New 1,3,4 - oxadiazole derivatives and their role in tumor processes

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Introduction

Cancer is a leading cause of death worldwide, deeply impacting the lives of millions. Concerted efforts have been made in the direction to develop effective molecules for the treatment of the cancer. The greatest interest is involved with 1,3,4-oxadiazoles, as in the last years a large number of compounds with cytotoxicity for several tumor lines have been reported.

Methods

The new 1,3,4-oxadiazole derivatives were obtained by the treatment of aromatic carboxylic acids with different hydrazide derivatives in the presence of phosphorus oxychloride. The cytotoxic effects of the new compounds were studied on two human cancer cell lines, namely, HT-29 (human colorectal adenocarcinoma) and MDA-MB-231 (human breast adenocarcinoma). Cell viability following treatment with compounds and the reference drug (cisplatin or doxorubicin) was determined by MTS assay at 24 and 48 h. The apoptosis processes and the cell cycle play important roles in the molecular pathogenesis of cancer and influence the response of the tumor cells to therapy. The distribution of cell cycle phases in HT-29 or MDA-MB-231 cells treated with Cis-Pt, DOX and oxadiazole derivatives, at concentrations of 10 µM, for 24 h, was assessed by flow cytometry.

Results

A series of new 2,5-diaryl/heteroaryl-1,3,4-oxadiazoles (3a-e) were designed and synthesized (Figure 1). The structure of the new derivatives (Table I) was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopic methods and elemental analyses.

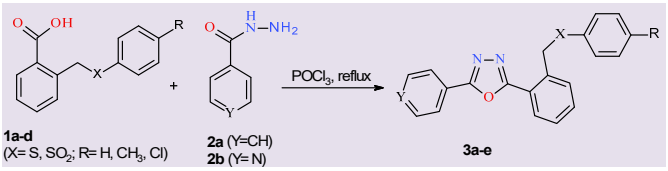

Figure 1. Synthesis of the 1,3,4-oxadiazole derivatives 3a-e

Compound	X	Y	R	Mol. Formula	M.p. (°C)	Yield %
3a	S	CH	H	$C_{21}H_{16}N_2OS$	111-112	69
3b	S	CH	CH_3	$C_{22}H_{18}N_2OS$	116-117	68
3c	S	CH	Cl	$C_{21}H_{15}ClN_2OS$	126-128	60
3d	SO_2	CH	H	$C_{21}H_{16}N_2O_3S$	195-196	59
3e	S	N	H	$C_{20}H_{15}N_3OS$	130-132	70

Table I. Characterization data of the new compounds

In the HT-29 cell line (Fig. 2), the tested compounds reduce viability in a similar way, regardless of the concentration, and in the MDA-MB231 line (Fig. 3), cell viability is affected when the compounds are used in a higher concentration (50 µM) and the chemical structure has a greater impact, with compound 3e having the strongest effect.

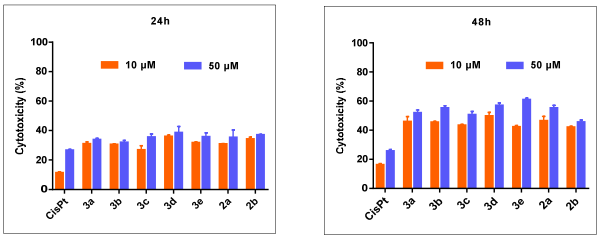

Figure 2. Anti-tumor effect of compounds against HT-29 colon cancer cells. Cells lysis was induced by treatment using two concentrations 10 µM or 50 µM for 24 h and 48 h. Untreated cells were considered to have 100% viability

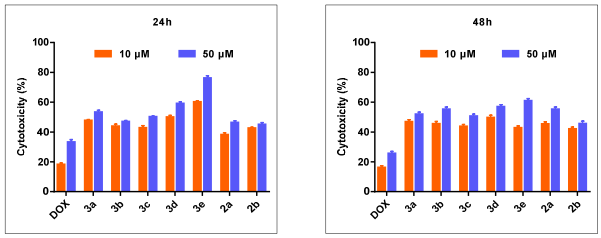

Figure 3. Anti-tumor effect of compounds against MDA-MB-231 breast cancer cells. Cells lysis was induced by treatment using two concentrations 10 µM or 50 µM for 24 h and 48 h. Untreated cells were considered to have 100% viability

