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Original article

# Possible anticancer agents: QSAR analogs of glutamamide: Synthesis and pharmacological activity of 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides

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**Abstract**

Based on our earlier QSAR prediction, a series of designed QSAR analogs of 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides were synthesized as possible anticancer agents. Inhibitions of tumor cell proliferation of the compounds were tested in tumor cell line IMR-32. Anticancer activities of these compounds were also evaluated on Swiss Albino mice against Ehrlich Ascites Carcinoma (EAC) cells. Tumor weight inhibition and tumor cell inhibition were considered as anticancer activity parameters. QSAR analysis of these compounds was performed on the basis of a set of descriptors like physicochemical, topological, quantum chemical and DRAGON whole molecular descriptors. The study showed that the increase of length of substituent at $R_2$ position and the increase of dipole moment of the molecule decrease the anticancer activity of these compounds, presence of bromine atom at $R_3$ position and hydrophilic substitution at $R_2$ position are advantageous to the activity. Nucleophilic attack at atom number 14 is advantageous and electrophilic attack at atom number 15 is detrimental to anticancer activity. Atom number 2 is important and may be involved in dispersive interactions of the compounds with enzymes. The results offer an opportunity for further tailoring of these analogs for an active member.


*Keywords:* Glutamamide; Anticancer activity; IMR-32; EAC; QSAR; Cluster analysis

## 1. Introduction

Glutamine is essential for rapidly proliferating tumor tissues as it is an important nutrient for rapidly growing cells [1–7]. Glutamine plays a key role in tumor cell growth by supplying its amide nitrogen atom in the biosyntheses of other amino acids, purines, pyrimidines, amino sugars and co-enzymes via a family comprised of 16 amidotransferase enzymes [8,9]. For cellular growth, glutamine provides multiple contributions by participating in protein, purine and pyrimidine metabolisms. Amide nitrogen of glutamine is utilized in a number of transfer reactions. Glutamine transports almost one third of the circulating amino acids and nitrogen; it is also the principle carrier of nitrogen from the skeletal muscles to the visceral organs [10]. As a principle metabolic fuel for the rapidly dividing cells including enterocytes, colonocytes, fibroblasts, lymphocytes, macrophages, neutrophils and tumor cells, it is as efficient as glucose. Through amidotransferase reactions, the amide nitrogen of glutamine serves as the precursor for the biosynthesis of many nitrogen-containing compounds and nucleotides such as pyridine nucleotide coenzymes, purines, pyrimidines, glucosamines, DPN and asparagine [10–13]. Amide nitrogen of glutamine is the precursor of nitrogen atom of carbamyl phosphate in many tissues [13]. It is reported that 2-(phenylacetyl) isoglutamine, which contains 1-*N*-amide, deserves anticancer

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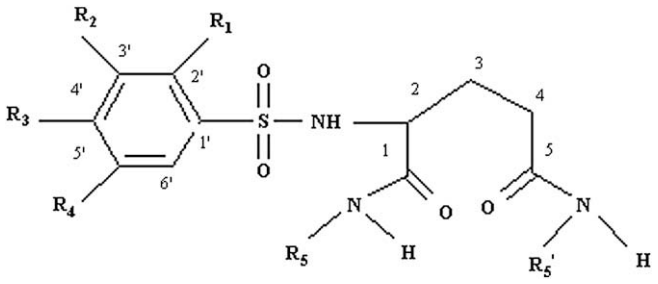


Fig. 1. General structure of 1,5-*N*,*N*′-disustituted-2-(substituted benzenesulphonyl) glutamamides (**26**–**57**).

activity [14]. As a part of the composite programme of drug design and discovery [15–20], our aim was to develop new compounds having possible anticancer activity. We have chosen to synthesize molecules that are structural variants of glutamine and/or glutamic acid as these variants may inhibit enzyme glutaminase and/or glutamine synthetase as well as glutamine receptor(s). Based on our earlier QSAR studies [15–19] on 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides, 32 new analogs of these glutamamides were designed and selected for synthesis and biological evaluation. The selected QSAR analogs were synthesized, characterized and biologically evaluated using in vitro and in vivo method. As these compounds were designed on the basis of earlier QSAR studies, these are termed as QSAR analogs to differentiate these analogs from the earlier synthesized non-designed analogs of Refs. [15–19]. To further explore the chemical structural features of these analogs, QSAR studies were performed on these newly synthesized QSAR analogs of 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides. The general structure of 1,5-*N*,*N*′-disubstituted-2-(substituted benzenesulphonyl) glutamamides is shown in Fig. 1.

