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RESEARCH ARTICLE

Synthesis and anticancer activity of 5-sulfonyl derivatives of 1,3-oxazole-4-carboxylates

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Abstract: A series of new 2-aryl 5-sulfonyl-1,3-oxazole-4-carboxylates for NCI anticancer screening protocol against 60 cancer cell lines were synthesized. Screening was performed *in vitro* on 60 cell lines of lungs, kidneys, CNS, ovaries, prostate, and breast cancer, leukemia, and melanoma. Methyl 5-benzylsulfonyl-2-phenyl-1,3-oxazole-4-carboxylate **15** exhibited potent and broad range of cytotoxic activity against tested human cancer cells with average GI_{50}, TGI, and LC_{50} values of $5.37 \cdot 10^{-6}$, $1.29 \cdot 10^{-5}$ and $3.6 \cdot 10^{-5}$ mol/L respectively. Molecular docking was used to evaluate the possible interaction of compound **15** with tubulin as well as a complex formation with CDK2.

Keywords: 5-sulfonyl-1,3-oxazole-4-carboxylates; synthesis; anticancer activity; selectivity; molecular docking.

Introduction

During the last years, the search for new biologically active compounds, in particular anticancer agents, among 1,3-oxazole-4-carboxylates has stimulated considerable synthetic efforts [1-3]. Oxazoles **I-VIII** containing arylsulfonyl [4] or sulfonamide [5-6] moiety displayed considerable cytotoxicity and selectivity towards diverse cancer subpanels with sub-micromolar GI_{50} values (Figure 1). It has been proposed that possible ways of anticancer influence of sulfonamide derivatives are associated with inhibition of the tubulin polymerization, similar to E7010 [5], DNA damage, BCL6, and NSD2 inhibition [6]. So, previous works [4-6] have focused mostly on 4-cyano-substituted 1,3-oxazoles.

In the present work, we replaced the nitrile with an ester group in oxazole derivatives and synthesized new 5-sulfonyl derivatives of 1,3-oxazole-4-carboxylate, investigated their anticancer screening and elucidated the

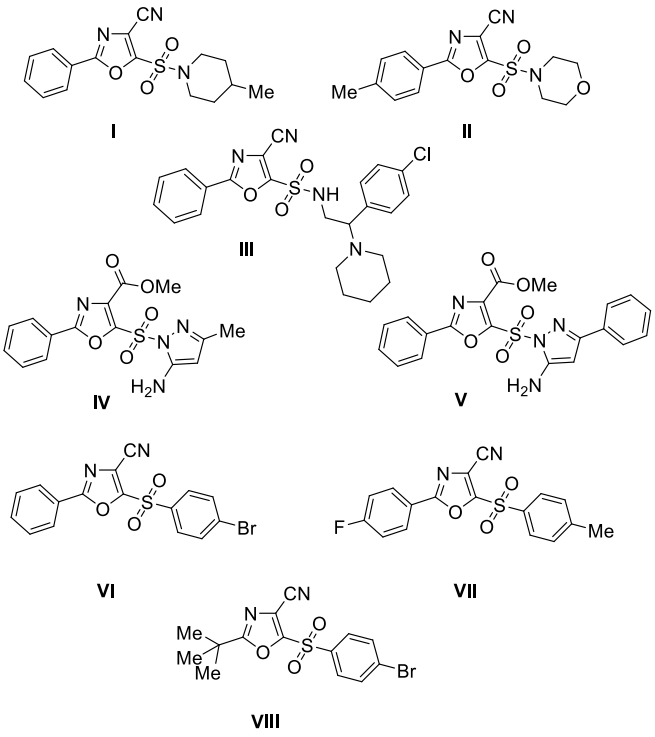

Figure 1. 5-Sulfonyl-substituted 1,3-oxazoles with anticancer activity.

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possible mechanism of their action by molecular docking approaches.

Although the nitrile group is quite robust and, in most cases, is not readily metabolized, there are some confirmed facts of its cleavage and modification leading to increased cytotoxicity [7]. Ester group in comparison with nitrile is less cytotoxic for normal cells and it is perspective moiety for the introduction in 1,3-oxazole-5-sulfonamide pharmacophore for the new anticancer drugs search.

Accordingly, in this study, we report the synthesis, characterization and biological activity of novel molecules combined 2-aryl-1,3-oxazole-4-carboxylate and sulfonamide scaffolds.

Results and Discussion

Chemistry

The synthesis of target compounds was accomplished by the reaction sequence illustrated in Scheme 1 and 2. The previously described in the literature [8] dichloroacrylates **1a,b** were chosen as the starting materials.

1,3-Oxazole-5-sulfonamides **3-12** were prepared from methyl 5-chlorosulfonyl-2-phenyloxazole-4-carboxylate (**2**) by refluxing with appropriate amines [9].

