

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 chromato-mass-spectrometry. The anti-cancer activities of all the newly synthesized compounds were evaluated via a single high dose (10 μ M) 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 anti-proliferative activity against the HOP-92 (carcinoma) of Non-Small Cell Lung Cancer subpanel, while N-(4-ethoxyphenyl)-2-[2-phenyl-4-(p-tolylsulfonyl)oxazol-5-yl]sulfanylacetamide 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 anti-cancer activity against different individual cancer cell lines, which makes it possible to consider it as a leading compound for further in-depth studies and synthesis of new 4-arylsulfonyl-1,3-derivatives oxazole with antitumor activity.

Keywords: 4-Arylsulfonyl-1,3-oxazoles, Synthesis, Anti-cancer 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 anti-cancer activity is required, among which an important place belongs to heterocyclic compounds, including 1,3-oxazole derivatives [1-4].

Anti-cancer activity, particularly in 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 Phorbasp. and its derivatives) [14], bis(benzoxazole from *Streptomyces* (UK-1) [15], 2-substituted benzoxazole [16], indolyloxazoles [17, 18], bis(carbomethoxymethylsulfonyl)amine linked bis heterocycles- bis-oxazoles [19], (2*S*)-2-amino-3-[4-[(5-amino-2-phenyl-1,3-benzoxazol-7-yl)methoxy]-3,5-dichlorophenyl]propanoic acid (JPH203) [20, 21], N-(dicyclopropylmethyl)-4,5-dihydrooxazol-2-amine (rilmenidin) [22], oxazoloisoindolinone SLMP53-1 [23, 24], 2-methyl-4,5-disubstituted oxazole derivatives [25], thio derivatives of combretastatin A-4 [26], diazomamide DZ-2384 [27], 3-(2-aminooxazol-5-yl)-2H-chromen-2-one derivatives [28], N-[5-[(5-tert-butyl-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 sulfonamides [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 belonging 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 hexaoxazole 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-arylsulfonyl-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-arylsulfonyl-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 RHIg: 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-*d*₆ 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) $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ 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).

Yield: 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). ^{13}C 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 $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{S}_2$, % : C 61.10; H 5.13; N 3.75; S 17.17. Found, % : C 61.12; H 5.24; N 3.61; S 17.23.

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

Yield: 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). ^{13}C 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 $\text{C}_{23}\text{H}_{19}\text{NO}_3\text{S}_2$, % : 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)

Yield: 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). ^{13}C 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 $\text{C}_{22}\text{H}_{16}\text{FNO}_3\text{S}_2$, % : 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).

Yield: 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). ^{13}C 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 $\text{C}_{23}\text{H}_{16}\text{ClNO}_4\text{S}_2$, % : 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).

Yield: 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). ^{13}C NMR: δ = 35.7,

125.1, 126.2, 127.2, 129.2, 129.7, 131.7, 134.3, 135.6, 139.9, 152.1, 160.8, 168.5. Anal. Calcd. for $C_{17}H_{14}N_2O_4S_2$, % : C 54.53; H 3.77; N 7.48; S 17.13. Found, % : C 54.40; H 3.85; N 7.30; S 17.24.

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). ^{13}C 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 $C_{23}H_{24}N_2O_4S_2$, %: C 60.50; H 5.30; N 6.14; S 14.05. Found, % : C 60.39; H 5.38; N 6.32; 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). ^{13}C 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 $C_{23}H_{17}FN_2O_4S_2$, %: 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). ^{13}C 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 $C_{25}H_{22}N_2O_5S_2$, %: 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). ^{13}C 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 $C_{17}H_{15}NO_3S_2$, %: 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). ^{13}C 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 $C_{19}H_{19}NO_3S_2$, %: 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]). 1H NMR: δ = 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: δ = 21.1, 36.8, 125.0, 126.3, 127.2, 127.6, 128.6, 128.8, 129.2, 130.1, 131.8, 136.9, 136.9, 138.4, 144.9, 150.3, 161.3. Anal. Calcd. for $C_{23}H_{19}NO_3S_2$, %: 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. 1H NMR: δ = 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: δ = 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 $C_{18}H_{16}N_2O_4S_2$, %: 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]sulfanyl-acetamide (D13).

Yield: 83%; m.p. 216-217°C. 1H NMR: δ = 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: δ = 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 $C_{24}H_{19}FN_2O_4S_2$, %: 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]sulfanyl-acetamide (D14).

Yield: 87%; m.p. 186-187°C. 1H NMR: δ = 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: δ = 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 $C_{26}H_{24}N_2O_5S_2$, %: 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]sulfanyl-acetamide (D15).

Yield: 80%; m.p. 136-137°C. 1H NMR: δ = 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: δ = 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 $C_{26}H_{24}N_2O_6S_2$, %: 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. ¹H NMR: δ = 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). ¹³C NMR: δ = 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), 137.3, 152.1, 161.5, 165.6 (d, *J*=253.6 Hz). ¹⁹F NMR: δ = -104.3. Anal. Calcd. for C₁₇H₁₄FN₃S₂, %: C 56.18; H 3.88; N 3.85; S 17.65. Found, % : C 56.13; H 3.90; N 3.82; S 17.60.

