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INTRODUCTION

Recent studies confirmed that 1,3-thiazolidin-5-yl derivatives may possess broad cytotoxic effects [4-8]. The group of new compounds with a skeleton structure of 1,3-thiazolidin-5-yl has been obtained, using three different heterocyclic scaffolds. The chosen synthesis method is depicted in Scheme 1. Structures were confirmed by NMR.

(2Z)-4-oxo-3-phenyl-2-[(1H-1,2,4-thiazol-3-yl)imino]-1,3-thiazolidin-5-ylacetic acid

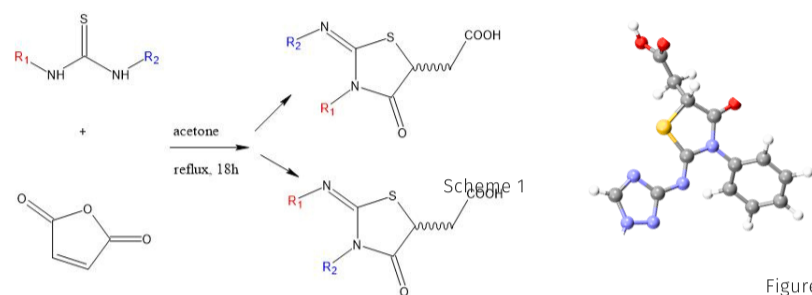


Figure 1

CYTOTOXICITY

Afterward, preliminary anticancer tests were conducted with the usage of the MTT method to establish IC₅₀ (μM) values. All 23 synthesized derivatives were screened for their in vitro cytotoxic properties towards a panel of cancer and normal cell lines. The best candidates were transferred for cell cycle arrest, apoptosis and human interleukin 6 (IL-6) to establish their mechanism of action.

Tabela 1. Cytotoxic activity of studied compounds estimated by MTT assay.^a

Compound	Cancer Cells				Normal Cells		
	A549 ^d		SW620 ^e		MDA ^f		HaCaT ^g
	IC ₅₀ ^b	SI ^c	IC ₅₀ ^b	SI ^c	IC ₅₀ ^b	SI ^c	IC ₅₀ ^b
TSDS 5	-	-	-	-	20,95 ± 0,29	6,98	146,5 ± 2,47
TSDS 7	43,57 ± 2,74	1,93	21,89 ± 1,61	5,10	38,38 ± 0,95	2,90	111,6 ± 5,93
TSDS 20	-	-	31,57 ± 2,74	0,68	-	-	20,15 ± 11,048
Ref ^h	0,63 ± 0,20	0,46	0,26 ± 0,10	1,11	1,83 ± 0,10	0,16	0,29 ± 0,1

^aThe MTT assay is a colorimetric assay for measuring cell metabolic activity. It is based on the ability of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cellular oxidoreductase enzymes to reduce the tetrazolium dye MTT to its insoluble formazan, which has a purple color. Data are expressed as mean SD, IC₅₀ (μM)—the concentration of the compound that corresponds to a 50% growth inhibition of cell line (as compared to the control) after the cells were cultured for 72 h with the individual compound. ^cThe SI (Selectivity Index) was calculated using formula: SI = IC₅₀ for normal cell line/IC₅₀ cancer cell line. ^dHuman lung cancer (A549), ^eHuman metastatic colon cancer (SW620), ^fHuman breast cancer (MDA) ^gHuman immortal keratinocyte cell line from adult human skin (HaCaT). ^hThe selected reference compound commonly used in cancer treatment (Doxorubicin).

STRUCTURAL EVALUATION AND PRELIMINARY ANTI TUMOR STUDIES OF NEWLY SYNTHESIZED 5-(FLUOROPHENYL)-1,3,4-OXADIAZOL-2-AMINE DERIVATIVES.

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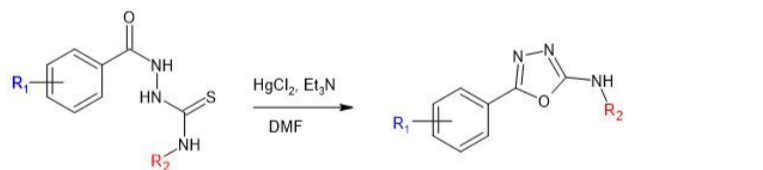
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INTRODUCTION

Core structures were chosen based on experience gained in working with similar heterocyclic derivatives in previous research [1-2] and scientific reports showing their cytotoxic potential. Final derivatives were synthesized via desulfurization-cyclization of suitable thiosemicarbazides (Scheme 1) [1,3]. Structures were investigated using NMR techniques, and X-Ray analysis.