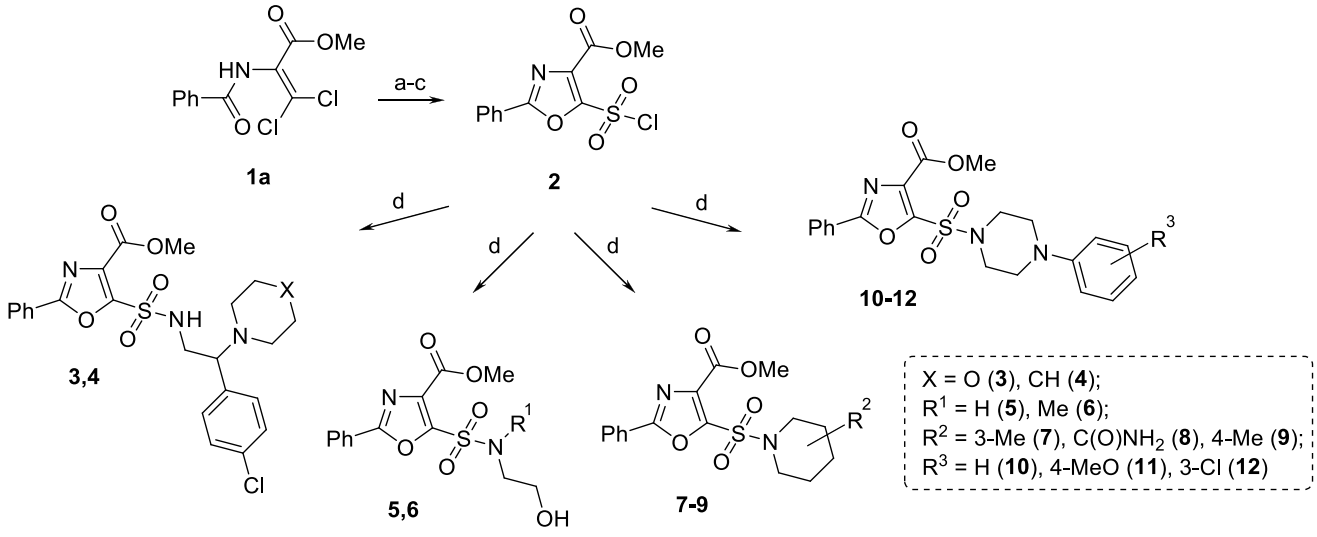
The preparation of arylsulfonyl derivatives **17** and **18** involves the reaction sequences as in Sheme 2. The starting methyl 2-(benzoylamino)-3,3-dichloroacrylate (**1a**) was reacted with sodium sulfide to yield methyl 5-mercapto-2-phenyl-1,3-oxazole-4-carboxylate (**13**), which was converted into methyl 5-(benzylsulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**15**) by alkylation with benzyl chloride and oxidation with hydrogen peroxide [10].

5-((3-Methoxyphenyl)sulfonyl)-2-(4-methylphenyl)-1,3-oxazole-4-carbonitrile (**18**) was synthesized following the transformation sequence **1b** → **16** → **17** → **18** in Sheme 2. Reaction of methyl 3,3-dichloro-2-((4-methylbenzoyl)-amino)acrylate (**1b**) with benzenemethanethiol in the presence of triethylamine yielded methyl 3,3-bis((3-methoxyphenyl)thio)-2-((4-methylbenzoyl)amino)acrylate (**16**), that was cyclized in the presence of silver carbonate to form methyl 5-((3-methoxyphenyl)thio)-2-(4-methyl-phenyl)-1,3-oxazole-4-carboxylate (**17**). The latter was converted into the corresponding sulfonyl derivative **18** by oxidation with hydrogen peroxide [10].

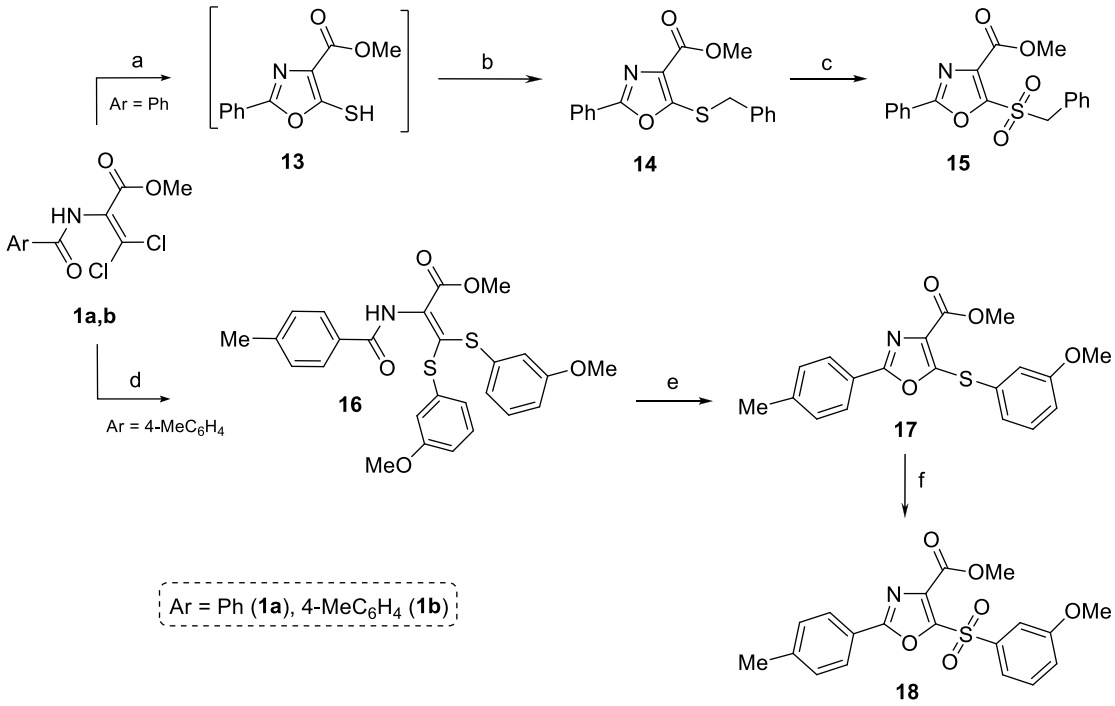
The structure and composition of all obtained compounds **3-12**, **15**, and **18** have been in good agreement with IR, NMR (^{1}H and ^{13}C NMR) spectroscopy, chromato-mass spectrometry (LC-MS), and elemental analysis data. The CH-protons of the methoxy group at the 4th position of the oxazole ring of synthesized compounds appear as a singlet at 3.61-3.93 ppm. All CH_2 and CH-proton signals of sulfamides **3-12** are visible in the ^{1}H NMR spectra. The signal of the OH group of 6 and 7 is located in ^{1}H NMR at 4.80-4.68 ppm. The signal at 8.32 ppm belongs to NH group of compound **3**. The strong absorption bands of SO_2 group appeared at 1152 to 1192 cm^{-1} and 1353 to 1386 cm^{-1} in the IR spectra of all compounds. Also, the broad strong bands at 1731 to 1732 cm^{-1} corresponded to C═O bond of esters.

In vitro evaluation of the anticancer activity

The synthesized 5-sulfonyl-1,3-oxazole-4-carboxylates were screened on human cancer cell lines at the NIH, Bethesda, Maryland, USA, under the drug discovery program of the NCI. Results for each compound were reported as a mean graph of the percent growth (GP%) of the treated cells when compared to the untreated control cells and one-dose screening data are summarized in Table 1.