2.2.17. 5-[(4-Fluorophenyl)methylsulfanyl]-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (D17).

Yield: 79%; m.p. 113-114°C. ¹H NMR: δ = 4.49 (2H, s), 7.08 (2H, t, *J*=8.6 Hz), 7.35 – 7.50 (4H, m), 7.49 – 7.68 (3H, m), 7.84 – 7.96 (2H, m), 7.95 – 8.03 (2H, m). ¹³C NMR: δ = 36.5, 115.8 (d, *J*=21.6 Hz), 117.4 (d, *J*=23.0 Hz), 125.4, 126.7, 129.7, 130.9 (d, *J*=10.1 Hz), 131.2 (d, *J*=8.3 Hz), 132.3, 133.6, 136.5, 138.7, 150.9, 161.9 (d, *J*=244.2 Hz), 161.9, 165.7 (d, *J*=253.9 Hz). Anal. Calcd. for C₂₂H₁₅F₂NO₃S₂, %: C 59.58; 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-ethanone (D18).

Yield: 82%; m.p. 157-158°C. ¹H 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). ¹³C NMR: δ = 40.4, 117.5 (d, *J*=22.9 Hz), 125.3, 126.6, 129.5, 129.6, 130.9, 131.0, 132.2, 134.1, 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 C₂₃H₁₅ClFNO₄S₂, %: C 56.61; H 3.10; Cl 7.27; N 2.87; S 13.14. Found, % : C 56.63; H 3.08; Cl 7.25; N 2.90; S 13.10.

2.2.19. 2-[4-(4-Fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (D19).

Yield: 85%; m.p. 198-199°C. ¹H NMR: δ = 4.01 (2H, s), 7.25 (1H, s), 7.41 – 7.63 (5H, m), 7.71 (1H, s), 7.92 (2H, d, *J*=7.3 Hz), 8.02 – 8.16 (2H, m). ¹³C 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. ¹⁹F NMR: δ = -104.2. Anal. Calcd. for C₁₇H₁₃FN₂O₄S₂, %: 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. ¹H 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). ¹³C 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. ¹⁹F NMR: δ = -119.2, -104.1. Anal. Calcd. for C₂₃H₁₆F₂N₂O₄S₂, %: 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. ¹H 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). ¹³C 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). ¹⁹F NMR: δ = -104.12. Anal. Calcd. for C₂₅H₂₁FN₂O₅S₂, %: 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. ¹H NMR: δ = 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). ¹³C NMR: δ = 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. ¹⁹F NMR: δ = -104.12. Anal. Calcd. for C₂₅H₂₁FN₂O₄S₂, %: 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. ¹H NMR: δ = 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). ¹³C NMR: δ = 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 C₂₅H₂₁ClN₂O₆S₂, %: 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. ¹H NMR: δ = 2.74 (3H, s), 7.47 – 7.60 (3H, m), 7.80 – 7.98 (6H, m). ¹³C NMR: δ = 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 C₁₆H₁₂BrNO₃S₂, %: 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-Bromophenyl)sulfonyl-5-isopropylsulfanyl-2-phenyl-1,3-oxazole (D25).

Yield: 68%; m.p. 138-139°C. ¹H NMR: δ = 1.36 (6H, s), 3.66 – 4.14 (1H, m), 7.13 – 8.24 (9H, m). ¹³C NMR: δ = 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 C₁₈H₁₆BrNO₃S₂, %: 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)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-1-phenyl-ethanone (D26).

Yield: 85%; m.p. 143-144°C. ¹H NMR: δ = 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). ¹³C NMR: δ = 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 $C_{23}H_{16}BrNO_4S_2$, %: 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. 1H NMR: δ = 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: δ = 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 $C_{17}H_{13}BrN_2O_4S_2$, %: 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. 1H NMR: δ = 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: δ = 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 $C_{23}H_{23}BrN_2O_4S_2$, %: 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. 1H NMR: δ = 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: δ = 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, 152.3, 157.5, 161.6, 165.9. ^{19}F NMR: δ = -119.13. Anal. Calcd. for $C_{23}H_{16}BrFN_2O_4S_2$, %: 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. 1H NMR: δ = 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: δ = 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 $C_{25}H_{21}BrN_2O_5S_2$, %: 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. 1H NMR: δ = 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: δ = 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 $C_{25}H_{21}BrN_2O_6S_2$, %: 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-tolyl)-1,3-oxazole (D32).

Yield: 68%; m.p. 155-156°C (157-159°C[42]). ¹H NMR: δ = 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). ¹³C NMR: δ = 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 C₁₇H₁₅NO₃S₂, %: 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-[4-(Benzenesulfonyl)-2-(4-tolyl)-1,3-oxazol-5-yl]sulfanylacetamide (D33).

Yield: 77%; m.p. 217-218°C. ¹H NMR: δ = 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). ¹³C NMR: δ = 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 C₁₈H₁₆N₂O₄S₂, %: 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* anti-cancer 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 a total of 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 anti-cancer 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% CO₂ 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 the measurement of cellular protein content. 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 repeated 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.

