Synthesis, Characterization, and in Vitro Anticancer Evaluation of 2-Aryl-4-Arylsulfonyl-5-RS-1,3-Oxazoles

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Abstract: A novel series of 4-arylsulfonyl-1,3-oxazoles have been synthesized and characterized by IR, 1H NMR, 13C NMR spectroscopy, elemental analysis, and chromatography-mass-spectrometry. The anticancer activities of all the newly synthesized compounds were evaluated via a single high dose (10 μM) against 59 cancer cell lines (without Melanoma SK-MEL-5) by the National Cancer Institute according to its screening protocol. Among these compounds, 2-[4-(4-chlorophenyl)sulfonyl-2-phenyl-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)acetamide exhibited the highest activity against lines SNB75 and SF-539 of the CNS Cancer subpanel present in Glioblastoma and Gliosarcoma, respectively, exerting a cytostatic effect. 2-[4-(4-Bromophenyl)sulfonyl-2-phenyl-oxazol-5-yl]sulfanylacetamide has the highest antiproliferative activity against the HOP-92 (carcinoma) of the Non-Small Cell Lung Cancer subpanel, while N-(4-ethoxyphenyl)-2-[2-phenyl-4-[(p-tolylsulfonyl)oxazol-5-yl]sulfanyl-acetamide exhibits cytotoxic activity against NCI-H226 (pleural mesothelioma) the Lung subpanel. The COMPARE analysis showed that the average graphs of the tested compounds have a weak or slightly moderate positive correlation with compounds with a known mechanism of antitumor activity, suggesting its specificity. These compounds demonstrated the anticancer activity against different individual cancer cell lines. This makes it possible to consider it a leading compound for further in-depth studies and synthesis of new 4-arylsulfonyl-1,3-derivatives of oxazole with antitumor activity.

Keywords: 4-Arylsulfonyl-1,3-oxazoles, Synthesis, Anticancer activity, COMPARE correlations.

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1. Introduction

Chemotherapy is carried out in treating malignant tumor diseases with the help of both natural and synthetic compounds that have a detrimental effect on the cells of malignant tumors with a comparatively less negative effect on the patient's organism. Unlike pharmacotherapy, in which there are only two objects – a pharmacological agent and the patient's organism exposed to it, three objects are involved in the process of chemotherapy - a pharmacological agent, a patient's organism, and a clone of malignant tumor cells. The latter's presence significantly complicates the treatment of the human body due to the development of serious side effects and the resistance of tumor cells to chemotherapeutic drugs. Therefore, a continuous search for new molecules with anticancer activity is required, among which an important place belongs to heterocyclic compounds, including 1,3-oxazole derivatives [1-4].

Anticancer activity, particularly human cancer cells, has been described for various compounds containing a 1,3-oxazole scaffold of natural and synthetic origin [5-13].
In addition to the structure presented in the above reviews, the following 1,3-oxazole-containing compounds have been synthesized and their antitumor screening has been performed: macrolides (phorboxazole A from marine Sponge Phorbas Sp., and its derivatives) [14], bis(benzoazoxole from Streptomyces (UK-1) [15], 2-substituted benzoxazole [16], indolyl oxazoles [17, 18], bis(carbethoxymethylsulfonyl)amine linked bis heterocycles- bis- oxazoles [19], (2S)-2-amino-3-[4-[(5-amino-2-phenyl-1,3-benzoxazol-7-yl)methoxy]-3,5- dichloro-phe-nyl]-propanoic acid (JPH203) [20, 21], N-(dicyclopentylmethyl)-4,5- dihydrooxazol-2-amine (rilmenidin) [22], oxazoloisoindolinone SLMP3-1 [23, 24], 2-methyl-4,5-disubstituted oxazole derivatives [25], thio derivatives of combretastatin A-4 [26], diazonamide DZ-2384 [27], 3-(2-aminooxazol-5-yl)-2H-chromen-2-one derivatives [28], N-[5-[(5-tert-buty1-1,3-oxazol-2-yl)methylsulfonyl]-1,3-thiazol-2-yl]piperidine-4-carboxamide (SNS-032) [29], 2-aryl 5-hydroxy benzo[d] oxazoles [30], 3-(benzo[d]oxazol-2-yl)-N,N- diethyl-2-imino-2H-chromen-7-amines [31], JPH203 [32], 5-(4-fluorophenyl)-N-(naphthalen-1-yl)oxazol-2-amine (AIU2008) [33], 1,3-oxazole sulfonamide [34], oxazolo[5,4-d]pyrimidines [35], oxazolo[4,5-b]pyridines [36], imidazo[2,1-b]oxazoles [37], and other condensed derivatives of oxazole [38].

These molecules were evaluated in the particular cell lines collectively belong to human adenocarcinoma, biliary tract, bladder, breast, cervical, colon, epidermoid, esophageal, glioma, gastric, leukemia, liver, lung, melanoma, neuroblastoma, oral, ovarian, pancreatic, prostate, renal cancers.

A range of oxazole derivatives have undergone more extensive in vitro cancer screening at the US National Cancer Institute, and the Japan cancer Chemotherapy Center based on panels of human tumor cell lines developed there. These include the following compounds: macrocyclic hexa oxazole derivatives (YM-216391) [39], 2-substituted benzoxazoles [40], oxazole telomestatin derivative [41], imidazo[2,1-b]oxazole derivatives [42], 2-(benzo[d]oxazol-2-ylamino)-N-(2-chloro-4-fluorophenyl)-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxamide [43], triterpenic C17-[5-methyl-1,3]-oxazoles [44], 2-phenanthro[9,10-d]oxazoles [45], 1,3-oxazole-5-sulfonamides [46], 2-substituted 5-aryl sulfonfonyl-1,3-oxazole-4-carbonitriles [47], 7-piperazin-substituted [1,3] oxazolo[4,5-d]pyrimidines [48], 7-(1,4-diazepan)-substituted [1,3] oxazolo[4,5-d]pyrimidines [49]. These data contain much information which is useful for further research.

Taking into account the pronounced antitumor activity of the tested aryloxazoles, we have synthesized new 4-aryl sulfonfonyl-1,3-oxazoles, hoping they will exhibit a significant antitumor effect.