Scheme 1

MOLECULAR STRUCTURE

X-ray diffraction experiment was performed for 5-(4-fluorophenyl)-N-(2,4,6-trichlorophenyl)-1,3,4-oxadiazol-2-amine. The analyzed derivative (Fig 1.) crystallizes in the monoclinic system, space group P2₁/n, with four molecules in the unit cell.

The crystal was positioned 40 mm from the PHOTON II detector with CPAD technology. A total of 3277 frames were measured with exposure time 3.34 hours. Data were collected using the APEX2 program, integrated with the Bruker SAINT software package and corrected for absorption effects using the multi-scan method (SADABS). The structure was solved and refined using the SHELX software package using Least Squares minimization. The atomic scattering factors were taken from the International Tables.

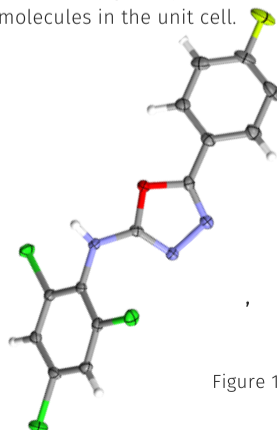


Figure 1

Compound	DSMW18
Empirical formula	C ₁₇ H ₁₁ Cl ₃ N ₃ O ₂ F
Formula weight	358.58
Temperature (K)	130
Space group	P2 ₁ /n
Unit cell dimensions	
a [Å]	7.3557(4)
b [Å]	25.2090(14)
c [Å]	8.2161(5)
α [°]	90
β [°]	110.285(3)
γ [°]	90
Volume V [Å ³]	1429.02(14)
Z (molecules/cell)	4
D _{calc} [g cm ⁻³]	1.667
Absorption coefficient μ _m ²	0.656
θ range for data collection [°]	2.76–25.00
Limiting indices	-8 < h < 8 -29 < k < 29 -9 < l < 9
Reflections collected/unique	41268/2495
Data/parameters	2495/203
Goodness of Fit	1.188
Final R index (I > 2σ)	0.0295
wR ²	0.0642
Largest diff. Peak and hole [Å ⁻¹]	0.272 and -0.205

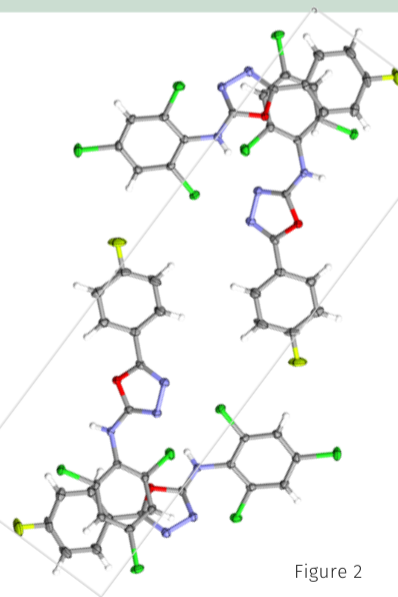


Figure 2

CYTOTOXICITY

Tabela 1. Cytotoxic activity of studied compounds estimated by MTT assay.^a

Compound	Cancer Cells				Normal Cells		
	A549 ^d		SW620 ^e		MDA ^f		HaCaT ^g
	IC ₅₀ ^b	SI ^c	IC ₅₀ ^b	SI ^c	IC ₅₀ ^b	SI ^c	IC ₅₀ ^b
DSMW19	18,43 ± 2,22	0,25	13,31 ± 1,20	0,2	12,68 ± 0,13	0,18	49,74 ± 2,12
DSMW22	17,91 ± 12,15	3,71	0,54 ± 12,13	0,11	1,77 ± 2,68	0,37	4,82 ± 3,15
DSMW23	5,19 ± 7,04	0,34	0,34 ± 7,05	0,02	3,89 ± 5,50	0,25	15,46 ± 0,26
Ref ^h	0,63 ± 0,20	0,46	0,26 ± 0,10	1,11	1,83 ± 0,10	0,16	0,29 ± 0,10

^aThe MTT assay is a colorimetric assay for measuring cell metabolic activity. It is based on the ability of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent cellular oxidoreductase enzymes to reduce the tetrazolium dye MTT to its insoluble formazan, which has a purple color. Data are expressed as mean SD, IC₅₀ (μM)—the concentration of the compound that corresponds to a 50% growth inhibition of cell line (as compared to the control) after the cells were cultured for 72 h with the individual compound. ^cThe SI (Selectivity Index) was calculated using formula: SI = IC₅₀ for normal cell line/IC₅₀ cancer cell line. ^dHuman lung cancer (A549), ^eHuman metastatic colon cancer (SW620), ^fHuman breast cancer (MDA) ^gHuman immortal keratinocyte cell line from adult human skin (HaCaT). ^hThe selected reference compound commonly used in cancer treatment (Doxorubicin).

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