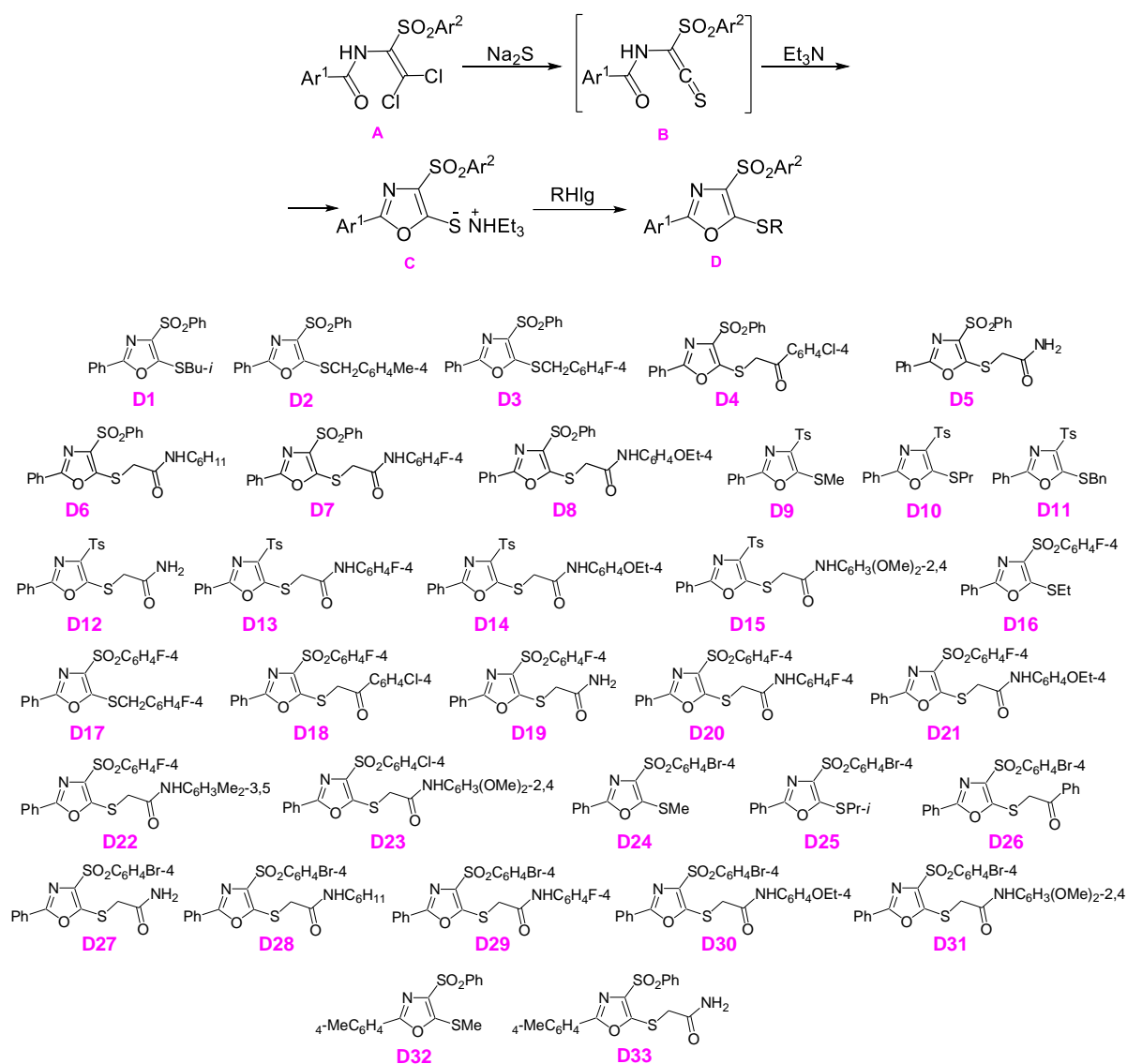
Compounds having similar activity profiles often have similar mechanisms of action and resistance. To measure the degree of similarity between novel compounds and known drugs in the NCI databases, a method has been developed using the Pearson correlation coefficient (PCC) as a comparison criterion (COMPARE 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 a 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-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 thioketene 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 SAIk, SCH₂Ar, SCH₂COAr, SCH₂CONHR groups at C5 ring atom was obtained for anti-cancer testing.



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 ($\geq 70\%$), 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 of anti-cancer screening data of the most active compounds against NCI-60 human tumor cell lines.