2. Materials and Methods

2.1. Chemistry.

Starting compounds, A were obtained analogously to the previously described N-(2,2-dichloro-1-tosylvinyl)benzamide [50]. Alkylating agents RHlg: alkyl iodides, benzyl bromides, 2-chloro-1-phenylethan-1-ones, 2-chloroacetamides (see below) were provided by Enamine, Kiev. 1H, 13C and 19F NMR spectra were acquired on Bruker Avance DRX 500 (500, 126, and 376MHz, respectively) spectrometers in DMSO-d6 using the residual solvent signals as standards. The carbon and hydrogen content was determined by the Pregl gravimetric method, nitrogen – by the Dumas gasometric method, and sulfur – by the Schöniger titration method. Melting points were determined on a Fisher-Johns apparatus.
2.2. General procedure for preparation of oxazoles D.

One of compounds A (32 mmol) was added in small portions to a suspension of 0.82 g (3.4 mmol) Na₂S·9H₂O and 0.45 mL (32 mmol) of triethylamine in 10 mL of ethanol while cooling to 10-15°C. The reaction mixture was stirred for 6 h at room temperature and then filtered. To the filtrate, 3.0 mmol of one of the following was added: methyl iodide, ethyl iodide, propyl iodide, isopropyl iodide, isobutyl iodide, benzyl bromide, p-methylbenzyl bromide, p-fluorobenzyl bromide, 2-chloro-1-phenylethan-1-one, 2-chloro-1-(4-chlorophenyl)ethan-1-one, 2-chloroacetamide, N-substituted 2-chloroacetamide. The reaction was left to stand for 3 days. The precipitate formed was filtered off, and washed with ethanol and hot water to get product D.

2.2.1. 4-(Benzenesulfonyl)-5-isobutylsulfanyl-2-phenyl-1,3-oxazole (D1).

Yeild: 75%; m.p. 92-93°C. ¹H NMR: δ = 0.97 (6H, d, J=6.7 Hz), 1.77 – 2.00 (1H, m), 3.14 (2H, d, J=6.7 Hz), 7.46 – 7.59 (3H, m), 7.63 – 7.71 (2H, m), 7.71 – 7.80 (1H, m), 7.88 – 7.96 (2H, m), 7.96 – 8.05 (2H, m). ¹³C NMR: δ = 21.2, 28.7, 39.8, 40.7, 125.1, 126.2, 127.1, 129.2, 129.7, 131.7, 134.2, 136.7, 140.0, 151.8, 160.9. Anal. Calcd. for C₁₅H₁₉NO₃S₂, % : C 65.53; H 4.54; N 3.32; S 15.21. Found, % : C 65.48; H 4.31; N 3.28; S 15.33.

2.2.2. 4-(Benzenesulfonyl)-2-phenyl-5-(4-tolylmethylsulfanyl)-1,3-oxazole (D2).

Yeild: 79%; m.p. 120-121°C. ¹H NMR: δ = 2.22 (3H, s), 4.47 (2H, s), 7.07 (2H, d, J=7.6 Hz), 7.25 (2H, d, J=7.5 Hz), 7.48 – 7.67 (5H, m), 7.70 – 7.78 (1H, m), 7.86 (2H, d, J=7.7 Hz), 7.91 (2H, d, J=7.2 Hz). ¹³C NMR: δ = 20.6, 36.6, 125.0, 126.3, 127.1, 128.7, 129.1, 129.2, 129.6, 131.8, 133.7, 134.2, 136.8, 138.0, 139.7, 150.8, 161.3. Anal. Calcd. for C₂₅H₂₉NO₃S₂, % : C 65.53; H 4.54; N 3.32; S 15.21. Found, % : C 65.48; H 4.31; N 3.28; S 15.32.

2.2.3. 4-(Benzenesulfonyl)-5-[[4-fluorophenyl)methylsulfanyl]-2-phenyl-1,3-oxazole (D3).

Yeild: 78%; m.p. 159-160°C. ¹H NMR: δ = 4.51 (2H, s), 7.01 – 7.21 (2H, m), 7.37 – 7.47 (2H, m), 7.47 – 7.68 (5H, m), 7.67 – 7.80 (1H, m), 7.79 – 8.01 (4H, m). ¹³C NMR: δ = 36.0, 115.4 (d, J=21.5 Hz), 124.9, 126.3, 127.1, 129.2, 129.6, 130.8 (d, J=8.3 Hz), 131.8, 133.2 (d, J=3.0 Hz), 134.2, 138.3, 139.7, 150.5, 161.4, 161.4 (d, J=244.2 Hz). Anal. Calcd. for C₅₂H₅₆FNO₅S₂, % : C 62.10; H 3.79; N 3.29; S 15.07. Found, % : C 62.05; H 3.82; N 3.15; S 15.01.

2.2.4. 2-[4-(Benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-1-(4-chlorophenyl)ethanone (D4).

Yeild: 80%; m.p. 160-161°C. ¹H NMR: δ = 5.09 (2H, s), 7.38 – 7.57 (3H, m), 7.59 – 7.73 (4H, m), 7.71 – 7.86 (3H, m), 8.00 (2H, d, J=7.6 Hz), 8.07 (2H, d, J=8.2 Hz). ¹³C NMR: δ = 40.0, 124.9, 126.1, 127.2, 129.0, 129.2, 129.7, 130.5, 131.8, 133.7, 134.3, 136.3, 139.0, 139.8, 151.3, 160.9, 192.7. Anal. Calcd. for C₃₆H₃₁ClNO₅S₂, % : C 58.78; H 3.43; Cl 7.54; N 2.98; S 13.65. Found, % : C 58.82; H 3.47; Cl 7.69; N 2.82; S 13.78.

2.2.5. 2-[4-(Benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (D5).

Yeild: 83%; m.p. 191-192°C. ¹H NMR: δ = 4.00 (2H, s), 7.23 (1H, s), 7.44 – 7.62 (3H, m), 7.62 – 7.81 (4H, m), 7.92 (2H, d, J=7.3 Hz), 8.02 (2H, d, J=7.7 Hz). ¹³C NMR: δ = 35.7,
2.2.6. 2-[4-(Benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-cyclohexyl-acetamide (D6).

