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Original article

Synthesis and in vitro antitumor activity of novel series 2-benzylthio-4-chlorobenzenesulfonamide derivatives

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Abstract

Three series of novel 2-benzylthio-4-chloro-5-R^1-benzenesulfonamides bearing the *N*-(benzoxazol-2-yl) (**10**–**19**), *N*-(benzothiazol-2-yl) (**20**–**21**) or *N*-(1,3-dihydro-2*H*-benzimidazol-2-ylidene) (**22**–**25**) moiety were synthesized by reacting *N*-(2-benzylthio-4-chloro-5-R^1-benzenesulfonyl) cyanamide potassium salts (**5**–**9**) with 2-aminophenols, 2-aminothiophenol and *o*-phenylenediamines, respectively. Compounds with carbamoyl substituent at position 5 (**14**–**16**, **21** and **25**, $R^1 = CONH_2$) were further dehydrated to the corresponding nitriles (**26**–**30**, $R^1 = CN$). The in vitro antitumor activity of the compounds obtained was determined at the National Cancer Institute (NCI), and the structure–activity relationships were discussed. *N*-(2-benzoxazolyl)-2-benzylthio-4-chloro-5-(4-fluorophenylcarbamoyl)benzenesulfonamide (**18**) is the prominent of the compounds due to its remarkable activity and selectivity toward non-small cell lung cancer (NCI-H522) and melanoma (SK-MEL-2) cell lines (GI_{50} = 0.1 μM, TGI = 0.5–0.6 μM).

Keywords: 2-Benzylthio-4-chlorobenzenesulfonamides; Benzoxazoles; Benzothiazoles; Benzimidazoles; Synthesis; Antitumor effect

1. Introduction

Various arylsulfonamides have been reported to possess anticancer [1–6] or/and anti-HIV [2–4,7] properties. Although they have a common structural motif of aromatic sulfonamide, there are a variety of mechanisms of their antitumor action. Indeed, for many of them the target is well known and the anticancer activity understood in great details, but in some other cases, particularly for very new types of leads, the molecular mechanism by which the antitumor activity is achieved are far less clear at this moment. Interestingly, one of the first sulfonamide to be recognized as antitumor agent was 4-amino-*N*-(5-chloroquinoxalin-2-yl)benzenesulfonamide (**CQS**) (Fig. 1), which demonstrates inhibition of colony formation against a variety of human solid tumors such as breast, lung, melanoma and ovarian carcinomas, and causes cell cycle arrest in the G0/G1 phase [8–10].

As a part of our research program aimed at search for new 2-mercaptobenzenesulfonamides as antitumor agents, we have previously reported the syntheses of variously substituted arylsulfonylaminoguanidine derivatives of type **I** [11], **II** [12] or **III** [13] (Fig. 1), and found that these compounds caused considerable growth inhibition on different human tumor cell lines. Recently, we have also found that *S*,*N*-disubstituted 4-chloro-2-mercaptobenzenesulfonamides of type **IV** (Fig. 1) exhibited anticancer properties [14]. These findings prompted us to synthesize a new series of sulfonamides such as **V** and **VI** depicted in Fig. 1.

Several methods for the synthesis of *N*-(2-benzoxazolyl)-, *N*-(2-benzothiazolyl)- or *N*-(1*H*-benzimidazol-2-yl)benzenesulfonamides are known. The simplest method employs the condensation of an arylsulfonyl chloride with benzothiazol-2-ylamine [15] or 1*H*-benzimidazol-2-ylamine [16]. A further method involves the reaction of either *N*-benzenesulfonyldithiocarbonimidic acid dimethyl esters [17] or benzenesulfonyl-carbonimidic acid dichlorides [18,19] with 2-aminophenol, 2-aminothiophenol or *o*-phenylenediamine, respectively. To our experience however, such 2-mercapto-benzenesulfonyl