Scheme 1. Synthesis of 5-sulfamide derivatives of 2-phenyl-1,3-oxazole-4-carboxylate **3-12**. Reagents and conditions: (a) 2.5 eq. NaSH; (b) BnCl; (c) Cl_2, AcOH, H_2O; (d) amine, Et_3N.



Scheme 2. Synthesis of 5-aryl-1,3-oxazole-4-carboxylates **15, 18**. Reagents and conditions: (a) 2.5 eq. Na_2S; HCl; (b) $PhCH_2Cl$, Et_3N; (c) H_2O_2, AcOH; (d) 2 eq. $3\text{-}MeOC_6H_4SH$, 2 eq. Et_3N; (e) 2.5 eq. Ag_2CO_3; (f) H_2O_2, AcOH, reflux.

The synthesized compounds showed differential anticancer activity pattern against different types of cancer and cell lines according to the primary one-dose anticancer assay [11-15]. The most active methyl 5-(benzylsulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**15**) had anticancer activity range from -78.70 to 109.63%. Thus, compound **15** revealed high cytotoxic effect on leukemia CCRF-CEM (GP = -6.08%), MOLT-4 (GP = -9.29%), SR (GP = -11.55%), colon cancer COLO 205 (GP = -42.98%), melanoma MALME-3M (GP = -78.70%), renal cancer ACHN (GP = -35.00%) cell lines.

Since compound **15** possessed a significant anticancer effect against several cell lines, it was tested additionally in the fifth-dose assay (10^{-4}-10^{-8} M) [13, 16] (Table 2). Three dose-dependent values were extrapolated from concentration-response curves for each cell line: GI_{50} – the drug concentration of the compound that inhibited 50% net cell growth; TGI – concentration of tested compound with total cell growth inhibition, LC_{50} – concentration of compound leading to 50% net cell death.

Compound **15** exhibited a potent and broad range of cytotoxic activity against tested human cancer cells with average GI_{50}, TGI, and LC_{50} $5.37\cdot10^{-6}$, $1.29\cdot10^{-5}$, and $3.6\cdot10^{-5}$ mol/L respectively. GI_{50} values were ranged from 1.48 μM (renal cancer UO-31 cell line) to 70.2 μM (ovarian cancer SK-OV-3 cell line), TGI – from 3.12 μM (non-small cell lung cancer NOP-92 cell line) to >100 μM (CNS Cancer SF-395 cell line, and Ovarian cancer SK-OV-3 cell line), and LC50 – from 5.45 μM (renal cancer UO-31 cell line) to >100 μM (leukemia panel, non-small cell lung cancer A549/ATCC cell line, ovarian cancer SK-OV-3, breast cancer MCF7, HS 578T, T-47D).

Table 1. Anticancer NCI one-dose screening data (10^{-5} M) for compounds **3-12**, **15**, **18**

Compd NSC	Mean growth, %	Range of growth, %	Most sensitive cell line growth, %
3 802758	65.66	from -21.00 to 120.90	-21.00 (CCRF-CEM/Leukemia) 4.12 (HL-60(TB)/Leukemia) 13.37 (K-562/Leukemia) 7.96 (MOLT-4/ Leukemia) 7.86 (RPMI-8226/ Leukemia) 1.88 (SR/ Leukemia) 23.78 (NCI-H522/ Non-small cell lung cancer) 18.71 (SW-620 / Colon cancer) 31.67 (MCF7/Breast cancer) 29.94 (MDA-MB-468/ Breast cancer)
4 802759	66.95	from -19.22 to 116.57	-19.22 (CCRF-CEM/Leukemia) 17.47 (HL-60(TB)/Leukemia) 9.15 (K-562/Leukemia) 1.79 (MOLT-4/ Leukemia) 20.02 (RPMI-8226/ Leukemia) -3.58 (SR/ Leukemia) 25.60 (NCI-H522/ Non-small cell lung cancer)
5 802760	93.48	from 67.00 to 136.78	67.00 (SR/ Leukemia) 67.05 (MDA-MB-468/ Breast cancer)
6 802761	65.83	from -24.58 to 112.08	16.16 (CCRF-CEM/Leukemia) -24.58 (HL-60(TB)/Leukemia) 22.17 (K-562/Leukemia) 6.31 (MDA-MB-468/ Breast cancer)

Table 1. (*Contd.*)

Compd NSC	Mean growth, %	Range of growth, %	Most sensitive cell line growth, %
7 802781	72.07	from 0.92 to 110.17	1.21 (CCRF-CEM/Leukemia) 14.99 (HL-60(TB)/Leukemia) 17.71 (K-562/Leukemia) 6.09 (MOLT-4/ Leukemia) 0.92 (SR/ Leukemia) 28.58 (NCI-H522/ Non-small cell lung cancer) 29.19 (MDA-MB-468/ Breast cancer)
8 802782	58.77	from -33.25 to 110.68	-3.72 (CCRF-CEM/Leukemia) -33.25 (HL-60(TB)/Leukemia) 14.77 (K-562/Leukemia) 1.95 (MOLT-4/ Leukemia) -3.16 (SR/ Leukemia) 0.81 (NCI-H522/ Non-small cell lung cancer) 20.64 (COLO 205/Colon cancer) 25.38 (SW-620 / Colon cancer) 16.19 (OVCAR-3/Ovarian cancer) 23.15 (TK-10/Renal cancer) -14.59 (MDA-MB-468/ Breast cancer)
9 802797	69.91	from 12.35 to 113.24	12.35 (CCRF-CEM/Leukemia) 22.72 (K-562/Leukemia) 23.59 (MOLT-4/ Leukemia) 17.56 (NCI-H522/ Non-small cell lung cancer) 38.26 (SW-620 / Colon cancer) 16.19 (OVCAR-3/Ovarian cancer)
10 802783	91.60	from 61.48 to 111.90	61.48 (CCRF-CEM/Leukemia) 62.10 (SR/ Leukemia)
11 802784	72.26	from -11.85 to 121.22	-11.85 (CCRF-CEM/Leukemia) 21.81 (HL-60(TB)/Leukemia) 20.41 (K-562/Leukemia) -1.38 (SR/ Leukemia) 22.65 (MDA-MB-468/ Breast cancer)
12 802796	74.57	from 4.91 to 111.22	4.91 (CCRF-CEM/Leukemia)
15 802778	69.01	from -78.70 to 109.63	-6.08 (CCRF-CEM/Leukemia) 2.87 (K-562/Leukemia) -9.29 (MOLT-4/ Leukemia) -11.55 (SR/ Leukemia) -42.98 (COLO 205/Colon cancer) -78.70 (MALME-3M/ Melanoma) -35.00 (ACHN/ Renal cancer) 5.41 (TK-10/Renal cancer)
18 802780	78.38	from -12.30 to 109.75	-9.09 (CCRF-CEM/Leukemia) 11.58 (K-562/Leukemia) -7.44 (MOLT-4/ Leukemia) 0.69 (SR/ Leukemia) -8.96 (COLO 205/Colon cancer) -12.30 (MALME-3M/ Melanoma)