Yield: 83%; m.p. 182-183°C. 1H NMR: δ = 0.96 – 1.35 (5H, m), 1.40 – 1.83 (5H, m), 3.41 – 3.64 (1H, m), 3.97 (2H, s), 7.42 – 7.61 (3H, m), 7.61 – 7.71 (2H, m), 7.74 (1H, d, J=7.3 Hz), 7.93 (2H, d, J=7.4 Hz), 7.96 – 8.10 (2H, m). 13C NMR: δ = 24.3, 25.1, 32.2, 35.8, 48.1, 125.0, 126.2, 127.2, 129.2, 129.7, 131.8, 134.3, 136.0, 139.9, 151.9, 160.9, 165.3. Anal. Calcd. for C23H24N2O4S2: %: C 60.50; H 3.6; N 7.3; S 14.3. Found, %: C 60.50; H 3.62; S 14.26.

2.2.7. 2-[4-(Benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-fluorophenyl)acetamide (D7).

Yield: 86%; m.p. 166-167°C. 1H NMR: δ = 4.25 (2H, s), 7.15 (2H, t, J=8.8 Hz), 7.44 (2H, t, J=7.5 Hz), 7.52 (1H, t, J=7.3 Hz), 7.57 – 7.70 (4H, m), 7.74 (1H, t, J=7.3 Hz), 7.87 (2H, d, J=7.5 Hz), 8.02 (2H, d, J=7.7 Hz), 10.62 (1H, s). 13C NMR: δ = 36.6, 115.4 (d, J=22.3 Hz), 121.0, 124.9, 126.1, 127.1, 129.1, 129.7, 131.7, 134.3, 135.1, 136.2, 139.8, 151.5, 158.1 (d, J=240.4 Hz), 161.0, 165.5. Anal. Calcd. for C23H17FN2O4S2: %: C 58.96; H 3.66; F 4.05; N 5.98; S 13.69. Found, %: C 58.96; H 3.66; F 4.05; N 5.98; S 13.69.

2.2.8. 2-[4-(Benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-ethoxyphenyl)acetamide (D8).

Yield: 83%; m.p. 140-141°C. 1H NMR: δ = 1.29 (3H, t, J=8.1, 4.1 Hz), 3.96 (2H, q, J=7.1 Hz), 4.22 (2H, s), 6.87 (2H, d, J=8.3 Hz), 7.36 – 7.58 (5H, m), 7.59 – 7.69 (2H, m), 7.70 – 7.80 (1H, m), 7.88 (2H, d, J=7.6 Hz), 8.02 (2H, d, J=7.7 Hz), 10.25 (1H, s). 13C NMR: δ = 14.6, 36.7, 63.1, 114.5, 120.7, 120.9, 124.9, 126.2, 127.2, 129.1, 129.7, 131.7, 134.3, 136.2, 139.9, 151.6, 154.7, 161.0, 165.0. Anal. Calcd. for C25H23N2O4S2: %: C 60.71; H 4.48; N 5.66; S 12.97. Found, %: C 60.75; H 4.43; N 5.61; S 12.92.

2.2.9. 2-Phenyl-5-methylsulfanyl-4-(4-tolylsulfonyl)-1,3-oxazole (D9).

Yield: 73%; m.p. 154-155°C. 1H NMR: δ = 2.38 (3H, s), 2.72 (3H, s), 7.46 (2H, d, J=8.0 Hz), 7.50 – 7.60 (3H, m), 7.87 (2H, d, J=8.1 Hz), 7.91 (2H, d, J=7.7 Hz). 13C NMR: δ = 14.5, 21.1, 125.2, 126.1, 127.1, 129.2, 130.1, 131.5, 135.4, 137.2, 144.9, 152.7, 160.6. Anal. Calcd. for C17H15NO3S2: %: C 59.11; H 4.38; N 4.05; S 18.56. Found, %: C 59.24; H 4.36; N 3.98; S 18.51.

2.2.10. 2-Phenyl-5-propylsulfanyl-4-(4-tolylsulfonyl)-1,3-oxazole (D10).

Yield: 69%; m.p. 130-131°C. 1H NMR: δ = 0.97 (3H, t, J=7.3 Hz), 1.68 (2H, q, J=7.2 Hz), 2.37 (3H, s), 7.45 (2H, d, J=8.0 Hz), 7.48 – 7.58 (3H, m), 7.82 – 7.95 (6H, m). 13C NMR: δ = 12.8, 21.1, 22.9, 34.5, 125.1, 126.1, 127.2, 129.2, 130.1, 131.6, 137.2, 137.3, 144.9, 151.3, 160.9. Anal. Calcd. for C19H19NO3S2: %: C 61.10; H 5.13; N 3.75; S 17.17. Found, %: C 61.13; H 5.10; N 3.78; S 17.12.
2.2.11. 5-Benzylsulfanyl-2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazole (D11).

Yield: 77%; m.p. 129-130°C (113-115°C[42]). $^1$H NMR: $\delta = 2.37$ (3H, s), 4.51 (2H, s), 7.18 – 7.33 (3H, m), 7.34 – 7.45 (4H, m), 7.46 – 7.60 (3H, m), 7.75 (2H, d, $J=8.1$ Hz), 7.90 (2H, d, $J=6.9$ Hz). $^{13}$C NMR: $\delta = 21.1$, 36.8, 125.0, 126.3, 127.2, 127.6, 128.6, 128.8, 129.2, 130.1, 131.8, 136.9, 138.4, 144.9, 150.2, 161.3. Anal. Calcd. for C$_{22}$H$_{19}$NO$_3$S$_2$, %: C 65.53; H 4.54; N 3.32; S 15.21. Found, %: C 65.51; H 4.50; N 3.29; S 15.25.

2.2.12. 2-[2-Phenyl-4-(4-tolylsulfonyl)-1,3-oxazol-5-yl]sulfanylacetamide (D12).

Yield: 78%; m.p. 195-196°C. $^1$H NMR: $\delta = 2.38$ (3H, s), 4.01 (2H, s), 7.31 (1H, s), 7.39 – 7.59 (5H, m), 7.72 (1H, s), 7.84 – 7.99 (4H, m). $^{13}$C NMR: $\delta = 21.1$, 35.7, 125.1, 126.2, 127.3, 129.2, 130.1, 131.7, 136.0, 137.1, 145.0, 151.6, 160.7, 168.5. Anal. Calcd. for C$_{18}$H$_{16}$N$_2$O$_4$S$_2$, %: C 55.65; H 4.15; N 7.21; S 16.51. Found, %: C 55.60; H 4.11; N 7.25; S 16.50.