Compound	Cancer cell subpanel				
	Lung	CNS	Ovarian	Renal	Colon
D13	HOP-92 (79)				
D14	NCI-H226 (121)	SF-539 (82)			HCT-116 (76)
D21		SF-539 (93)			HCT-116 (78)
D23	NCI-226 (98)	SNB75 (102) SF-539 (100)	-	RXF393 (84)	
D27	HOP-92 (95)	SNB-75 (90)	-	786-0 (74)	
D29	HOP-62 (72)	U251 (77)	OVCAR-8 (71)	786-0 (79)	

The compounds added at a concentration ($1 \cdot 10^{-5}$ 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 detection of both 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 anti-proliferative 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 anti-proliferative 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-arylsulfonyl-1,3-oxazoles with different substituents 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**

Compound	Correlating drug	Correlation coefficient	Reported Mechanism(s)
GI₅₀			
D14	Morpholinodoxorubicin	0.54	Intercalates DNA and stimulates DNA topoisomerase I-induced cleavage at specific DNA sites [53]. Its active microsomal metabolites alkylate DNA [54]
D23	4-Nitroestrone 3-methyl ether	0.50	Inhibits estrogen sulfotransferase, a progesterone-induced secretory endometrial enzyme that affects estrogen receptor levels [55]
D27	Nitroestrone Tamoxifen	0.48	Tamoxifen reduces DNA synthesis by inhibiting the binding of estradiol to estrogen receptors, as well as acting on a number of signal proteins (calmodulin, protein kinase C, phospholipase C, phosphoinositide kinase, P-glycoprotein) [56]
TGI			
D14	Bleomycin	0.34	Bleomycin causes oxidative damage to DNA, leading to single-strand and double-strand breaks and G2 cell cycle arrest [57]
D23	Ftorafur Bleomycin	0.47	Ftorafur inhibits thymidylate synthase during the pyrimidine pathway involved in DNA synthesis [58]
D27	Dihydroleoneperone	0.50	Dihydroleoneperone inhibits the growth of lung cancer cells [59]. The mechanism of molecular action is not found in the available literature.
LC₅₀			
D14	Bleomycin	0.34	See above
D23	DHAD (mitoxantrone)	0.51	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]
D27	DHAD Diaziquone (AZQ)	0.47	Diaziquone selectively alkylates and crosslinks DNA at the 5'-GNC-3' sequence, inhibiting DNA replication, inducing apoptosis, and inhibiting tumor cell proliferation [61]

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 anti-cancer 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 a highly 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 anti-cancer activities. Among their compounds, **D14**, **D23** and **D27** had the most activity. These compounds demonstrated the anti-cancer 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.

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Supplementary Material

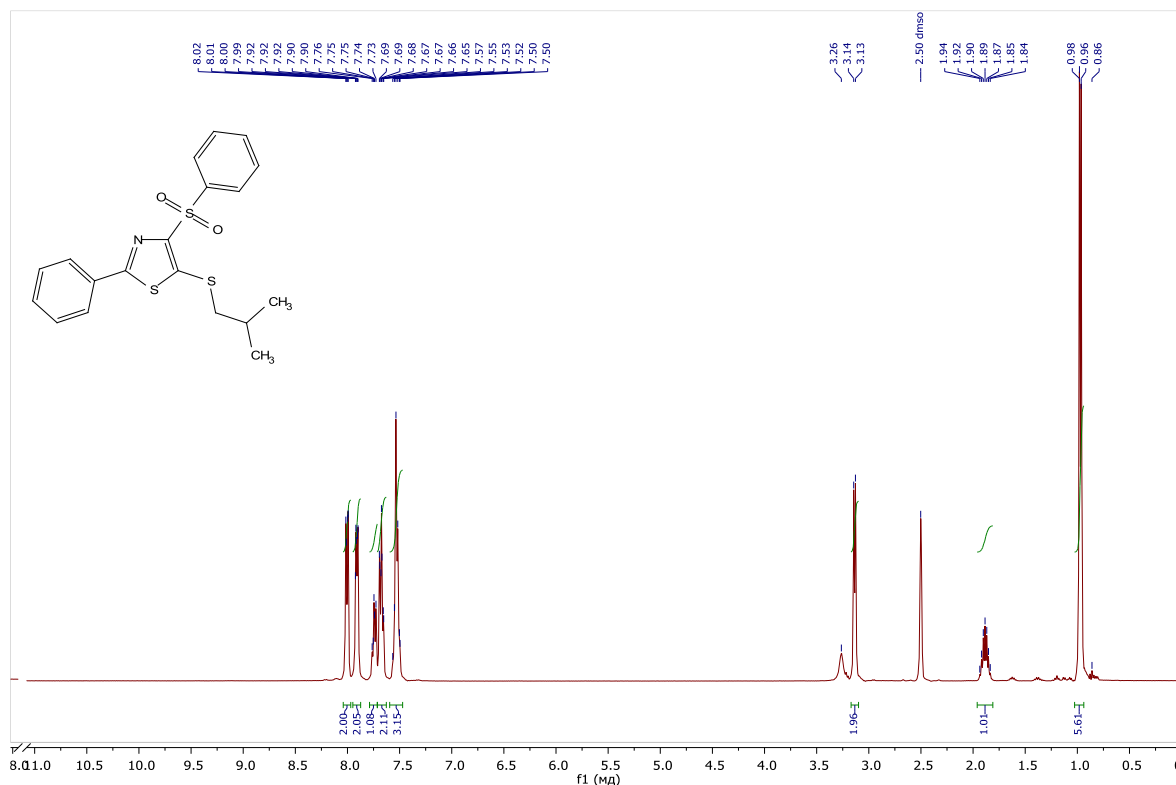


Figure S1. ¹H NMR spectrum of 4-(benzenesulfonyl)-5-isobutylsulfanyl-2-phenyl-1,3-oxazole (D1).