Table 2. Anticancer NCI five-dose-response parameters for compound **15**.

Panel	Cell line	GI_{50}, M	TGI, M	LC_{50}, M
Leukemia	CCRF-CEM	$2.91 \cdot 10^{-6}$	$8.41 \cdot 10^{-6}$	$>1.00 \cdot 10^{-4}$
	HL-60(TB)	$2.30 \cdot 10^{-6}$	$6.22 \cdot 10^{-6}$	$>1.00 \cdot 10^{-4}$
	K-562	$2.07 \cdot 10^{-6}$	$5.29 \cdot 10^{-6}$	$>1.00 \cdot 10^{-4}$
	MOLT-4	$2.11 \cdot 10^{-6}$	$5.57 \cdot 10^{-6}$	$>1.00 \cdot 10^{-4}$
Non-Small Cell Lung Cancer	HOP-92	$1.61 \cdot 10^{-6}$	$3.12 \cdot 10^{-6}$	$6.06 \cdot 10^{-6}$
	NCI-H522	$1.52 \cdot 10^{-6}$	$3.29 \cdot 10^{-6}$	$7.13 \cdot 10^{-6}$
Colon Cancer	COLO 205	$1.84 \cdot 10^{-6}$	$3.66 \cdot 10^{-6}$	$7.30 \cdot 10^{-6}$
	HCT-116	$2.58 \cdot 10^{-6}$	$6.23 \cdot 10^{-6}$	$2.16 \cdot 10^{-5}$
	HCT-15	$1.79 \cdot 10^{-6}$	$3.58 \cdot 10^{-6}$	$7.15 \cdot 10^{-6}$
	SW-620	$2.05 \cdot 10^{-6}$	$4.14 \cdot 10^{-6}$	$8.33 \cdot 10^{-6}$
Melanoma	MALME-3M	$1.73 \cdot 10^{-6}$	$3.44 \cdot 10^{-6}$	$6.85 \cdot 10^{-6}$
Ovarian Cancer	OVCAR-3	$1.94 \cdot 10^{-6}$	$3.52 \cdot 10^{-6}$	$6.40 \cdot 10^{-6}$
	OVCAR-4	$1.82 \cdot 10^{-6}$	$3.40 \cdot 10^{-6}$	$6.32 \cdot 10^{-6}$
Renal Cancer	ACHN	$1.77 \cdot 10^{-6}$	$3.15 \cdot 10^{-6}$	$5.62 \cdot 10^{-6}$
	CAKI-1	$1.84 \cdot 10^{-6}$	$3.42 \cdot 10^{-6}$	$6.37 \cdot 10^{-6}$
	RXF 393	$1.87 \cdot 10^{-6}$	$3.50 \cdot 10^{-6}$	$6.55 \cdot 10^{-6}$
	TK-10	$1.74 \cdot 10^{-6}$	$3.19 \cdot 10^{-6}$	$5.86 \cdot 10^{-6}$
	UO-31	$1.48 \cdot 10^{-6}$	$2.84 \cdot 10^{-6}$	$5.45 \cdot 10^{-6}$
Breast Cancer	MDA-MB-468	$1.85 \cdot 10^{-6}$	$4.02 \cdot 10^{-6}$	$8.75 \cdot 10^{-6}$
Average values		$5.37 \cdot 10^{-6}$	$1.29 \cdot 10^{-5}$	$3.6 \cdot 10^{-5}$

Previously, anticancer activity of 2-substituted 5-arylsulfonyl-4-cyano-1,3-oxazoles was proposed to be related to the inhibition of tubulin polymerization [5]. Given the interest in microtubule-targeting agents [17], as well as to possible inhibitors of oncogenic signaling pathways [18], two series of molecular docking simulations for the 5-sulfonyl-1,3-oxazole-4-carboxylates were carried out in this paper. The compounds were docked into colchicine binding site of tubulin (PDB code 1SA0 [19]) and ATP-binding sites of cyclin-dependent kinases CDK1, CDK2, CDK7 and CDK9 (PDB codes 4Y72 [20], 3QQJ, 1UA2 [21], 4BCF [22], respectively). The highest affinity of compound **15** was observed towards CDK2.

The molecular docking of 5-benzylsulfonyl derivative of 1,3-oxazole-4-carboxylate **15** into colchicine binding site of αβ-tubulin heterodimer structure showed calculated binding affinity of -8.0 kcal/mol. According to the obtained model (Figure 2A), the 5-(benzylsulfonyl)oxazole fragment of ligand provided electrostatic, van der Waals, and hydrophobic interactions with amino acids residues Val238, Leu248, Leu255, Lys352, and Ile378 of β-tubulin subunit (B chain). The complex exhibited hydrogen bond of methyl acetate moiety of ligand with backbone amino group of Ala250 (B chain). The 5-benzylsulfonyl fragment of the

ligand was located near amino acids residue Asn101, Thr179, Ala180, and Val181, which belong to α-tubulin subunit (A chain).