2.2.13. N-(4-fluorophenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazol-5-yl]sulfanylacetamide (D13).

Yield: 83%; m.p. 216-217°C. $^1$H NMR: $\delta = 2.36$ (3H, s), 4.22 (2H, s), 6.85 – 7.27 (2H, m), 7.27 – 7.77 (7H, m), 7.88 (4H, m), 10.48 (1H, s). $^{13}$C NMR: $\delta = 21.0$, 36.7, 115.4 (d, $J=22.3$ Hz), 121.0 (d, $J=7.7$ Hz), 124.9, 126.1, 127.2, 129.1, 130.1, 131.7, 135.0, 136.8, 136.9, 145.0, 150.8, 158.2 (d, $J=240.5$ Hz), 160.9, 165.5. Anal. Calcd. for C$_{26}$H$_{23}$FN$_2$O$_4$S$_2$, %: C 59.74; H 3.97; N 5.81; S 13.29. Found, %: C 59.72; H 3.91; N 5.87; S 13.25.

2.2.14. N-(4-ethoxyphenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazol-5-yl]sulfanylacetamide (D14).

Yield: 87%; m.p. 186-187°C. $^1$H NMR: $\delta = 1.27$ (3H, t, $J=6.9$ Hz), 2.33 (3H, s), 3.95 (2H, q, $J=6.9$ Hz), 4.27 (2H, s), 6.86 (2H, d, $J=8.5$ Hz), 7.36 – 7.44 (4H, m), 7.45 – 7.52 (1H, m), 7.55 (2H, d, $J=8.4$ Hz), 7.89 (4H, d, $J=7.7$ Hz), 10.66 (1H, s). $^{13}$C NMR: $\delta = 14.6$, 21.1, 36.6, 63.1, 114.4, 120.7, 125.0, 126.2, 127.2, 129.1, 130.1, 131.6, 131.9, 136.7, 137.0, 144.9, 151.1, 154.7, 161.0, 165.1. Anal. Calcd. for C$_{26}$H$_{24}$N$_2$O$_4$S$_2$, %: C 61.40; H 4.76; N 5.51; S 12.61. Found, C %: 61.38; H 4.75; N 5.55; S 12.63.

2.2.15. N-(2,4-dimethoxyphenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazol-5-yl]sulfanylacetamide (D15).

Yield: 80%; m.p. 136-137°C. $^1$H NMR: $\delta = 2.35$ (3H, s), 3.55 – 3.96 (6H, m), 4.26 (2H, s), 6.47 (1H, d, $J=8.8$ Hz), 6.60 (1H, s), 7.29 – 7.63 (5H, m), 7.72 (1H, d, $J=8.7$ Hz), 7.78 – 8.14 (4H, m), 9.44 (1H, s). $^{13}$C NMR: $\delta = 21.5$, 36.9, 55.7, 56.1, 99.2, 104.5, 120.4, 123.6, 125.5, 126.7, 127.7, 129.6, 130.6, 137.4, 137.4, 145.4, 151.4, 151.6, 157.4, 161.5, 165.9. Anal. Calcd. for C$_{26}$H$_{24}$N$_2$O$_4$S$_2$, %: C 59.53; H 4.61; N 5.34; S 12.22. Found, %: C 59.52; H 4.65; N 5.37; S 12.20.

2.2.16. 5-Ethylsulfanyl-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (D16).

Yield: 72%; m.p. 121-122°C. $^1$H NMR: $\delta = 1.34$ (3H, t, $J=7.3$ Hz), 3.24 (2H, q, $J=7.2$ Hz), 7.40 – 7.60 (5H, m), 7.91 (2H, d, $J=7.2$ Hz), 8.07 (2H, dd, $J=8.5$, 5.2 Hz). $^{13}$C NMR: $\delta = 15.5$, 27.6, 117.4 (d, $J=23.0$ Hz), 125.5, 126.6, 129.6, 130.9 (d, $J=9.9$ Hz), 132.1, 136.7 (d, $J=2.8$ Hz).
(2H, dd, J=23.0 Hz, 135.4, 132.7, 132.0, 132.2, 134.1, 136.5, 136.6 (d, J=3.3 Hz), 136.7, 139.4, 151.7, 161.4, 165.7 (d, J=253.7 Hz), 193.1. Anal. Calcd. for C_{17}H_{14}FNO_{3}S_{2}, %: C 56.58; H 3.41; N 3.16; S 14.46. Found, %: C 59.55; H 3.38; N 3.19; S 14.48.

2.2.18. 1-(4-Chlorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D18).

Yield: 82%; m.p. 157-158°C. {^1}H NMR: δ = 5.03 (2H, d, J=3.4 Hz), 7.36 – 7.57 (5H, m), 7.62 (2H, d, J=6.3 Hz), 7.80 (2H, d, J=7.6 Hz), 7.96 – 8.18 (4H, m). {^{13}}C NMR: δ = 35.7, 117.0 (d, J=23.1 Hz), 125.0, 126.2, 129.2, 130.4 (d, J=9.9 Hz), 131.7, 135.6, 136.2, 152.0, 160.8, 165.2 (d, J=253.8 Hz), 168.4. {^{19}}F NMR: δ = -104.2. Anal. Calcd. for C_{17}H_{13}F_{2}N_{2}O_{4}S_{2}, %: C 52.03; H 3.34; N 7.14; S 16.34. Found, %: C 52.01; H 3.31; N 7.10; S 16.39.

2.2.20. N-(4-fluorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D20).

Yield: 89%; m.p. 215-216°C. {^1}H NMR: δ = 4.22 (2H, d, J=2.4 Hz), 7.06 – 7.27 (2H, m), 7.34 – 7.57 (5H, m), 7.54 – 7.67 (2H, m), 7.87 (2H, d, J=7.7 Hz), 8.08 (2H, dd, J=8.8, 5.2 Hz), 10.49 (1H, t, J=6.3 Hz). {^{13}}C NMR: δ = 36.7, 115.4 (d, J=22.3 Hz), 117.0 (d, J=23.0 Hz), 120.9 (d, J=7.8 Hz), 124.9, 126.1, 129.1, 130.5 (d, J=10.0 Hz), 131.7, 135.0, 136.1, 136.3, 151.4, 158.1 (d, J=240.1 Hz), 161.1, 165.2 (d, J=253.8 Hz), 165.4. {^{19}}F NMR: δ = -119.2, -104.1. Anal. Calcd. for C_{23}H_{16}F_{2}N_{2}O_{4}S_{2}, %: C 56.78; H 3.31; N 5.76; S 13.18. Found, %: C 56.80; H 3.27; N 5.80; S 13.15.

