European Journal of Medicinal Chemistry 109 (2016) 247–253

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

# Development of certain new 2-substituted-quinazolin-4-yl-aminobenzenesulfonamide as potential antitumor agents

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ARTICLE INFO

*Article history:*
Received 14 November 2015
Received in revised form
18 December 2015
Accepted 4 January 2016
Available online 6 January 2016

*Keywords:*
Quinazoline
Sulfonamides
Sulfonylthioureas
Carbonic anhydrase
Antitumor

ABSTRACT

Carbonic anhydrases (CA I, II, IX and XII) are known to be highly expressed in various human malignancies. CA IX is overexpressed in colorectal cancer specifically in hereditary nonpolyposis colorectal cancer. Inhibition of CA activity by small molecular CA inhibitor like sulphonamides, sulphonamide derivative (SU.D2) or HIF1a inhibitor Chetomin leads to inhibition of tumorigenesis. Eighteen new quinazolin-4-sulfonamide derivatives were prepared and characterized by means of IR, NMR and mass spectra. Certain selected derivatives were tested for their ability to inhibit four isoforms of the metalloemzyme CA, namely, CA I, CA II, CA IX and CA XII. Compound **3c** was found to be highly effective in inhibiting the cancer cell proliferation. **3c** decreased cell viability of human HT-29 cells in dose and time dependent manner and with $IC_{50}$ of 5.45 μM. Moreover, it was tested on metastatic colon cancer cell SW-620 where it was found to be equally effective on human SW-620 cells. This novel compound inhibited the CA IX and CA XII protein expression in HT-29 cells without affecting CA I and CA II expression. These findings indicate that **3c** inhibits cellular proliferation in two human colon cancer cells by specifically targeting the CA IX and CA XII expression.

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## 1. Introduction

Cancer as a dreadful disease was responsible for about 13% of the total worldwide mortality. It is the second major cause of death, and is projected to become the world's single leading cause of morbidity by 2030. Colorectal cancer is the second leading cause of cancer related deaths worldwide and the 3rd most common cancer in USA among men and women. According to American Cancer Society data, 93,090 colon cancer and 39,610 rectal cancers are diagnosed in 2015 [1]. In spite of the substantial progress and efforts in many aspects of cancer research, there is very little progress as indicated by the scarcity of candidates reaching the clinical trials phase [2].

Several problems delay the reach to an ideal drug that could effectively combat cancer. The complexity of tumors, the lack of discrimination between healthy and tumor cell in addition to the development of drug resistance are some of such obstacles [3].

Tumor growth depends on multiple factors, like activation of various signaling pathway including the physiological process of angiogenesis. There are two major research directions in this respect, the first one rely on the opportunities for tumor inhibition

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http://dx.doi.org/10.1016/j.ejmech.2016.01.001
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with mono-targeted therapies and are currently being evaluated for clinical efficacy. In this approach, a single pathway is blocked with a specific agent in combination regimens with cytotoxins [4].

However, the other approach suggested that optimal therapy may require inhibition of several signaling pathways including angiogenesis. This understanding directed researchers to speculate that compounds which simultaneously inhibit multiple pathways are preferred to achieve maximal clinical efficacy. The feasibility of identifying these multiplex inhibitors was demonstrated with the entry of several such inhibitors into clinical trials [5].

In many types of hypoxic tumors, two isoforms of the metalloenzyme carbonic anhydrase (CA) are highly overexpressed, CA IX and XII, but they lack from normal tissues [6]. They are involved in tumor acidification, metastasis and invasion and their inhibition leads to a profound antitumor effect and are commonly referred to as the tumor associated isoforms [7]. Promising model antitumor agents, based on our search for mono-targeted agents, that hopefully are anticipated to inhibit CA IX and/or CA XII, with limited or no noticeable inhibitory effect on CA I and/or CA II, so as to minimize the untoward effect are receiving a considerable interest.

Based on the fact that various sulfonamide derivatives are potent CA inhibitors, this became clear from the numerous research publications, patents and candidates in clinical trials reporting their ability to concentrate in hypoxic tumors and effectiveness to combat cancer [8–11]. Herein, we propose to synthesize novel sulfonamides linked to the quinazoline scaffold for testing their ability to inhibit CA I, II, IX and XII expression.

## 2. Results and discussion

### 2.1. Chemistry

The target quinazoline derivatives **3a**–**p** were prepared *via* a generalized route are depicted in Scheme 1. The key intermediates 4-chloroquinazolines **2a**–**h**, were prepared *via* heating the quinazoline derivatives **1a**–**h** under reflux temperature with phosphorus oxychloride in presence of catalytic amount of *N,N*-dimethylaniline which act as acid binder [11–15].