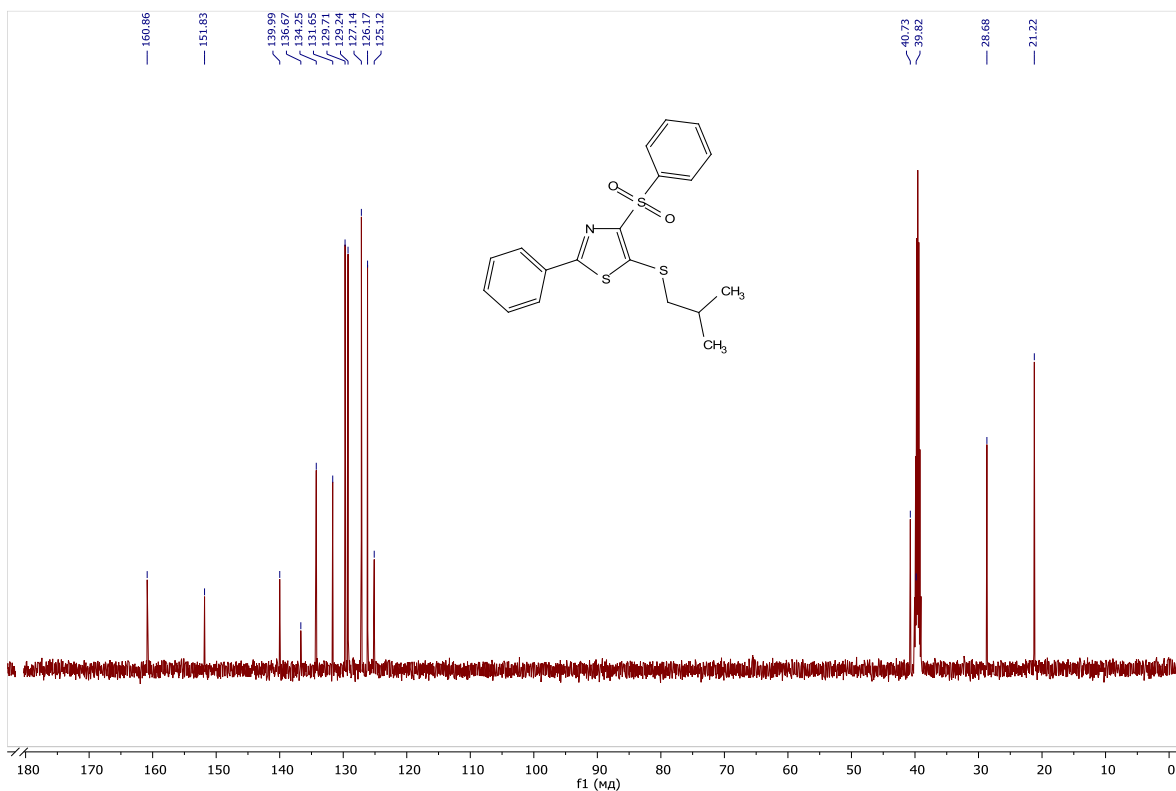


Figure S2. ¹³C NMR spectrum of 4-(benzenesulfonyl)-5-isobutylsulfanyl-2-phenyl-1,3-oxazole (D1).