2.2.21. N-(4-ethoxyphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D21).

Yield: 91%; m.p. 187-188°C. {^1}H NMR: δ = 1.29 (3H, t, J=6.9 Hz), 3.97 (2H, q, J=6.8 Hz), 4.20 (2H, s), 6.87 (2H, d, J=8.6 Hz), 7.29 – 7.70 (6H, m), 7.89 (2H, d, J=7.7 Hz), 8.07 (2H, dd, J=8.6, 5.1 Hz), 10.35 (1H, s). {^{13}}C NMR: δ = 14.6, 36.6, 63.1, 114.4, 117.0 (d, J=23.0 Hz), 120.7, 124.9, 126.2, 129.1, 130.4, 130.5, 131.7, 131.8, 136.1, 151.6, 154.7, 161.0, 164.9,
165.2 (d, J=253.7 Hz). $^{19}$F NMR: $\delta = -104.12$. Anal. Calcd. for C$_{25}$H$_{21}$FN$_2$O$_5$S$_2$: %: C 58.58; H 4.13; N 5.47; S 12.51. Found, %: C 58.55; H 4.17; N 5.50; S 12.53.

2.2.22. N-(3,5-dimethylphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D22).

Yield: 86%; m.p. 228-229°C. $^1$H NMR: $\delta = 2.21$ (6H, s), 4.19 (2H, s), 6.70 (1H, s), 7.18 (2H, s), 7.39 – 7.51 (4H, m), 7.49 – 7.61 (1H, m), 7.88 (2H, d, J=7.7 Hz), 8.08 (2H, dd, J=8.7, 5.2 Hz), 10.22 (1H, s). $^{13}$C NMR: $\delta = 21.0, 36.8, 116.9, 117.0$ (d, J=22.3 Hz), 124.9, 125.2, 126.2, 129.1, 130.5 (d, J=10.1 Hz), 131.8, 136.1, 137.8, 138.4, 151.3, 161.0, 165.0 (d, J=193.5 Hz), 165.4, 166.2. $^{19}$F NMR: $\delta = -104.12$. Anal. Calcd. for C$_{25}$H$_{21}$FN$_2$O$_5$S$_2$: %: C 60.47; H 4.26; N 5.64; S 12.91. Found, %: C 60.45; H 4.29; N 5.66; S 12.88.

2.2.23. 2-[4-(4-Chlorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)-acetamide (D23).

Yield: 90%; m.p. 185-186°C. $^1$H NMR: $\delta = 3.69$ (3H, s), 3.71 (3H, s), 4.24 (2H, s), 6.44 (1H, d, J=7.7 Hz), 6.57 (1H, s), 7.37 – 7.55 (3H, m), 7.56 – 7.76 (3H, m), 7.89 (1H, d, J=7.6 Hz), 7.96 (1H, d, J=8.2 Hz), 9.40 (1H, s). $^{13}$C NMR: $\delta = 36.4, 55.3, 55.6, 98.8, 104.0, 119.8, 123.3, 124.9, 126.3, 129.1, 129.9, 131.8, 136.2, 138.6, 139.3, 151.2, 151.7, 157.0, 161.2, 165.4. Anal. Calcd. for C$_{25}$H$_{21}$CIN$_2$O$_5$S$_2$: %: C 55.09; H 3.88; Cl 6.50; N 5.14; S 11.77. Found, %: C 55.05; H 3.90; Cl 6.53; N 5.15; S 11.72.

2.2.24. 4-(4-Bromophenyl)sulfonyl-5-methylsulfanyl-2-phenyl-1,3-oxazole (D24).

Yield: 70%; m.p. 153-154°C. $^1$H NMR: $\delta = 2.74$ (3H, s), 7.47 – 7.60 (3H, m), 7.80 – 7.98 (6H, m). $^{13}$C NMR: $\delta = 14.4, 125.1, 126.2, 128.4, 129.0, 129.2, 131.6, 132.9, 134.4, 139.2, 153.6, 160.7. Anal. Calcd. for C$_{18}$H$_{12}$BrNO$_3$S$_2$: %: C 46.84; H 2.95; Br 19.47; N 3.41; S 15.63. Found, %: C 46.82; H 2.98; Br 19.41; N 3.45; S 15.60.

2.2.25. 4-(4-Isopropylsulfanyl-5-phenyl)sulfon-1-2-phenyl-1,3-oxazole (D25).

Yield: 68%; m.p. 138-139°C. $^1$H NMR: $\delta = 1.36$ (6H, s), 3.66 – 4.14 (1H, m), 7.13 – 8.24 (9H, m). $^{13}$C NMR: $\delta = 23.8, 39.8, 125.5, 126.8, 129.0, 129.7, 129.8, 132.3, 133.3, 139.2, 139.5, 150.9, 162.1. Anal. Calcd. for C$_{18}$H$_{16}$BrNO$_3$S$_2$: %: C 49.32; H 3.68; Br 18.23; N 3.20; S 14.63. Found, %: C 49.30; H 3.65; Br 18.27; N 3.17; S 14.65.

2.2.26. 2-[4-(4-Bromophenyl)sulfon-2-phenyl-1,3-oxazol-5-yl)sulfanyl-1-phenyl-ethanone (D26).

Yield: 85%; m.p. 143-144°C. $^1$H NMR: $\delta = 5.14$ (2H, s), 7.38 – 7.47 (2H, m), 7.47 – 7.52 (1H, m), 7.53 – 7.62 (2H, m), 7.70 (1H, t, J=7.3 Hz), 7.77 (2H, d, J=7.6 Hz), 7.86 (2H, d, J=8.4 Hz), 7.93 (2H, d, J=8.2 Hz), 8.07 (2H, d, J=7.7 Hz). $^{13}$C NMR: $\delta = 40.5, 125.3, 126.5, 126.6, 129.0, 129.3, 129.6, 132.2, 133.3, 134.4, 135.4, 136.2, 139.5, 152.3, 161.4, 193.9. Anal. Calcd. for C$_{23}$H$_{18}$BrNO$_3$S$_2$: %: C 53.70; H 3.14; Br 15.53; N 2.72; S 12.47. Found, %: C 53.68; H 3.17; Br 15.54; N 2.69; S 12.50.
2.2.27. 2-[4-(4-Bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (D27).

