glutamine antagonists in mouse LI210 leukemia. J Biol Chem. 1990; 265: 11377-11381.

11. Dumitras DM, Popa M, Sune V. Synthesis of N-(3-nitrobenzoyl)-glutamic acid and its immobilization by esteric bond on gellan. Revue Rovmaine de Chimie 2007; 52: 383-392.

12. Dash P, Sahu NR, Sunil M, Das S N, Mahapata SK. Synthesis of compounds – a pathway for investigation and characterization. IntRJPharmSci 2010; 01: 42-45.

13. Gayen S, Debnath B, Somanta S, Ghosh B, Basu A, Jha T. 1,5 N,N'-disubstituted-2-(substituted benzenesulphonyl)-glutamamide analogues as anticancer agent-part 3: synthesis, biological screening and QSAR study. Internet Electronic Journal of Molecular Design 2003; 2: 1-25.

14. Srikanth K, Debanth B, Jha T. Synthesis, biological evaluation and QSAR study on antitumor activity of 1,5-N,N'-disubstituted-2-(substituted benzenesulphonyl) glutamamides. Bioorganic & Medicinal Chemistry 2002; 10: 1841-1854.

15. Gayan S, Jha T, Debnath B, Somanta S, Ghosh B, Basu A. 1,5 N,N'-disubstituted-2-(substituted benzenesulphonyl)-glutamamide analogues as anticancer agent-part 3: synthesis, biological screening and and QSAR study. Internet Electronic Journal of Molecular Design 2005; 4: 556-578.

16. Halder AK, Adhikary N, Maity MK and Jha T. synthesis, pharmacological activity and comparative QSAR modeling of 1,5-

N,N'- substituted-2-(substituted napthalenesulphonyl) glutamamides as possible anticancer agent. European journal of Medicinal chemistry 2010; 45(5): 1760-1771.

17. Deb B, Pal A, Ghosh RS, Khandakar S, Choudhury S. Fujita ban analysis of some substituted glutamamides. Kathmandu University Journal of science, Engineering and technology 2009; 5:212-129.