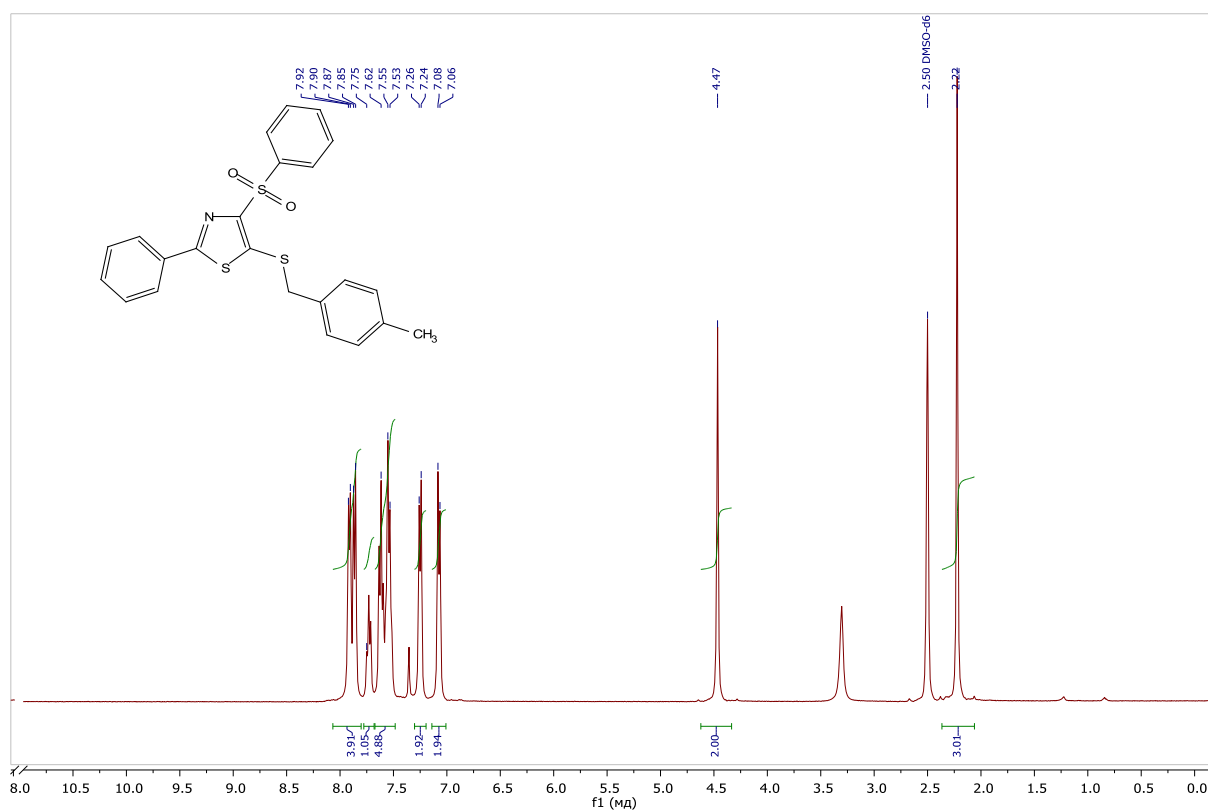


Figure S3. ¹H NMR spectrum of 4-(benzenesulfonyl)-2-phenyl-5-(4-tolylmethylsulfanyl)-1,3-oxazole (**D2**).

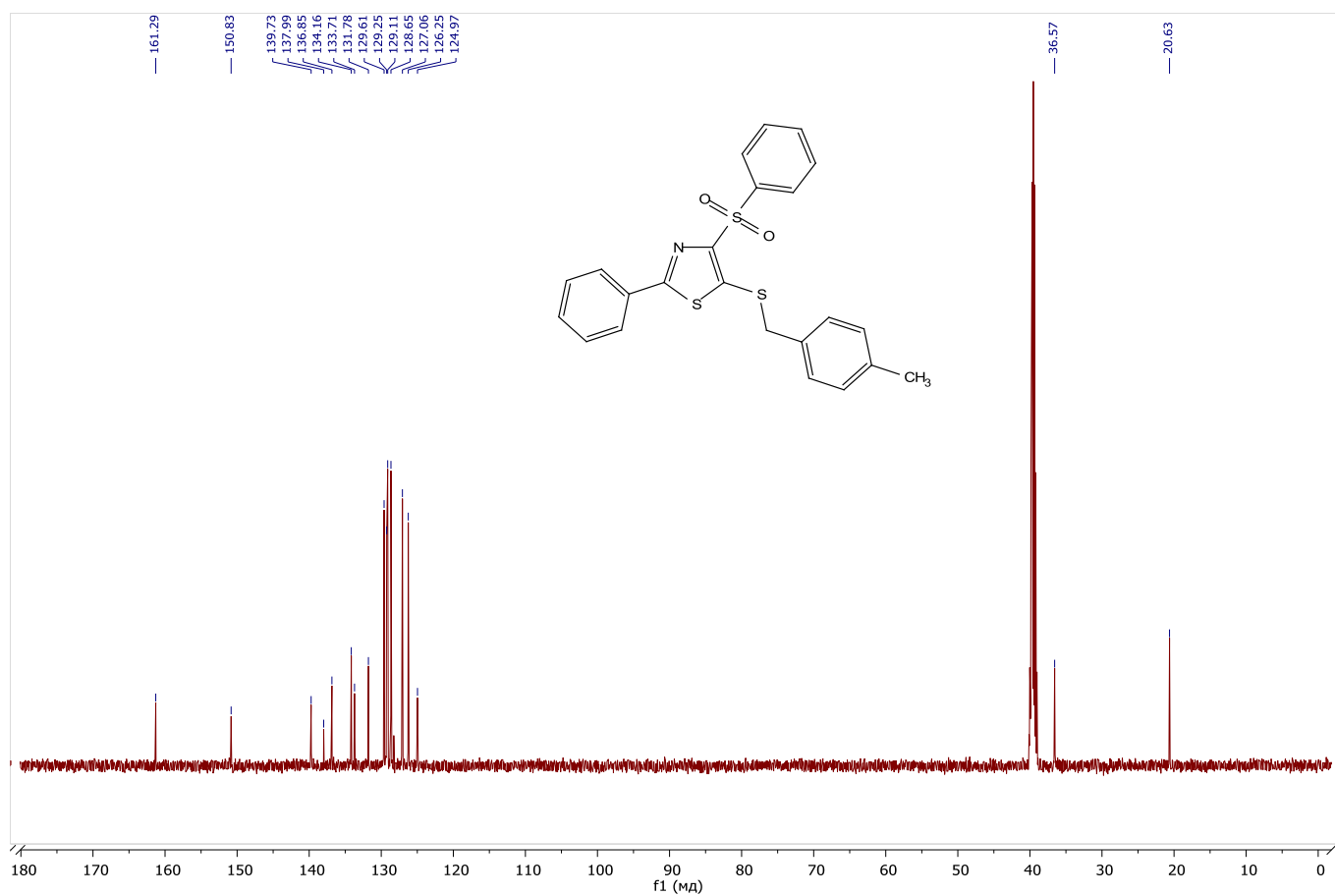


Figure S4. ¹³C NMR spectrum of 4-(benzenesulfonyl)-2-phenyl-5-(4-tolylmethylsulfanyl)-1,3-oxazole (**D2**).