Yield: 87%; m.p. 223-224°C. $^1$H NMR: $\delta = 4.02$ (2H, s), 7.32 (1H, s), 7.48 – 7.61 (3H, m), 7.75 (1H, s), 7.83 – 8.00 (6H, m). $^{13}$C NMR: $\delta = 35.7, 125.0, 126.2, 128.5, 129.2, 129.2, 131.8, 132.9, 135.2, 139.1, 152.5, 160.9, 168.5. Anal. Calcd. for C$_{17}$H$_{13}$BrN$_2$O$_5$S$_2$, %: C 45.04; H 2.89; Br 17.63; N 6.18; S 14.15. Found, %: C 45.07; H 2.91; Br 17.65; N 6.15; S 14.14.

2.2.28. 2-[4-(4-Bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-cyclohexylacetamide (D28).

Yield: 69%; m.p. 231-232°C. $^1$H NMR: $\delta = 0.88 – 1.37$ (5H, m), 1.43 – 1.84 (5H, m), 3.50 (1H, s), 3.96 (2H, s), 7.47 – 7.63 (3H, m), 7.83 – 7.99 (7H, m). $^{13}$C NMR: $\delta = 24.3, 25.1, 32.2, 35.8, 48.1, 118.9, 125.0, 126.3, 128.5, 129.2, 131.8, 132.9, 135.6, 139.1, 152.2, 161.0, 165.3. Anal. Calcd. for C$_{23}$H$_{23}$BrN$_2$O$_4$S$_2$, %: C 51.59; H 4.33; Br 14.92; N 5.23; S 11.98. Found, %: C 51.55; H 4.31; Br 14.95; N 5.22; S 12.01.

2.2.29. 2-[4-(4-Bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-fluorophenyl)-acetamide (D29).

Yield: 92%; m.p. 244-245°C. $^1$H NMR: $\delta = 4.23$ (2H, s), 7.15 (2H, t, J=8.7 Hz), 7.45 (2H, t, J=7.6 Hz), 7.50 – 7.67 (3H, m), 7.79 – 7.89 (4H, m), 7.92 (2H, d, J=8.4 Hz), 10.49 (1H, s). $^{13}$C NMR: $\delta = 37.2, 115.8$ (d, J=22.5 Hz), 121.4, 121.5, 125.4, 126.7, 129.0, 129.6, 132.3, 133.3, 135.5 (d, J=2.5 Hz), 136.4, 139.5, 152.2, 157.5, 161.6, 165.9. $^{19}$F NMR: $\delta = -119.13$. Anal. Calcd. for C$_{23}$H$_{18}$BrF$_3$N$_2$O$_5$S$_2$, %: C 50.46; H 2.95; Br 14.60; F 3.47; N 5.12; S 11.71. Found, %: C 50.44; H 2.97; Br 14.58; F 3.45; N 5.16; S 11.75.

2.2.30. 2-[4-(4-Bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-ethoxyphenyl)-acetamide (D30).

Yield: 89%; m.p. 227-228°C. $^1$H NMR: $\delta = 1.29$ (3H, t, J=7.0 Hz), 3.98 (2H, d, J=7.4 Hz), 4.19 (2H, s), 6.87 (2H, d, J=8.3 Hz), 7.39 – 7.52 (4H, m), 7.51 – 7.60 (1H, m), 7.79 – 7.85 (2H, m), 7.86 – 8.08 (4H, m), 10.23 (1H, s). $^{13}$C NMR: $\delta = 14.7, 36.7, 63.1, 114.5, 120.7, 124.9, 126.2, 128.5, 129.1, 129.2, 131.6, 131.8, 132.9, 135.9, 139.0, 151.9, 154.8, 161.1, 164.9. Anal. Calcd. for C$_{25}$H$_{21}$BrN$_2$O$_5$S$_2$, %: C 52.36; H 3.69; Br 13.93; N 4.88; S 11.18. Found, %: C 52.34; H 3.71; Br 13.95; N 4.84; S 11.20.

2.2.31. 2-[4-(4-Bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)acetamide (D31).

Yield: 82%; m.p. 182-183°C. $^1$H NMR: $\delta = 3.72$ (3H, s), 3.74 (3H, s), 4.27 (2H, s), 6.47 (1H, dd, J=8.8, 2.6 Hz), 6.60 (1H, d, J=2.6 Hz), 7.42 – 7.52 (2H, m), 7.51 – 7.60 (1H, m), 7.70 (1H, d, J=8.8 Hz), 7.80 (2H, d, J=8.2 Hz), 7.87 – 7.96 (4H, m), 9.42 (1H, s). $^{13}$C NMR: $\delta = 36.4, 55.3, 55.6, 98.8, 104.0, 119.8, 123.2, 125.0, 126.3, 128.5, 129.1, 131.8, 132.8, 136.2, 139.0, 151.2, 151.7, 157.0, 161.2, 165.4. Anal. Calcd. for C$_{25}$H$_{21}$BrN$_2$O$_5$S$_2$, %: C 50.94; H 3.59; Br 13.55; N 4.75; S 10.88. Found, %: C 50.96; H 3.57; Br 13.51; N 4.77; S 10.91.

2.2.32. 4-(Benzenesulfonyl)-5-methylsulfanyl-2-(4-toly)-1,3-oxazole (D32).

Yield: 68%; m.p. 155-156°C (157-159°C[42]). $^1$H NMR: $\delta = 2.34$ (3H, s), 2.71 (3H, s), 7.23 – 7.44 (2H, m), 7.64 – 7.70 (2H, m), 7.70 – 7.76 (1H, m), 7.79 (2H, d, J=7.9 Hz), 7.99
(2H, d, J=7.6 Hz). $^{13}$C NMR: $\delta=14.5, 21.1, 122.5, 126.1, 127.1, 128.3, 129.7, 134.2, 134.9, 140.1, 141.7, 152.7, 160.9$. Anal. Calcd. for $C_{17}H_{15}NO_{3}S_{2}$, %: C 59.11; H 4.38; N 4.05; S 18.56. Found, %: C 59.07; H 4.40; N 4.08; S 18.51.

2.2.33. 2-[(Benzenesulfonyl)-2-(4-tolyl)-1,3-oxazol-5-yl]sulfanylacetamide (D33).