Binding mode of compound **15** into ATP-binding site of cyclin-dependent kinase 2 with binding affinity -9.2 kcal/mol is shown in Figure 2B. In this model, 5-(benzylsulfonyl)-oxazole fragment of ligand was located in hydrophobic pocket and had electrostatic, Wan der Waals, and hydrophobic interaction with amino acids residues Val18, Ile10, Ala31, Val64, Phe80, Leu83, Leu134, and Ala144 as well as showed π-stacking interaction with Phe82. The sulfonyl group of 5-benzylsulfonyl moiety was adjacent to Gln85, Asp86, and Lys89 residues.

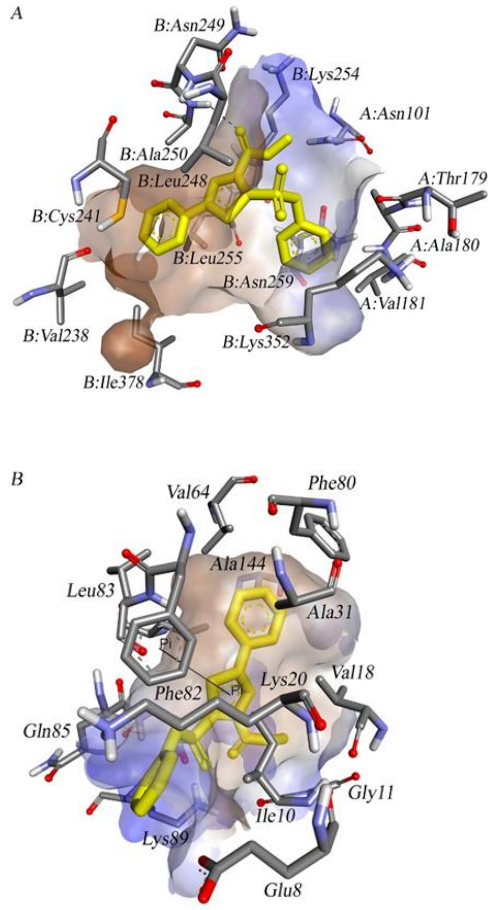


Figure 2. Possible binding modes of 5-benzylsulfonyl derivative of 1,3 oxazole-4-carboxylate **15** into colchicine binding site of tubulin (A) and ATP-binding site of CDK2 (B).

Conclusions

All the reported in this paper substances showed significant inhibitory activity and selectivity over 60 cell lines. Leukemia and non-small cell lung cancer NCI-H522 cell lines were particularly sensitive to all synthesized compounds except **5** and **10**. Colon cancer COLO 205 cell line was sensitive to compounds **15**, **18**, and **8**. Melanoma MALME-3M cell line appeared to be sensitive to compounds **15** and **18**.

The study of the antitumor activity of 5-sulfonyl derivatives of 1,3-oxazole-4-carboxylates towards the NCI 60 human cancer cell lines revealed «leader compound» – methyl 5-benzylsulfonyl-2-phenyl-1,3-oxazole-4-carboxylate (**15**). The Non-Small Cell Lung Cancer, Colon Cancer, Melanoma, Ovarian, Renal and Breast Cancer cell lines showed a significant sensitivity to this compound with sub-micro molar LC_{50} values.

The results of NCI screening make the reported 1,3-oxazole-4-carboxylate derivatives not only interesting for further chemical optimization but also for the elucidation of their mechanism of action. In this regard, molecular docking approaches were used to evaluate the possible interaction between compound **15** and tubulin as well as *in silico* binding to CDK2.

Experimental section

Chemistry

All reagents and solvents used in synthetic procedures were purchased from Aldrich and used as received. Reaction progress was monitored by TLC on Merck Silica gel 60 F_{254} aluminium sheets. Melting points were determined on a Fisher-Johns apparatus. FT-IR (KBr pellet) spectra were performed on a Bruker VERTEX 70 spectrometer and only the most representative frequencies were reported. Absorption bands are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 (500 and 125 MHz, respectively) or Varian Mercury 400 (400 MHz) spectrometers in DMSO-d_6 taking its residual protons signal as a standard. Mass spectra were recorded on an Agilent 1200 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)). Combustion elemental analysis was performed in the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry analytical laboratory, their results were found to be in good agreement (±0.4%) with the calculated values. The carbon and hydrogen contents were determined using the Pregl gravimetric method, nitrogen – using the Duma's gasometrical micromethod, sulfur – by the Scheininger titrimetric method, chlorine – by the mercurometric method.

*General procedure for preparation of compounds (**3**-**12**).*

A mixture of a solution of 0.001 mol of methyl 5-(chlorosulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**2**), 15 ml of anhydrous dioxane, 0.001 mol of the corresponding amine, and 0.001 mol of Et_3N was refluxed for 2 h. Then the mixture was incubated at 20-25 °C during 12 h; the precipitate was filtered off, and the solvent was removed in vacuum. The residue was treated with water, filtered off, dried, and recrystallized.

*Methyl 5-(((2-(4-chlorophenyl)-2-morpholin-4-ylethyl)-amino)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**3**).*

Yield: 0.36 g, 71%; mp 172-174 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H, N*H*), 8.01-7.98 (m, 2H, Ar), 7.64-7.58 (m, 3H, Ar), 7.29-7.25 (m, 2H, Ar),

7.18-7.15 (m, 3H, Ar), 3.88 (s, 3H, OC*H*$_3$), 3.67-3.63 (m, 1H, C*H*), 3.57-3.55 (m, 1H, C*H*), 3.43-3.40 (m, 5H, C*H*, C*H*$_2$), 2.52 (br s, 1H, C*H*), 2.24 (m, 2H, C*H*$_2$), 2.16 (m, 2H, C*H*$_2$). IR (KBr) *v*, 2817, 1718 (C=O), 1552, 1486, 1400, 1342 (SO_2), 1237, 1161, 1113, 1073, 1056, 852, 714, 688. LC/MS (CI) m/z 505.9 $(M+1)^+$. Anal. Calcd. for $C_{23}H_{24}ClN_3O_6S$: C, 54.60; H, 4.78; Cl, 7.01; N, 8.30; S, 6.34. Found: C, 54.58; H, 4.76; Cl, 7.14; N, 8.45; S, 6.52.