The target compounds **3a**–**p** was synthesized by condensing sulfanilamide or sulfathiazole with corresponding 4-chloroquinazolines **2a**–**h** in refluxing 2-propanol. The I.R. spectra of compounds **3a**–**p** showed two absorption bands at 1370 and 1190 $cm^{-1}$ for $SO_2$ in addition to the absorption bands of $NH_2$ and NH groups in the region 3400–2330 $cm^{-1}$ for compounds **3a**–**h** and absorption bands of 2 NH groups in the region $\delta$ 3300–3200 $cm^{-1}$ for compounds **3i**–**p** whereas, their $^1H$ NMR showed $D_2O$ exchangeable signals of NH and $NH_2$ groups in the expected regions $\delta$ 11.0–12.0 and $\delta$ 7.30–7.50, respectively. Their mass spectra revealed, in each case, a peak corresponding to the molecular ion.

Furthermore, the reaction of compounds **3c, e** with phenyl isothiocyanate in the presence of dry potassium carbonate in refluxing dry acetone afforded sulfonylthioureas derivatives **4a, b**.

The IR spectra of these compounds exhibited two bands at 1380 $cm^{-1}$ and 1190 $cm^{-1}$ due to $SO_2$ group as well as thiourea carbonyl absorption at 1715 $cm^{-1}$. The $^1H$ NMR of these compounds revealed 3 $D_2O$ exchangeable signals of 3 NH protons around 8.80, 9.70 and 11.80.

### 2.2. Effect of compounds on cell viability

All of the eighteen compounds were tested for cell viability on human colon cancer cell line HT-29. Compound **3c** was found to inhibit cell viability significantly to 12% (Fig. 1A). Effect of various concentration of **3c** was tested on the cell viability of HT-29. Compound **3c** decreased cell viability in a dose dependent (Fig. 1B) and time dependent (Fig. 1C) manner. The IC50 for compound **3c** was found to be 5.45 μM. The effect of **3c** was also assessed on another colon cancer cell line SW-620. Similar to earlier finding with HT-29, **3c** also inhibited cell viability significantly in SW-620 metastatic colon cancer cells (Fig. 1D). Taken together these findings thus indicate that **3c** inhibits cell proliferation in human colon cancer cell lines.

### 2.3. Inhibition of carbonic anhydrase IX and XII expression

Human colon cancer cell line HT-28 was known to express high level of CA IX [16]. To assess the effect of compound **3c** on the CA IX expression, we treated human HT-29 cells with increasing amount of compound **3c**. Treatment with compound **3c** was associated with a concentration dependent inhibition in CA IX expression (Fig. 2). Similar inhibition was also found for CA XII. However this compound has no effect on CA I and CA II expression. Equal loading was confirmed by immunoblotting with antibody against β-actin (Fig. 2). These findings indicate that compound **3c** inhibits CA IX and CA XII expression. Compound **3c** was found to be very effective in reducing CA IX and CA XII expression in human colon cancer cells. CA IX plays important role in producing and maintaining an intracellular pH favorable for tumor cell growth and survival along with increasing the acidic extracellular space thereby enhancing cancer cell invasion [17]. Blocking CA IX expression would disrupt pH regulation and impair tumor growth and metastasis. Depletion of CA IX in breast cancer xenografts resulted in primary tumor growth attenuation. Colorectal cancer cell xenografts also regressed with CA IX and CA XII depletion [18]. CA IX and CA XII expression in cancer cells is regulated by the activation of PI3K and component of MAPK pathway during hypoxia [19,20]. The possible mechanism for downregulation of CA expression might result from inhibition of PI3K and MAPK pathway. Another principal regulator of CA transcription is HIF1α [21]. The inhibition of CA IX and CA XII protein expression might result from decrease in HIF1α binding to HRE (hypoxia responsive element) present in CA promoter and thereby inhibiting CA transcription.

## 3. Conclusion

The impaired removal of $CO_2$ during increased metabolic production and accumulation of lactic acid can result in a highly acidic microenvironment. Adaptation of tumor cells to this acidic environment is important for cancer cell survival. This adoption to acidic environment is being coordinated by increased expression of CA specifically CA IX and CA XII. Both of them are known to express highly in numerous cancer types. CA IX is a biomarker for poor clinical outcome. CA is an important target for anticancer drug discovery. Most of biochemical data point to targeting CA IX by developing small molecule inhibitors. These inhibitors inhibit tumor-associated CA IX for hypoxic tumors. Targeting CA would provide therapeutic agents that might alter the extracellular acidification induced by CA IX and CA XII. Many small molecule inhibitors of CA IX have been developed and pharmalogical evaluation is still going on. This study demonstrates that this new derivative of sulphonamide inhibits cellular proliferation of colon cancer cells. This inhibitor also demonstrates its specificity by targeting CA IX and CA XII protein expression not all the CAs like CAI and CA II. In this regard CA IX and CA XII specific inhibitors, such as **3c** would provide greater selectivity. This inhibition in CA expression might be at the transcription level by involving HIF1α as well as by blocking PI3K and MAPK pathway. This compound may be developed for treating colon tumor or other solid tumor which are overexpressing CA IX and CA XII. This new derivative of

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