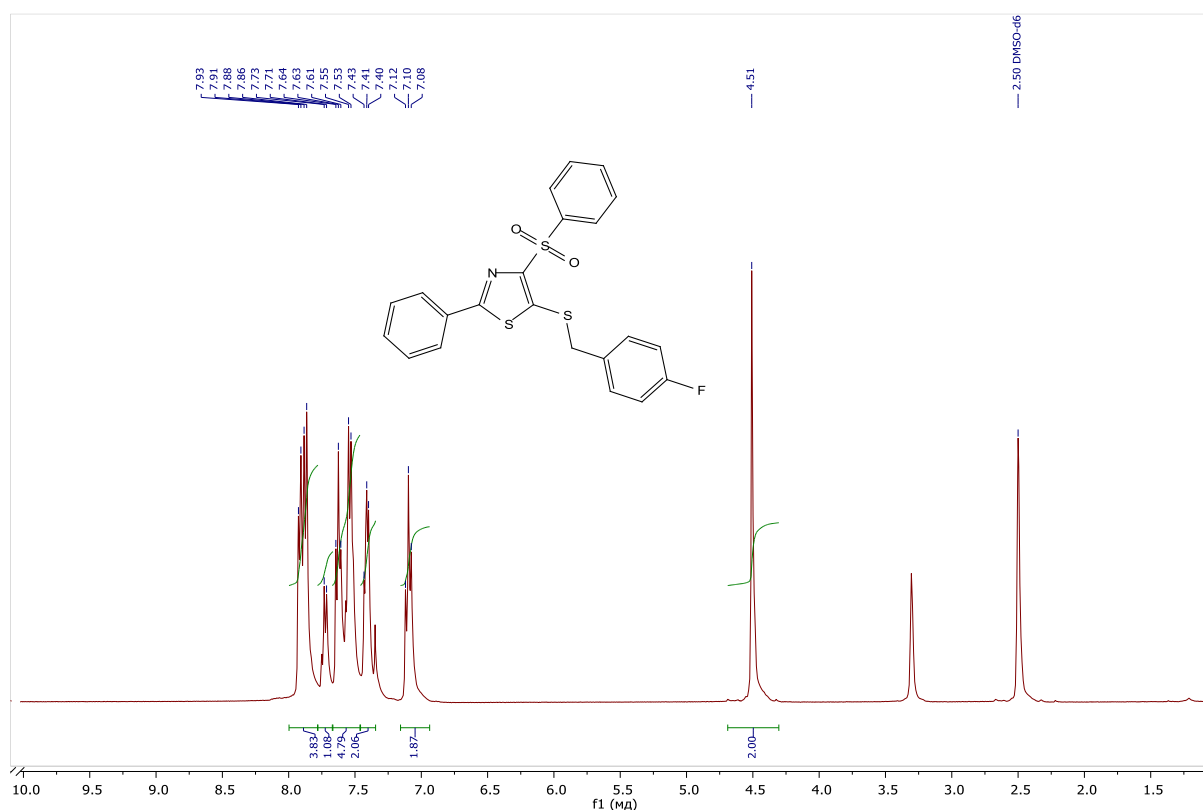


Figure S5. ^1H NMR spectrum of 4-(benzenesulfonyl)-5-[(4-fluorophenyl)methylsulfanyl]-2-phenyl-1,3-oxazole (**D3**).