*Methyl 5-(((2-(4-chlorophenyl)-2-piperidin-1-ylethyl)-amino)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**4**).*

Yield: 0,37 g, 73%; mp 134-136 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01-7.98 (m, 2H, Ar), 7.65-7.57 (m, 3H, Ar), 7.27-7.24 (m, 2H, Ar), 7.15-7.11 (m, 2H, Ar), 3.87 (s, 3H, OC*H*$_3$), 3.65-3.58 (m, 2H, C*H*$_2$), 2.53 (br s, 1H, C*H*), 2.24 (br s, 2H, C*H*, C*H*$_2$), 2.04 (br s, 2*H*, C*H*$_2$), 1.33 (br s, 4H, C*H*$_2$), 1.15 (br s, 2*H*, C*H*$_2$). IR (KBr) *v*, 3198 (NH), 2935, 2797, 1718 (C=O), 1558, 1490, 1397, 1340 (SO_2), 1245, 1188, 1158, 1069, 820, 714, 689. LC/MS (CI) m/z 504.0 $(M+1)^+$. Anal. Calcd. for $C_{24}H_{26}ClN_3O_5S$: C, 57.19; H, 5.20; Cl, 7.03; N, 8.34; S, 6.36. Found: C, 57.16; H, 5.18; Cl, 7.19; N, 8.45; S, 6.26.

*Methyl 5-(((2-hydroxyethyl)amino)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**5**).*

Yield: 0,25 g, 76%; mp 108-110 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (br s, 1H, N*H*), 8.03-7.99 (m, 2H, Ar), 7.65-7.56 (m, 3H, Ar), 4.71-4.68 (m, 1H, O*H*), 3.86 (s, 3H, C*H*$_3$), 3.43-3.37 (m, 2H, C*H*$_2$), 3.14-3.09 (m, 2H, C*H*$_2$). IR (KBr) *v*, 3538 (OH), 3213 (NH), 2955, 2887, 1726 (C=O), 1556, 1484, 1354, 1338 (SO_2), 1235, 1179, 1153, 1056, 820, 710, 616. LC/MS (CI) m/z 326.3 $(M+1)^+$. Anal. Calcd. for $C_{13}H_{14}N_2O_6S$: C, 47.85; H, 4.32; N, 8.58; S, 9.83. Found: C, 47.82; H, 4.31; N, 8.68; S, 9.93.

*Methyl 5-(((2-hydroxyethyl)(methyl)amino)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**6**).*

Yield: 0,26 g, 75%; mp 119-121 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02-8.01 (m, 2H, Ar), 7.65-7.57 (m, 3H, Ar), 4.80-4.79 (m, 1H, O*H*), 3.87 (s, 3H, OC*H*$_3$), 3.54-3.53 (m, 2H, C*H*$_2$), 3.00 (s, 3H, NC*H*$_3$), 2.52 (br s, 2H, C*H*$_2$). IR (KBr) *v*, 3434 (OH), 2950, 2873, 1742 (C=O), 1557, 1486, 1375 (SO_2), 1297, 1224, 1173, 1082, 1069, 987, 924, 814, 714, 598. LC/MS (CI) m/z 340.4 $(M+1)^+$. Anal. Calcd. for $C_{13}H_{14}N_2O_6S$: C, 49.41; H, 4.74; N, 8.23; S, 9.42. Found: C, 49.38; H, 4.76; N, 8.33; S, 9.52.

*Methyl 5-((3-methylpiperidin-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**7**).*

Yield: 0,27 g, 73%; mp 100-102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05-8.01 (m, 2H, Ar), 7.69-7.61 (m, 3H, Ar), 3.90 (s, 3H, OC*H*$_3$), 3.69 (dd, *J* 22,1 Hz, *J* 11,6 Hz, 1H, C*H*), 2.88 (t, *J* 12 Hz, 1H, C*H*), 2.59-2.54 (m, 1H, C*H*), 1.75-1.61 (m, 3H, C*H*, C*H*$_2$), 1.52-1.43 (m, 1H, C*H*), 1.06-0.98 (m, 1H, C*H*), 0.87 (d, *J* 6,8 Hz, 3H, C*H*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.8, 160.4, 147.0, 134.8, 133.0, 129.9, 127.5, 125.3, 53.3, 52.6, 46.4, 31.5, 30.7, 24.7, 19.0. IR (KBr) *v*, 2954, 2929, 1749 (C=O), 1545, 1481, 1374 (SO_2), 1363, 1224, 1179, 1144, 1070, 1053, 1008, 930, 818, 749, 716, 621, 581. LC/MS (CI) m/z 364.4 $(M+1)^+$. Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.00; H, 5.50; N, 7.79; S, 8.89.

*Methyl 5-((4-(aminocarbonyl)piperidin-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**8**).*

Yield: 0,28 g, 77%; mp > 210 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, *J* 7.6 Hz, 2H, Ar), 7.69-7.60 (m, 3H, Ar), 7.17 (s, 1H, C(O)N*H*$_2$), 6.70 (s, 1H, C(O)N*H*$_2$), 3.91 (s, 3H, OC*H*$_3$), 3.83 (d, *J* 12,4 Hz, 2H, C*H*$_2$), 2.98 (t, *J* 10.8 Hz, 2H, C*H*$_2$), 2.26 (t, *J* 10.8 Hz, 1H, C*H*), 1.84 (d, *J* 10.4 Hz, 2H, C*H*$_2$), 1.62-1.53 (m, 2H, C*H*$_2$). IR (KBr) *v*, 3380 (NH_{amide}), 3192, 2943, 1749 (C=O), 1651, 1552, 1449, 1372 (SO_2), 1336, 1299, 1221, 1178, 1148, 1067, 1054, 954, 815, 720, 714, 675, 610, 582. LC/MS (CI) m/z 364.4 $(M+1)^+$. Anal. Calcd. for $C_{17}H_{19}N_3O_6S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 51.90; H, 4.87; N, 10.68; S, 8.15.