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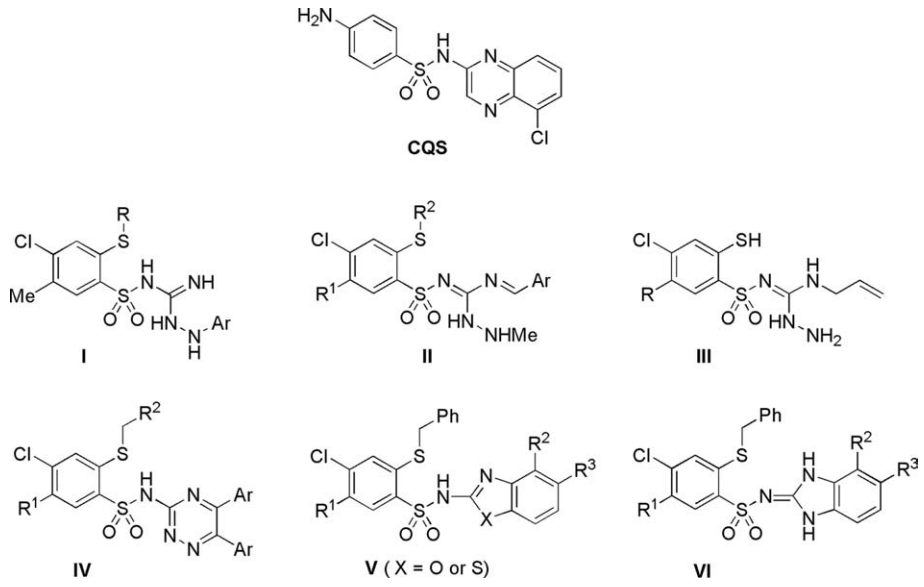


Fig. 1.

starting analogues are not attainable, due to formation of an intractable mixture of products.

2. Results and discussion

2.1. Chemistry

The starting 3-methylthiobenzodithiazines **1** [20], **2** [21] and *N*-(benzenesulfonyl)cyanamide potassium salts **5** [22], **6** and **7** [14] were prepared according to the known methods. Analogously were prepared the novel substrates **3** and **4**, and the corresponding *N*-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)cyanamide potassium salts **8** and **9** (Scheme 1).

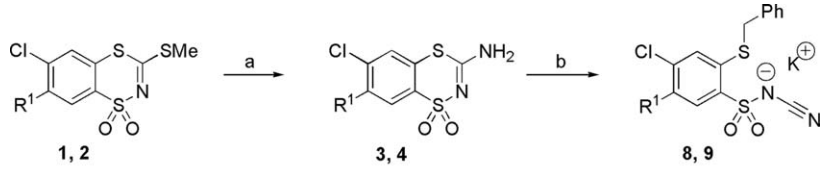
The desired *N*-(2-benzoxazolyl or 2-benzothiazolyl)-2-benzylthio-4-chlorobenzenesulfonamides (**10**–**21**) were obtained by reacting 2-aminophenols or 2-aminothiophenol with *N*-(2-benzylthio-4-chlorobenzenesulfonyl)cyanamide potassium salts (**5**–**9**) in boiling glacial acetic acid, as shown in Scheme 2. An analogous reaction of the corresponding *o*-phenylenediamines with **5** or **6** led to the formation of 2-benzylthio-4-chloro-*N*-(1,3-dihydro-2*H*-benzimidazol-2-ylidene) benzenesulfonamides (**22**–**25**). The amide compounds (**14**–**16**, **21** and **25**) were further dehydrated with phosphorus oxychloride to the target nitriles **26**–**30** in 55–75% yield (Scheme 2).

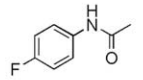
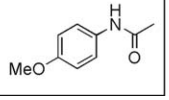
In order to shed light into the course of the reaction of **5** with dinucleophilic *o*-aminophenols, we attempted to isolate intermediates initially formed. Thus, when the reaction of **5** with 2-aminophenol was interrupted after 0.5 h, the corresponding guanidine derivative **31** was separated from the reaction mixture in 37% yield as depicted in Scheme 2. This compound was then transformed into the final benzoxazole **10** by further heating in boiling glacial acetic acid for 3 h (Scheme 2).

All the final products were characterized by IR and ^{1}H NMR spectroscopy as shown in Section 4. Elemental analyses were in accordance with the proposed structure.

2.2. Biology

Compounds **10**, **11**, **14**, **15**, **17**, **18**, **20**–**27**, **29**–**31** were submitted to the US National Cancer Institute (NCI; Bethesda,



Compds	1, 3, 8	2, 4, 9
R^1		

Scheme 1. Synthesis of *N*-(2-benzylthio-4-chloro-5-phenylcarbamoylbenzenesulfonyl)cyanamide potassium salts (**8**, **9**). Reagents, conditions and yields: (a) 25% NH_4OH/EtOH (1.1 molar equiv.), r.t. 24 h, 65–76%; (b) anhydrous K_2CO_3 (excess), $PhCH_2Cl$ (1.1 molar equiv.), dry THF, reflux 20 h, 68–73%.