Apoptotic cells were determined by flow cytometry using Annexin V-FITC/PI double labeling. The live cell population and the cells undergoing early apoptosis (Annexin+/PI−), late apoptosis (Annexin+/PI+) and necrosis (Annexin−/PI+) were quantified (Table II). Treatment of HT-29 cells for 24 h with 10 µM of compounds 3a-e increased the total apoptosis in the range of 9.4 - 51.2 %, compared to the untreated cells (control, 5.9 %). The new oxadiazole compounds had greater effects on the MDA-MB-231 cells compared to those observed on HT-29 cells, with total apoptosis percent's in the range of 45.2 - 62.7 %. All compounds had close to 3 folds stronger effects as those of the positive control. The observed structure activity relationships are similar, but the impact of the structural transformation is smaller. The compound 3e determined the greatest effect in the oxadiazoles series, but smaller when compared with its precursor hydrazide 2b (Fig. 4).

After the treatment of HT-29 cells for 24 h with the studied compounds, the oxadiazoles 3a-d didn't alter significantly the proportion of G0/G1 phase cells compared to untreated cells, while increasing the number of S phase cells. Compound 3e caused a different effect augmenting the G0/G1 phase accompanied by a decrease in the S phase. In flow cytometry analysis on the cell cycle of the MDA-MB-231 tumor cells, the analyzed compounds determined the arrest of cells in the G0/G1 phase accompanied by a decrease in the S and G2+M phases. The compound 3e had the greatest impact of the oxadiazoles series increasing the number of cells in G0/G1 and significantly reducing those in the S phase (Fig. 5).

	HT-29 cells			MDA-MB-231 cells		
	Early Apoptosis (%)	Late Apoptosis (%)	Total Apoptosis (%)	Early Apoptosis (%)	Late Apoptosis (%)	Total Apoptosis (%)
Control	4.8	1.1	5.9	4.2	0.5	4.7
CisPt	16.5	4.2	20.7	-	-	-
DOX	-	-	-	11.4	2.3	13.7
3a	23.5	2.2	25.7	41.7	8.0	49.7
3b	21.7	4.8	26.5	40.5	4.7	45.2
3c	6.4	3.0	9.4	40.8	5.0	45.8
3d	16.5	2.7	19.2	44.3	6.6	50.9
3e	43.9	7.3	51.2	51.8	10.9	62.7
2a	53.0	12.7	65.7	45.9	12.9	58.8
2b	44.8	6.8	51.6	55.5	17.3	72.8

Table II. Apoptosis of HT-29 and MDA-MB-231 cells induced by 24 h treatment with the tested compounds or CisPt / DOX

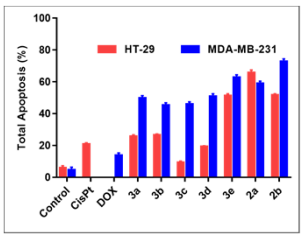

Figure 4. The tested compounds effects on cells' apoptosis. The cells were treated with the test compounds at 10 µM for 24 h. The effects on HT-29 cells can be observed compared to cisplatin (CisPt) and the effects on MDA-MB-231 cells are reported to doxorubicin (DOX)

	HT-29 cells			MDA-MB-231 cells		
	G0/G1 (%)	S (%)	G2+M (%)	G0/G1 (%)	S (%)	G2+M (%)
Control	54.0	21.2	24.8	68.9	5.1	26.0
CisPt	21.2	43.5	35.3	-	-	-
DOX	-	-	-	13.7	42.4	43.9
3a	47.5	29.1	23.4	58.4	20.3	21.3
3b	53.5	39.3	7.2	55.2	27.9	16.9
3c	50.7	19.3	30.0	62.0	33.6	4.4
3d	62.0	29.8	8.2	51.8	29.5	18.7
3e	76.2	15.7	8.1	61.6	30.4	8.0
2a	76.3	15.7	8.0	49.3	24.4	26.3
2b	58.4	13.6	28.0	59.8	29.8	10.4

Figure 5. The tested compounds' effects on cell cycle phases. The cells were treated with the test compounds at 10 µM for 24 h. The effects on HT-29 cells can be observed compared to cisplatin (CisPt) and the effects on MDA-MB-231 cells are reported to doxorubicin (DOX)

Conclusions

The analysis of the results shows that the compound with pyridine ring (3e) presented the best antitumor profile of the series, probably due to the presence of the pyridine ring next to the oxadiazole structure, acting differently on the two tumor cell lines. The obtained results support the antitumor effect of the analyzed compounds and encourage the extension of the study on other tumor cells in order to improve the anticancer activity and reduce the toxicological risks of the obtained compounds.

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