*Methyl 5-((4-methylpiperidin-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**9**).*

Yield: 0,28 g, 78%; mp 102-104 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* 7.6 Hz, 2H, Ar), 7.67-7.60 (m, 3H, Ar), 3.90 (s, 3H, OC*H*$_3$), 3.78 (d, *J* 12,4 Hz, 2H, C*H*$_2$), 2.89 (t, *J* 12 Hz, 2H, C*H*$_2$), 1.71 (d, *J* 13,2 Hz, 2H, C*H*$_2$), 1.48 (br s, 1H, C*H*), 1.14 (dd, *J* 23.6 Hz, *J* 13.2 Hz, 2H, C*H*$_2$), 0.88 (d, *J* 6.4 Hz, 3H, C*H*$_3$). IR (KBr) *v*, 2942, 1746 (C=O), 1547, 1449, 1371 (SO_2), 1337, 1221, 1157, 1049, 927, 815, 726, 689, 617, 592. LC/MS (CI) m/z 365.2 $(M+1)^+$. Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 55.90; H, 5.50; N, 7.58; S, 8.19.

*Methyl 2-phenyl-5-((4-phenylpiperazin-1-yl)sulfonyl)-1,3-oxazole-4-carboxylate (**10**).*

Yield: 0,31 g, 73%; mp 119-121 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (d, *J* 8 Hz, 2H, Ar), 7.66-7.57 (m, 3H, Ar), 7.19 (t, *J* 7 Hz, 2H, Ar), 6.92 (d, *J* 7.5 Hz, 2H, Ar), 6.79 (t, *J* 7.5 Hz, 1H, Ar), 3.90 (s, 3H, OC*H*$_3$), 3.48 (br s, 4H, 2C*H*$_2$), 3.25 (br s, 4H, 2C*H*$_2$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.6, 159.9, 150.4, 146.1, 134.9, 132.5, 129.5, 129.0, 127.1, 125.0, 119.7, 116.2, 52.9, 48.2, 45.6. IR (KBr) *v*, 2842, 1737 (C=O), 1598, 1555, 1495, 1451, 1380 (SO_2), 1322, 1225, 1181, 1149, 1069, 1052, 953, 816, 771, 713, 698, 688, 596. LC/MS (CI) m/z 427.5 $(M+1)^+$. Anal. Calcd. for $C_{21}H_{21}N_3O_5S$: C, 59.00; H, 4.95; N, 9.83; S, 7.50. Found: C, 59.03; H, 4.91; N, 9.70; S, 7.62.

*Methyl 5-((4-(4-methoxyphenyl)piperazin-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**11**).*

Yield: 0,34 g, 74%; mp 119-121 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, *J* 7 Hz, 2H, Ar), 7.66-7.58 (m, 3H, Ar), 6.88 (d, *J* 9 Hz, 2H, Ar), 6.82-6.79 (m, 2H, Ar), 3.90 (s, 3H, OC*H*$_3$), 3.65 (s, 3H, OC*H*$_3$), 3.47 (br s, 4H, 2C*H*$_2$), 3.11 (br s, 4H, 2C*H*$_2$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.6, 160.3, 153.6, 146.0, 144.7, 134.9, 132.6, 129.5, 129.0, 127.1, 125.0, 118.3, 114.4, 55.2, 52.9, 49.6, 45.8. IR (KBr) *v*, 2832, 1747 (C=O), 1552, 1513, 1485, 1449, 1374 (SO_2), 1323, 1270, 1249, 1224, 1180, 1151, 1116, 1034, 1052, 951, 818, 732, 716, 688, 614, 601. LC/MS (CI) m/z 457.5 $(M+1)^+$. Anal. Calcd. for $C_{22}H_{23}N_3O_6S$: C, 57.76; H, 5.07; N, 9.18; S, 7.01. Found: C, 57.78; H, 5.04; N, 9.26; S, 7.13.

*Methyl 5-((4-(3-chlorophenyl)piperazin-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**12**).*

Yield: 0,34 g, 75%; mp 119-121 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, *J* 7 Hz, 2H, Ar), 7.66-7.58 (m, 3H, Ar), 6.88-6.79 (m, 4H, Ar), 3.87 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.42 (br s, 4H, 2CH_2), 3.15 (br s, 4H, 2CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.0, 160.3, 151.9, 146.4, 135.3, 134.3, 133.0, 130.9, 130.0, 127.5, 125.4, 119.2, 115.7, 114.7, 53.3, 47.9, 45.8. IR (KBr) *v*, 2849, 1738 (C=O), 1596, 1556, 1484, 1450, 1380 (SO_2), 1320, 1220, 1181, 1147, 954, 856, 786, 724, 712, 687, 599, 543. LC/MS (CI) m/z 461.9 $(M+1)^+$. Anal. Calcd. for $C_{21}H_{20}ClN_3O_5S$: C, 54.60; H, 4.36; N, 9.10; S, 6.94. Found: C, 54.62; H, 4.38; N, 9.19; S, 6.99.

*Synthesis of methyl 5-(benzylsulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (**15**).*

To a suspension of 0.01 mol of methyl 2-benzoylamino-3,3-dichloroacrylate (**1a**) in 40 ml of methanol 0.025 mol of sodium sulfide was added while stirring, the suspension was mixed for 2-3 h, then kept for 12 h at 20-25 °C. The precipitate was filtered off. The filtrate was diluted with water, acidified with hydrochloric acid to pH < 7, to form red precipitate **13**.

A mixture of methyl 5-mercapto-2-phenyl-1,3-oxazole-4-carboxylate (**13**, 0.01 mol), chloromethylbenzene (0.01 mol) and triethylamine (0.01 mol) was refluxed for 2-3 h. The precipitate was filtered off, the solvent was removed in vacuo, the residue was treated with water, filtered off, and dried to form compound **14**.

A solution of 0.01 mol of methyl 5-benzylthio-2-phenyl-1,3-oxazole-4-carboxylate (**14**) in 40 ml of glacial acetic acid was heated to reflux, then H_2O_2 was added in three portions during 2 h, then the reaction mixture was left for 12 h at room temperature. The mixture was kept for 8 h at 20-25 °C, and the precipitate was filtered off and purified by recrystallization from ethanol to form compound **15**. Yield: 0,26 g, 72%; mp 143-145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, *J* 7.6 Hz, 1H, Ar), 7.84 (d, *J* 6.4 Hz, 1H, Ar), 7.68-7.58 (m, 1H, Ar), 7.41-7.35 (m, 7H, Ar), 5.05 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3). IR (KBr) *v*, 2954, 1739 (C=O), 1614, 1545, 1494, 1345 (SO_2), 1318, 1301, 1237, 1180, 1140, 1085, 1062, 825, 776, 736, 696, 652, 640, 540, 522. LC/MS (CI) m/z 357.4 $(M+1)^+$. Anal. Calcd. for $C_{18}H_{15}NO_5S$: C, 60.49; H, 4.23; N, 3.92; S, 8.97. Found: C, 60.46; H, 4.21; N, 3.99; S, 8.85.

