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Research paper

Novel 2-benzylthio-5-(1,3,4-oxadiazol-2-yl)benzenesulfonamides with anticancer activity: Synthesis, QSAR study, and metabolic stability

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ABSTRACT

A series of novel 2-benzylthio-4-chloro-5-(5-substituted 1,3,4-oxadiazol-2-yl)benzenesulfonamides (**4**–**27**) have been synthesized as potential anticancer agents. MTT assay was carried out to determine the cytotoxic activity against three human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7 and cervical cancer HeLa as well as to determine the influence on human keratinocyte cell line HaCaT. Relatively high (IC_{50}: 7–17 μM) cytostatic activity and selectivity against HeLa cell line was found for compounds **6, 7, 9**–**11** and **16.** While compounds **23**–**27** bearing styryl moieties attached to a 1,3,4-oxadiazole ring at position 5, exhibited significant activity against two and/or three cancer cell lines with IC_{50}: 11–29 μM. Further quantitative structure-activity relationships based on molecular descriptors calculated by DRAGON software, were investigated by Orthogonal Projections to Latent Structures (OPLS) technique and Variable Influence on Projection (VIP) analysis. Considering molecular descriptors with the highest influence on projection (highest VIP values) lipophilicity of tested compounds was pointed as main factor affecting activity towards HCT-116 cell line, while structural parameters associated with presence of styryl substituent in position 5 of 1,3,4-oxadiazole ring were identified as essential for activity towards MCF-7 breast cancer. *In vitro* tests for metabolic stability in the presences of pooled human liver microsomes and NADPH showed that some of the most active compounds **26** and **27** presented favorable metabolic stability with $t_{1/2}$ in the range of 28.1–36.0 min.

1. Introduction

Neoplastic disease are a leading cause of death worldwide and a number of new cases of tumor is steadily rising. The most common method for cancer treatment is chemotherapy however, it is becoming ineffective because of tumor multidrug resistance. Thus, the search for new anticancer agents is the issue of great urgency [1].

Sulfonamides were introduced to medicine in the 30-ies of the twentieth century as antibacterial drugs. Since then, their therapeutic importance has increased and today we know that they have a number of other important biological properties including anti HIV activity [2,3], inhibition of cysteine proteases or γ-secretase involved in Alzheimer's disease [4,5], antifilarial activity [6], antimicrobial activity [7], T-type calcium channel blockers as neuropathic pain drug candidates [8] and also antitumor activity [9–22]. The most important sulfonamides (Fig. 1) which are regarded as new, effective anticancer drugs characterized by novel mechanism of action, are indisulam - a novel cell cycle inhibitor that block cell cycle progression at multiple points, although its target remains unclear, GSK 2126458 - selective inhibitor of the serine-threonine kinase (PI3K), SLC-0111 - selective inhibitor of hCA IX, and KCN1

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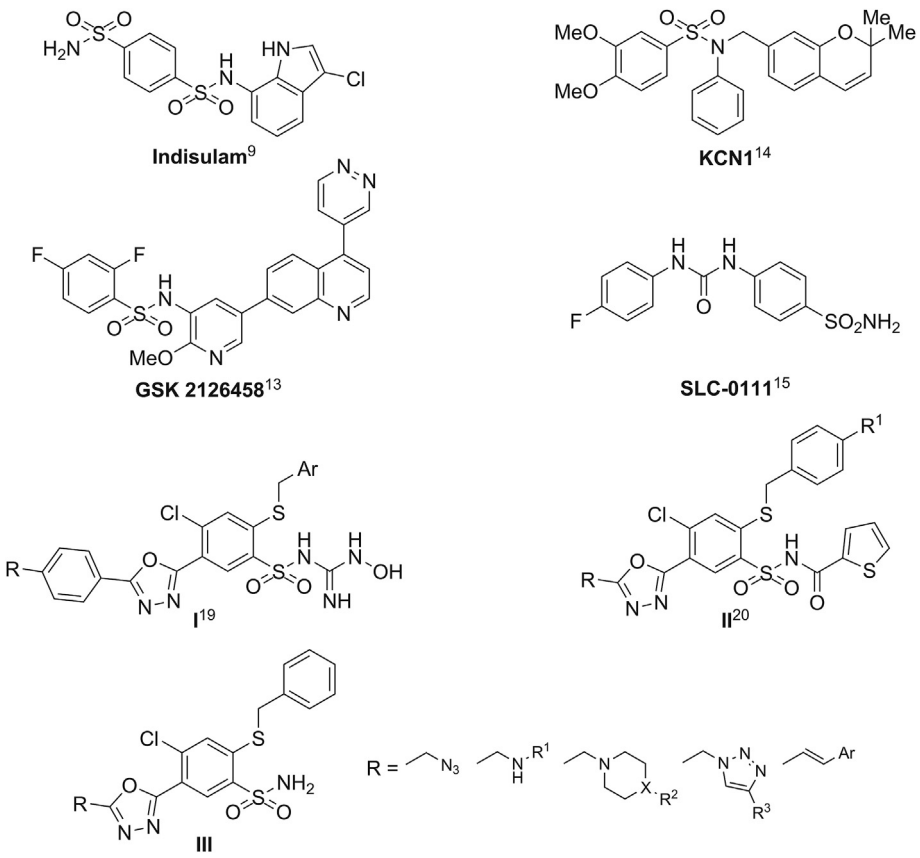