Yield: 77%; m.p. 217-218°C. $^1$H NMR: $\delta=2.36$ (3H, s), $3.98$ (2H, s), $7.23$ (1H, s), $7.34$ (2H, d, $J=7.8$ Hz), $7.60-7.72$ (3H, m), $7.71-7.77$ (1H, m), $7.81$ (2H, d, $J=7.8$ Hz), $8.01$ (2H, d, $J=7.7$ Hz). $^{13}$C NMR: $\delta=21.1, 35.7, 122.4, 126.2, 127.2, 129.7, 129.8, 134.3, 135.5, 139.9, 141.9, 151.7, 161.0, 168.5$. Anal. Calcd. for $C_{18}H_{16}N_{2}O_{4}S_{2}$, %: C 55.65; H 4.15; N 7.21; S 16.51. Found, %: C 55.66; H 4.11; N 7.25; S 16.47.

2.3. In Vitro anticancer screening of the tested compounds

2.3.1. One dose full NCI 60 cell panel assay

Synthesized compounds were submitted to the National Cancer Institute NCI, Bethesda, Maryland, U.S.A., under the Developmental Therapeutic Program DTP. The cell line panel engaged 60 different human tumor cell lines derived from nine cancer types, including lung, colon, melanoma, renal, ovarian, brain, leukemia, breast, and prostate.

Primary in vitro one-dose anticancer screening was initiated by cell inoculating of each 60-panel line into a series of standard 96-well microtiter plates at 5000-40000 cells/well in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine (day 0), and then preincubated in the absence of drug at 37 °C and 5% CO$_2$ for 24 h. Test compounds were then added to the plates at one concentration of $10^{-5}$ M (day 1) followed by incubation for a further 48 h under the same conditions. Then the media were removed, and the cells were fixed in situ, washed, and dried (day 3). The sulforhodamine B assay was used for cell density determination based on cellular protein content measurement. After an incubation period, cell monolayers were fixed with 10% (wt/vol) trichloroacetic acid and stained for 30 min, after which the excess dye was removed by repeatedly washing with 1% (vol/vol) acetic acid. The bound stain was resolubilized in 10 mM Tris base solution and measured spectrophotometrically on automated microplate readers for OD determination at 510 nm.

2.3.2. NCI 60 cell panel COMPARE correlations.

Compounds having similar activity profiles often have similar mechanisms of action and resistance. To measure the degree of similarity between novel compounds and known drugs in the NCI databases, a method has been developed using the Pearson correlation coefficient (PCC) as a comparison criterion (COMPARE analysis) [https://dtp.cancer.gov/databases_tools/docs/compare/compare_methodology.htm#specon]. The graph of mean values for compounds was subsequently used to run the COMPARE algorithm from the Developmental Therapeutics Program, NCI, and calculate the correlation coefficient with respect to compounds from the standard agent database with a known mechanism of action. The following scale of interpretation of pair correlation coefficients was used [51]: insignificant (0.00-0.30), weak (0.30-0.50), moderate (0.50-0.70), high (0.70-0.90) and very high (0.9-1.0) connection with a standard drug. Accordingly, pairwise correlation coefficients greater than 0.3 were used as a threshold to assess whether seeded compounds and standard agents could have a similar mechanism of action.
3. Results and Discussion

\[N-((1-Arylsulfonyl)-2,2\text{-dichlorovinyl})amides\] are known to undergo the 1,3-oxazole ring closure under the action of sodium hydrogen sulfide [52].

In the present work, we exploited an improved version of this method using a sodium sulfide with a triethylamine mixture instead of sodium hydrogen sulfide (Scheme 1). This avoids the hydrogen sulfide gas evolution during the transformation of the starting enamides \(A\) into thietene intermediate \(B\). These later cyclize in the presence of triethylamine to give ammonium 1,3-oxazole-5-thiolates \(C\), which was not isolated but were used in ethanol solution for the production of the final compounds \(D\). This way, a series of 1,3-oxazoles \(D\) with different \(SAk, SCH_2Ar, SCH_2COAr, SCH_2CONHR\) groups at C5 ring atom was obtained for anticancer testing.

![Scheme 1. Preparation of 1,3-oxazoles D.](https://biointerfaceresearch.com/)

3.1. The one-dose assay.

The individual cell lines showed a distinctive sensitivity against synthesized compounds. Seventeen compounds (D2, D3, D5, D8-D12, D15, D16, D21-D23, D25, D27, D29, D30) have had low toxicity with growth inhibition of the tested cell lines less than 50%. Seven compounds (D1, D4, D6, D7, D17, D19, D28) inhibited growth at 51-60% from one to three cell lines, which are A498, HOP-92, T-47D, SNB-75, SR, NCI-226, SF-539, UACC-62, and HCT-116. Compounds D13, D14, D21, D23, D27, and D29 showed significant inhibition.
(≥70%), but each only for some cell lines belonging to CNS, Lung, Ovarian, Renal, or Colon cancer. These compounds are shown in Table 1.

Table 1. One dose anticancer screening data of the most active compounds against NCI-60 human tumor cell lines.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lung</th>
<th>Cancer cell subpanel</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D13</td>
<td>HOP-92</td>
<td>CNS</td>
<td>Ovarian</td>
<td>Renal</td>
<td>Colon</td>
</tr>
<tr>
<td>D14</td>
<td>NCI-H226</td>
<td>SF-539</td>
<td></td>
<td></td>
<td>HCT-116</td>
</tr>
<tr>
<td>D21</td>
<td>SF-539</td>
<td></td>
<td></td>
<td>HCT-116</td>
<td></td>
</tr>
<tr>
<td>D23</td>
<td>NCI-226</td>
<td>SNB75</td>
<td>SF-539</td>
<td>-</td>
<td>RXF393</td>
</tr>
<tr>
<td>D27</td>
<td>HOP-92</td>
<td>SNB-75</td>
<td>-</td>
<td></td>
<td>786-0</td>
</tr>
<tr>
<td>D29</td>
<td>HOP-62</td>
<td>U251</td>
<td>OVCAR-8</td>
<td></td>
<td>786-0</td>
</tr>
</tbody>
</table>

The compounds added at a concentration (1∙10⁻⁵ M), and the culture incubated for 48 h. The number reported for the one-dose assay is growth inhibition (%) relative to the no-drug control, and relative to the time zero number of cells. This allows the detection of growth inhibition (values between 0 and 100) and lethality (values more than 100). A value of 200 means all cells are dead. The percentage of growth inhibition of compounds is shown in parentheses.

