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Short communication

Synthesis and *in vitro* antiproliferative activity of new 1,3,4-oxadiazole derivatives possessing sulfonamide moiety

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ABSTRACT

Synthesis of a new series of 1,3,4-oxadiazole derivatives possessing sulfonamide moiety is described. Their *in vitro* antiproliferative activities against NCI-58 human cancer cell lines of nine different cancer types were tested. Compound **1k** with *p*-methoxybenzenesulfonamido moiety showed the highest mean %inhibition value over the 58 cell line panel at 10 μM concentration. It showed broad-spectrum antiproliferative activity over many cell lines of different cancer types. For instance, compound **1k** inhibited the growth of T-47D breast cancer cell line by 90.47% at 10 μM. And it inhibited growth of SR leukemia, SK-MEL-5 melanoma, and MDA-MB-468 breast cancer cell lines by more than 80% at the same test concentration. Compound **1k** showed superior activity than Paclitaxel and Gefitinib against the most sensitive cell lines.

1. Introduction

Cancer is a collection of different life-threatening diseases characterized by uncontrolled growth of cells, leading to invasion of surrounding tissue and often metastasizing to other parts of the body. According to the statistics, cancer is the second most common cause of death worldwide after cardiovascular diseases [http://www.cdc.gov/nchs/fastats/lcod.htm]. Despite the availability of improved drugs including targeted cancer therapies, the worldwide cancer burden is expected to increase by as much as 15 million new cancer cases per year by 2020, according to the World Health Organization (WHO), unless further preventive measures are put into practice [1,2]. The development of new anticancer drugs represents a major interest and challenge to the contemporary medicinal chemistry.

Much attention has been paid to the chemistry and biological activities of 1,3,4-oxadiazole nucleus. Several compounds possessing 1,3,4-oxadiazole scaffold have been recently reported as potential antiproliferative agents [3–11]. Apart from anticancer activity, other biological activities have been reported for 1,3,4-oxadiazole derivatives such as antidiabetic [12], antitubercular [13], antifungal [14], antiinflammatory [15], and antibacterial activities [16]. Furthermore, many sulfonamide derivatives have been highlighted as anticancer agents [17–22].

In the present study, we report synthesis of a new series of 1,3,4-oxadiazole derivatives possessing terminal sulfonamide moiety. Their *in vitro* antiproliferative activities against NCI-58 cancer cell line panel are reported.

2. Results and discussion

2.1. Chemistry

Synthesis of the target compounds **1a**–**q** was achieved through the pathway illustrated in Scheme 1. Refluxing the benzoate esters **2a**–**c** with hydrazine monohydrate in ethanol afforded the corresponding benzohydrazide derivatives **3a**–**c** [23]. Cyclization to 2-(chloromethyl)-5-aryl-1,3,4-oxadiazole analogs **4a**–**c** was carried out through refluxing the hydrazides **3a**–**c** with chloroacetic acid in phosphorus oxychloride [24]. Nucleophilic substitution of chloro group of compounds **4a**–**c** with 2-fluoro-4-nitrophenol was done by reflux in acetonitrile in the presence of potassium carbonate to

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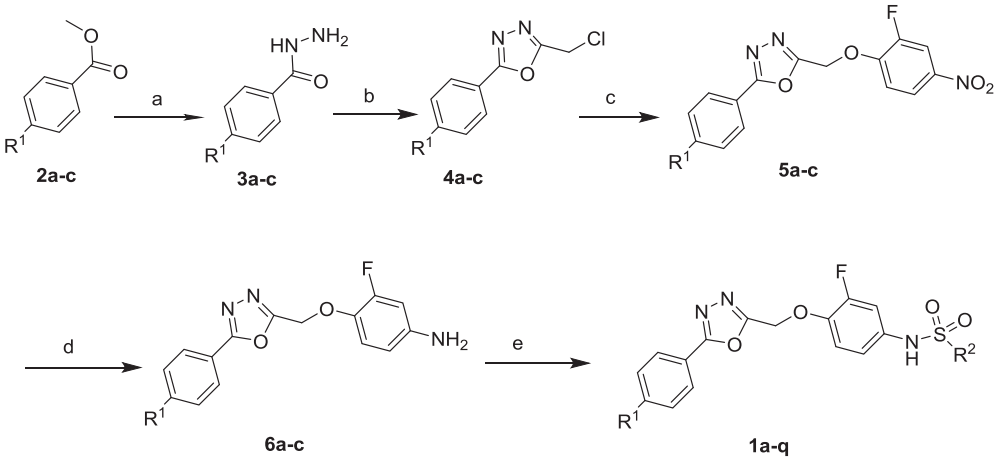


2-6: **a**: R^1 = H; **b**: R^1 = Cl; **c**: R^1 = OCH_3
1a-f: R^1 = H; **1g-k**: R^1 = Cl; **1l-q**: R^1 = OCH_3
R^2 = CH_3, *n*-Pr, C_6H_5, 4-Cl(C_6H_4), 4-Tolyl, and 4-MeO(C_6H_4)