*Synthesis of 5-((3-methoxyphenyl)sulfonyl)-2-(4-methylphenyl)-1,3-oxazole-4-carbonitrile (**18**).*

A mixture of 3,3-dichloro-2-((4-methylbenzoyl)-amino)acrylate (**1b**, 0.01 mol), triethylamine (0.02 mol) and the corresponding 3-methoxybenzenethiol (0.02 mol) in 30 ml of acetonitrile was stirred on a magnetic stirrer at 20-25 °C C for 8 h. The precipitate was filtered off, the solvent was removed in vacuo, the residue was treated with water, filtered and dried. The mixture of formed *N*-(1-cyano-2,2-bis((3-methoxyphenyl)thio)vinyl)-4-methylbenz-amide (**16**, 0.01 mol) and dried silver carbonate (0.025 mol) in 40 ml of acetonitrile was stirred on a magnetic stirrer at reflux for 8-10 h, then left at 20-25 °C for 8 h. The precipitate was filtered off, the solvent was removed in vacuo, the residue was washed with water, filtered off, dried and purified by recrystallization.

The formed 5-((3-methoxyphenyl)thio)-2-(4-methyl-phenyl)-1,3-oxazole-4-carbonitrile (**19**, 0.01 mol) was heated to boiling in glacial acetic acid (20 ml), then 30% H_2O_2 was added in three 2 ml portions over 2 hours. The mixture was left at 20-25 ºC for 8 hours. The precipitate formed was filtered off, dried and recrystallized from ethanol. Yield: 0,27 g, 70%; mp 93-95 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* 7.6 Hz, 2H, Ar), 7.71-7.61 (m, 3H, Ar), 7.40-7.37 (m, 3H, Ar), 3.90 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 2.39 (s, 4H, 2CH_2). IR (KBr) *v*, 3530, 1742 (C=O), 1597, 1496, 1482, 1353 (SO_2), 1333, 1291, 1251, 1227, 1172, 1144, 1036, 821, 734, 702, 677, 642, 618, 534. LC/MS (CI) m/z 387.4 $(M+1)^+$. Anal. Calcd. for $C_{19}H_{17}NO_6S$: C, 58.91; H, 4.42; N, 3.62; S, 8.28. Found: C, 58.93; H, 4.40; N, 3.70; S, 8.39.

In vitro anticancer assay

In vitro screening methodology, screening interpretation information and cancer cell growth calculation method is described in details at the NCI Development Therapeutics Program site [23].

Molecular docking calculation

Molecular docking was carried out by Autodock Vina software [24]. Before the calculation, ligands, water molecules and amino acids conformers were removed from crystal structures of tubulin (PDB code 1SA0 [18]), CDK1, CDK2, CDK7, and CDK9 (PDB codes 4Y7*2* [20], 3QQJ, 1UA2 [21], and 4BCF [22], respectively), which were downloaded from PDB server (https://www.rcsb.org) [25]. The structure of 5-benzylsulfonyl derivative of 1,3 oxazole-4-carboxylate **15** was drawn using MarvinSketch [26] and optimized with the AM1 semi-empirical quantum mechanical method in MOPAC software [27]. Files for docking were prepared by using AutoDockTools (version 1.5.6) [28]. Analysis of models was performed in program Discovery Studio 3.5 Visualizer (Accelrys Inc., San Diego, CA, USA).

Notes

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Author contributions. **S. G. P.**: synthesis of compounds, investigation, formal analysis. **O. P. K.**: synthesis of compounds, investigation, formal analysis. **V. V. Z.**: COMPARE analysis. **M. V. K.**: writing most of the manuscript. **O. L. K.**: analysis of literature and molecular docking calculation. **A. I. V.**: conceptualization, writing, review. **V. S. B.**: conceptualization, supervision, writing - review & editing.

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Синтез та протипухлинна активність 5-сульфонільних похідних 1,3-оксазол-4-карбоксилатів

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Резюме: На основі попередніх досліджень протипухлинної активності 5-сульфонілзаміщених 1,3-оксазолів було синтезовано ряд нових 2-арил-5-сульфоніл-1,3-оксазол-4-карбоксилатів для проведення скринінгу щодо 60 ракових клітинних ліній NCI: недрібноклітинного раку легень (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522), раку нирок (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, UO-31), ЦНС (SF-268, SF-295, SF-539, SNB-19, SNB-75, U251), яєчників (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, NCI/ADR-RES, SK-OV-3), простати (PC-3, DU-145), товстого кишкивніка (COLO 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, SW-620), молочної залози (MCF7, MDA-MB-231/ATCC, HS 578T, BT-549, T- 47D, MDA-MB-468), лейкемії (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, RPMI-8226, SR) та меланоми (LOX IMVI, MALME-3M, M14, MDA-MB-435, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62). Серед досліджуваних речовин «сполукою-лідером» виявився метил 5-бензилсульфоніл-2-феніл-1,3-оксазол-4-карбоксилат (**15**), який показав значну цитотоксичність на багатьох лініях досліджених ракових клітин людини із середнім значенням GI_{50}, TGI та LC_{50} $5{,}37\cdot10^{-6}$, $1{,}29\cdot10^{-5}$ та $3{,}6\cdot10^{-5}$ моль/л відповідно. Молекулярний докінг було використано для оцінки взаємодій між сполукою **15** і тубуліном, а також для моделювання комплексів сполуки **15** з CDK2, енергія зв'язування в якому становила -9.2 ккал/моль. Серед нових похідних 1,3-оксазолу знайдено перспективні сполуки для подальшого дослідження протиракової активності щодо різних ліній.

Ключові слова: 5-сульфоніл-1,3-оксазол-4-карбоксилати; синтез; протипухлинна активність; селективність; молекулярний докінг.