Thus, compound D23 exhibits the highest activity against lines SNB75 and SF-539 of the CNS Cancer subpanel present in Glioblastoma and Gliosarcoma, respectively, exerting a cytostatic effect. Compound D27 has the highest antiproliferative activity against the HOP-92 (carcinoma) Non-Small Cell Lung Cancer subpanel, while D14 exhibits cytotoxic activity against NCI-H226 (pleural mesothelioma) in the Lung subpanel. These compounds were analyzed to elucidate possible molecular action mechanisms when compared with standard drugs with established mechanisms.

Structure-activity analysis shows that halogenation of the p-tolyl group (compound D21) eliminated the cytotoxicity of D14 relative to the NCI-H226 line, and the replacement of N-(4-ethoxyphenyl) in D21 with N-(2,4-dimethoxyphenyl) (D23) restored only antiproliferative activity against NCI-H226, close to cytostatic. The last substitution was also accompanied by the appearance of cytostatic activity D23 against the SNB75 line. In general, the functionalization of 4-aryl sulfonyl-1,3-oxazoles with different substituents generally only changed the sensitivity of a small number of different cell lines of the 5 indicated subpanels.

3.2. COMPARE correlations.

The results of a comparative analysis of the similarity of the tested parameters of antitumor activity of compounds D14, D23, D27, and D29 with known standard antitumor agents present in the NCI public databases are shown in Table 2.

Table 2. Standard agent COMPARE correlations for compounds D14, D23 and D27

<table>
<thead>
<tr>
<th>Compound</th>
<th>Correlating drug</th>
<th>Correlation coefficient</th>
<th>Reported Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14</td>
<td>Morpholinodoxorubicin</td>
<td>0.54</td>
<td>Intercalates DNA and stimulates DNA topoisomerase 1-induced cleavage at specific DNA sites [53]. Its active microsomal metabolites alkylate DNA [54]</td>
</tr>
<tr>
<td>D23</td>
<td>4-Nitroestrone 3-methyl ether</td>
<td>0.50</td>
<td>Inhibits estrogen sulfotransferase, a progesterone-induced secretory endometrial enzyme that affects estrogen receptor levels [55]</td>
</tr>
<tr>
<td>D27</td>
<td>Nitroestrone</td>
<td>0.48</td>
<td>Tamoxifen reduces DNA synthesis by inhibiting the binding of estradiol to estrogen receptors, as</td>
</tr>
</tbody>
</table>
TGI

<table>
<thead>
<tr>
<th>Compound</th>
<th>Correlating drug</th>
<th>Correlation coefficient</th>
<th>Reported Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14</td>
<td>Bleomycin</td>
<td>0.34</td>
<td>Bleomycin causes oxidative damage to DNA, leading to single-strand and double-strand breaks and G2 cell cycle arrest [57]</td>
</tr>
<tr>
<td>D23</td>
<td>Flotafur, Bleomycin</td>
<td>0.47</td>
<td>Flotafur inhibits thymidylate synthase during the pyrimidine pathway involved in DNA synthesis [58]</td>
</tr>
<tr>
<td>D27</td>
<td>Dihydrolenperone</td>
<td>0.50</td>
<td>Dihydrolenperone inhibits the growth of lung cancer cells [59]. The mechanism of molecular action is not found in the available literature.</td>
</tr>
</tbody>
</table>

LC₅₀

<table>
<thead>
<tr>
<th>Compound</th>
<th>Correlating drug</th>
<th>Correlation coefficient</th>
<th>Reported Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14</td>
<td>Bleomycin</td>
<td>0.34</td>
<td>See above</td>
</tr>
<tr>
<td>D23</td>
<td>DHAD (mitoxantrone)</td>
<td>0.51</td>
<td>Mitoxantrone intercalates into and crosslinks DNA, thereby disrupting DNA and RNA replication. This agent also binds to topoisomerase II, resulting in DNA strand breaks and inhibition of DNA repair [60]</td>
</tr>
<tr>
<td>D27</td>
<td>DHAD, Diaziquone (AZQ)</td>
<td>0.47</td>
<td>Diaziquone selectively alkylates and cross-links DNA at the 5'-GNC-3' sequence, inhibiting DNA replication, inducing apoptosis, and inhibiting tumor cell proliferation [61]</td>
</tr>
</tbody>
</table>

All test compound vectors have a weak positive correlation with standard compounds, with the exception of compounds D14 and D23, whose LC₅₀ correlates moderately with morpholino doxorubicin and mitoxantrone, respectively, in the lower part of the range.

The results obtained suggest that the above mechanisms of anticancer action of the standard compounds are not the main ones for the tested compounds. In addition, the high selectivity of the synthesized compounds with respect to individual cell lines most likely indicates their effect on specific molecular mechanisms inherent or playing a leading role only in the life cycle of these lines.

Tumors exhibit genetic and epigenetic heterogeneity, hence the need to study a panel of cell lines for each type of cancer to capture this heterogeneity and variability in drug response. However, there is also some heterogeneity between different cell lines in each subpanel of the NCI-60 panel [62].

Tumor heterogeneity is an important factor in the development of drug resistance because chemotherapy can select a drug-resistant subpopulation, leading to cancer treatment failure. Among a heterogeneous population of tumor cell lines, there may be only individual lines that are resistant to chemotherapy drugs indicated for the treatment of a particular tumor. Then compounds that are able to suppress resistant cell lines can help solve this problem.

From this point of view, compounds with high selective activity for even one cell line are of interest for further testing in tumor models that have developed resistance to specific drugs against a heterogeneous population of cell lines of a particular tumor after determining the appropriate resistance line.

4. Conclusions

The novel series of 4-arylsulfonyl-1,3-oxazoles have been synthesized in good yields and displayed different anticancer activity. Among their compounds, D14, D23 and D27 had the most activity. These compounds demonstrated the anticancer activity against different individual cancer cell lines. This makes it possible to consider it a leading compound for further...
in-depth studies and synthesis of new 4-arylsulfonyl-1,3-derivatives oxazole with antitumor activity.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References


Supplementary materials

Figure S1. $^1$H NMR spectrum of 4-(benzenesulfonyl)-5-isobutylsulfanyl-2-phenyl-1,3-oxazole (D1).

Figure S2. $^{13}$C NMR spectrum of 4-(benzenesulfonyl)-5-isobutylsulfanyl-2-phenyl-1,3-oxazole (D1).
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