Scheme 1. Reagents and conditions: a) hydrazine monohydrate, EtOH, reflux, overnight; b) $ClCH_2COOH$, $POCl_3$, reflux, 6 h; c) 2-fluoro-4-nitrophenol, K_2CO_3, acetonitrile, reflux, 36 h; d) Raney Ni, H_2, THF, rt, 24 h; e) alkyl or aryl sulfonyl chloride, C_5H_5N, CH_2Cl_2, rt, overnight.

obtain the ether derivatives **5a**–**c**. The nitro group of compounds **5a**–**c** was reduced to amino using Raney Nickel in hydrogen atmosphere. Treatment of the aniline derivatives **6a**–**c** with the appropriate alkyl or aryl sulfonyl chloride derivatives in presence of pyridine as a base afforded the target sulfonamide derivatives **1a**–**q**.

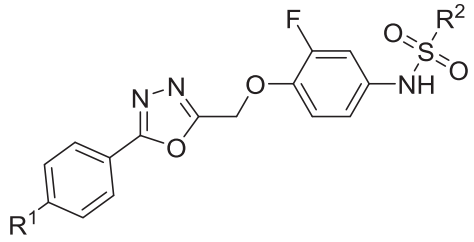
2.2. In vitro antiproliferative activity

Structures of the synthesized target compounds were submitted to National Cancer Institute (NCI), Bethesda, Maryland, USA [25], and the thirteen compounds shown in Table 2 were selected on the basis of degree of structural variation and computer modeling techniques for evaluation of their antineoplastic activity. The selected compounds were subjected to *in vitro* anticancer assay against tumor cells in a full panel of 58 cell lines taken from nine different tissues (blood, lung, colon, CNS, skin, ovary, kidney, prostate, and breast). The compounds were tested at a single-dose concentration of 10 μM, and the percentages of growth inhibition over the 58 tested cell lines were determined. The mean % growth of the NCI-58 cancer cell line panel after treatment with each of the tested compounds is illustrated in Table 1.

Upon comparing the effect of aryl ring directly attached to 1,3,4-oxadiazole ring on activity, it was found that compounds **1m** and **1o** possessing *p*-methoxyphenyl were more active than compounds **1b** and **1d** with phenyl ring. Compounds **1h** and **1k** containing *p*-chlorophenyl showed higher antiproliferative activity than the corresponding *p*-methoxyphenyl analogs **1n** and **1q**. Compound **1g** with *p*-chlorophenyl was more active that the corresponding methoxy derivative **1l**, and **1l** exerted higher activity than **1a** with unsubstituted phenyl ring. So it can be concluded that *p*-chlorophenyl is the most optimum and unsubstituted phenyl is the least optimum for activity of this series of compounds. This can be attributed to steric and/or electronic differences between chloro, methoxy, and hydrogen groups.

The effect of alkyl(aryl)sulfonamide moiety on activity was also investigated. Among aliphatic derivatives, *n*-propylsulfonamido compounds **1b** and **1m** were more active than the corresponding methylsulfonamido analogs **1a** and **1l**. So homologation to a longer chain alkyl group could be favorable for activity, may be due to stronger hydrophobic interaction at the receptor site and/or the increased lipophilicity enhanced penetration into the cancer cells. The influences of aliphatic and aromatic sulfonamido moieties on activity were compared. The aromatic derivatives were found generally more active than aliphatic analogs (compound **1d** more active than **1a** and **1b**), (compounds **1h**, **1j**, and **1k** more active than **1g**), and (compounds **1o**–**q** more active than **1l** and **1m**). Furthermore, substituted phenyl moieties were more optimal for activity than unsubstituted phenyl (compounds **1j** and **1k** were more active than **1h**, and **1o**–**q** showed higher activity than **1n**). The *p*-methoxybenzenesulfonamido compounds **1k** and **1q** exerted superior activity compared to the corresponding *p*-toluenesulfonamido derivatives **1j** and **1p**. This may be rationalized that methoxy

Table 1
Mean %growth of the 58 cancer cell line panel after treatment with the tested target compounds (10 μM concentration).



Compound no.	R^1	R^2	Mean %growth
1a	H	CH_3	100.73
1b	H	*n*-Pr	98.89
1d	H	4-Cl(C_6H_4)	97.14
1g	Cl	CH_3	93.74
1h	Cl	C_6H_5	91.95
1j	Cl	4-Tolyl	84.99
1k	Cl	4-MeO(C_6H_4)	**57.53**
1l	OMe	CH_3	97.56
1m	OMe	*n*-Pr	91.00
1n	OMe	C_6H_5	97.55
1o	OMe	4-Cl(C_6H_4)	73.29
1p	OMe	4-Tolyl	83.27
1q	OMe	4-MeO(C_6H_4)	72.40

The bold figure indicates the most active compound.