Fig. 1. Structures of benzenesulfonamides with anticancer activity [9,13–15,19,20].

which displays anti-HIF-1 pathway activity.

Our previous research for sulfonamide chemotherapeutics have revealed the significant anticancer activity of a series of benzenesulfonamides (**I, II** Fig. 1) among which we have reported some derivatives containing 1,3,4-oxadiazole moiety [19,20]. This heterocyclic ring have been found to possess considerable biological activities including antimicrobial [23], antiviral [24], anti-inflammatory [25] and anticancer activity [26,27]. The level of interest in oxadiazole ring as pharmacophore fragment is not only due to biological activity but also to their structural and electronic properties. For example, this scaffold can be used as a fragment favorably contributing to ligand binding [28] or act as a flat, aromatic linker to modulate molecule's shape by placing the substituents in the favorable orientation or positioning them in the periphery of molecule [29,30].

A continuation of above mentioned studies for new 2-mercaptobenzenesulfonamides with the ability to inhibit the growth of cancer cells has led us for novel low-molecular weight compounds of type **III** (Fig. 1) containing 1,3,4-oxadiazole ring as a modulator of cytostatic properties with promising *in vitro* anticancer activity. The results of these research we presented herein.

2. Results and discussion

2.1. Chemistry

The desired compounds possessing varied 5-substituted-1,3,4-oxadiazole ring in position 5 of benzenesulfonamide scaffold were obtained in multistep reactions, as shown in Schemes 1–3, starting from 2,4-dichloro-5-(carbazoyl)benzenesulfonamide **1** which synthesis was described previously [17]. In the first step, treatment of **1** with phenylmethanethiol and tetra-*n*-butylammonium iodide (TBAI) as phase transfer catalyst in acetonitrile at room temp. resulted in selective substitution of chlorine atom in position 2 of benzene ring to afford 2-benzylthio-4-chloro-5-(carbazoyl) benzenesulfonamide **2**. The main intermediate: 2-benzylthio-4-chloro-5-[5-(chloromethyl)-1,3,4-oxadiazol-2-yl]benzenesulfonamide **3** was obtained by condensation of hydrazide **2** with triethyl orthochloroacetate in boiling 1,4-dioxane. Subsequent nucleophilic substitution of aliphatic chlorine atom of **3** with appropriate secondary amines such as morpholine, piperidine or piperazine in ethanol led to the compounds **4**–**11** (Scheme 1).

Furthermore refluxing of **3** with sodium azide in acetonitrile yielded 5-[5-(azidomethyl)-1,3,4-oxadiazol-2-yl]-2-benzylthio-4-chlorobenzenesulfonamide **12** which was suitable substrate for introduction of 1,2,3-triazole ring (**13**–**17**) or amino moiety (**18**–**21**) (Scheme 2). Applying the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reactions on azide **12** and appropriate terminal alkynes led to the formation of 5-{[(4-R^2-1*H*-1,2,3-triazol-1-yl)methyl]-1,3,4-oxadiazol-2-yl}benzenesulfonamides **13**–**17**. On the other hand reducing of **12** with triphenylphosphine (Staudinger reaction) gave primary amine **18**, which could be further acylated with benzoyl chloride (**19**) or sulfonylated with 4-chlorobenzenesulfonic chloride (**20**). Also aza-Wittig reaction performed on **12** followed by reduction of intermediate imine furnished 2-benzylthio-4-chloro-5-{5-[(4-chlorobenzyl) aminomethyl]-1,3,4-oxadiazol-2-yl}benzenesulfonamide hydrochloride **21** (Scheme 2).

To obtain a series of 5-(R^4-styryl)-1,3,4-oxadiazoles **23**–**27** the Wittig reaction was applied. Thus, compound **3** was transformed into triphenylphosphonium chloride **22,** by refluxing with triphenylphosphine in acetonitrile, and then reacted with substituted