Pharmacological evaluation showed that some of these compounds have good anticancer activities. The pharmacological activity data has been used as a preliminary biological activity dataset for QSAR study to find out the structural requirements of these compounds to improve the anticancer activity. For QSAR study, a set of descriptors like physicochemical, topological, quantum chemical and DRAGON whole molecular descriptors are used to build significant models. The study was performed on all these glutamamide analogs using percentage tumor weight inhibition (TWI) and tumor cell inhibition (TCI) as biological activity parameters.

## 2. Materials and method

### 2.1. Chemistry

2-(Substituted benzenesulphonyl)glutamic acids (**14**–**19**) were prepared by condensing L-glutamic acid (**13**) with substituted benzenesulphonyl chlorides (**7**–**12**) [21] which were synthesized by chlorosulphonylation of substituted benzenes (**1**–**6**) [22]. 2-(Substituted benzenesulphonyl)glutamic acid dichlorides (**20**–**25**) were obtained by treating the diacids (**14**–**19**) with thionyl chloride and title compounds were prepared by amination of acid chlorides (**20**–**25**) according to the methods described earlier [15–19]. The structures of the synthesized compounds were confirmed by IR, $^1$H NMR and mass spectra as well as by elemental analyses. Melting points of all synthesized compounds were determined in capillary tubes with a Mel-Temp Electrothermal apparatus and are uncorrected. The $^1$H NMR spectra were determined with a BRUKER DRX 300 MHz and referenced to the solvent. Chemical shifts are expressed in ppm and coupling constants ($J$) are in Hz, (s) singlet, (d) doublet, (t) triplet, (m) multiplet. Position of hydrogen described in $^1$H NMR interpretation are as per general structure (Fig. 1) and substitution at $R_5$ position are represented by the superscript ‘″’ (double dash) and the same for $R_5'$ position are represented by the superscript ‘‴’ (triple dash). FAB+ mass spectra were obtained on a JEOL JMS-SX-102 mass spectrometer. *m*-Nitrobenzyl alcohol (MNBA) was used as the matrix ($M^+$) which showed the M + 1 peak at 154, 2M + 1 peak at 307. Elemental analyses were performed by 2400 Series-II CHN analyzer of Perkin–Elmer and gave combustion values for C, H, N within 0.4% of the theoretical values. Reactions were monitored by analytical thin layer chromatography performed on silica gel G plates.

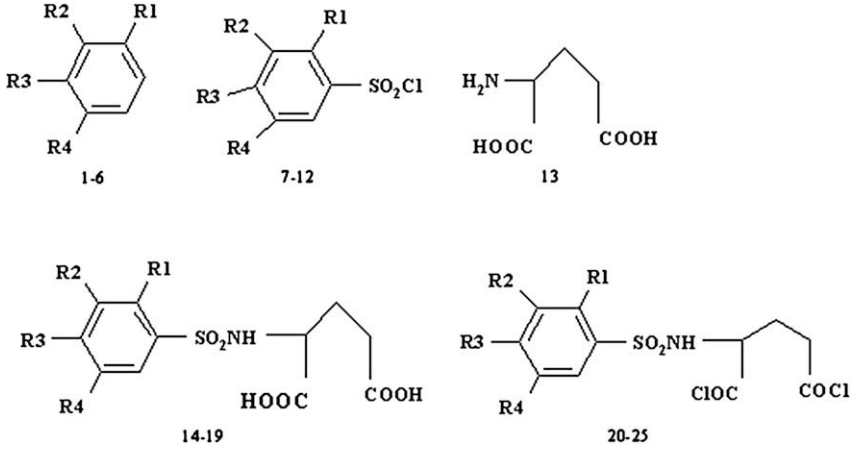


Fig. 2. General structures of starting materials and intermediates.