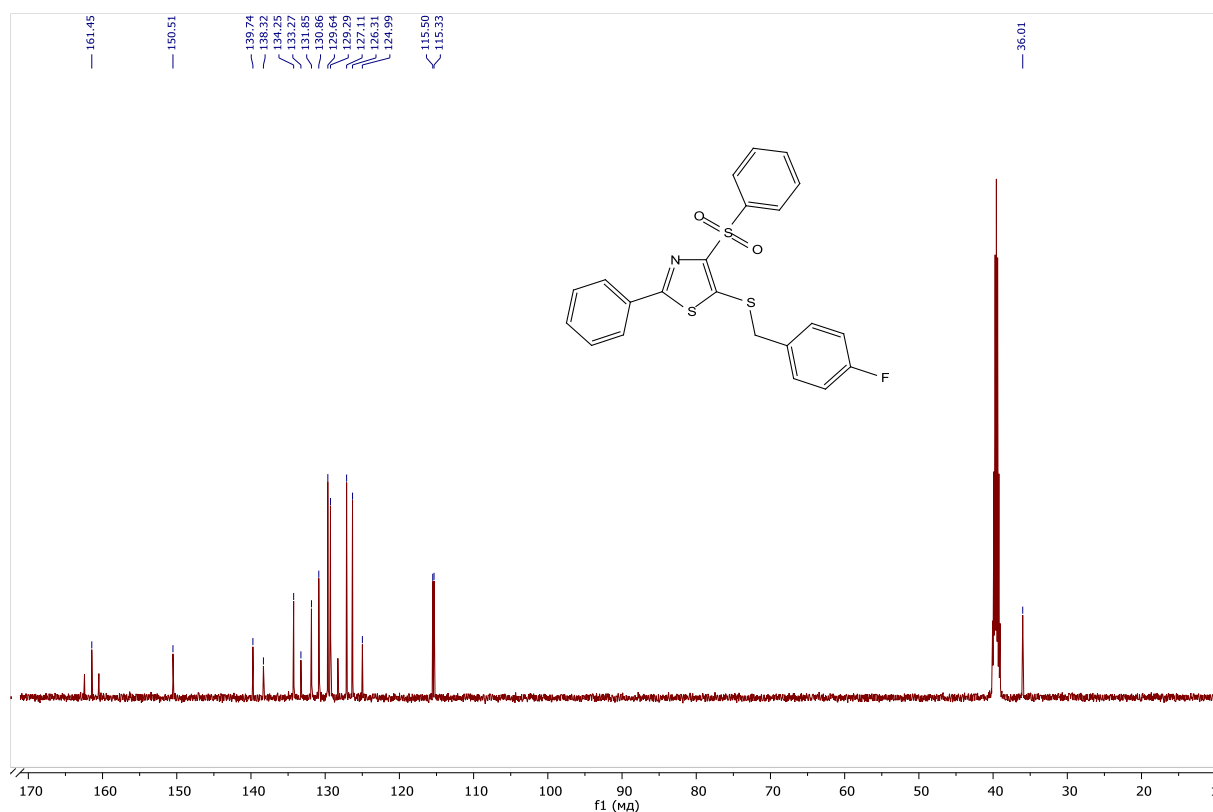
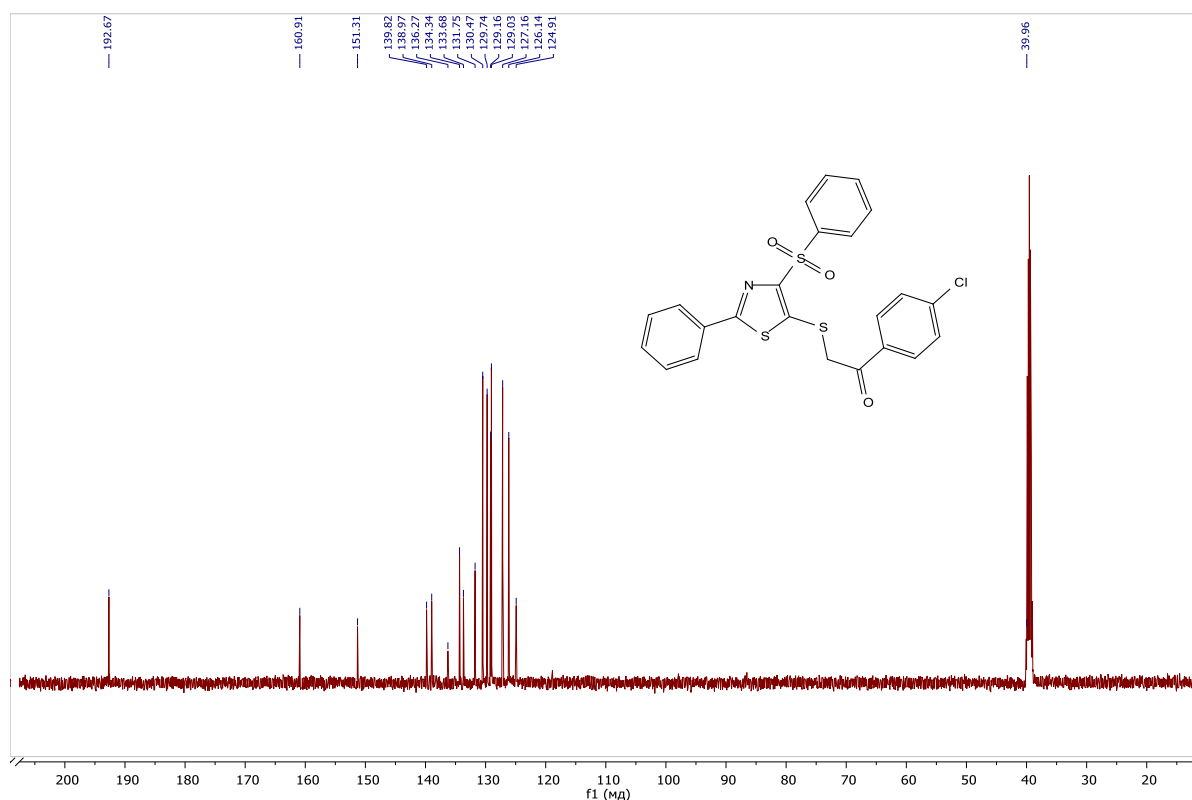
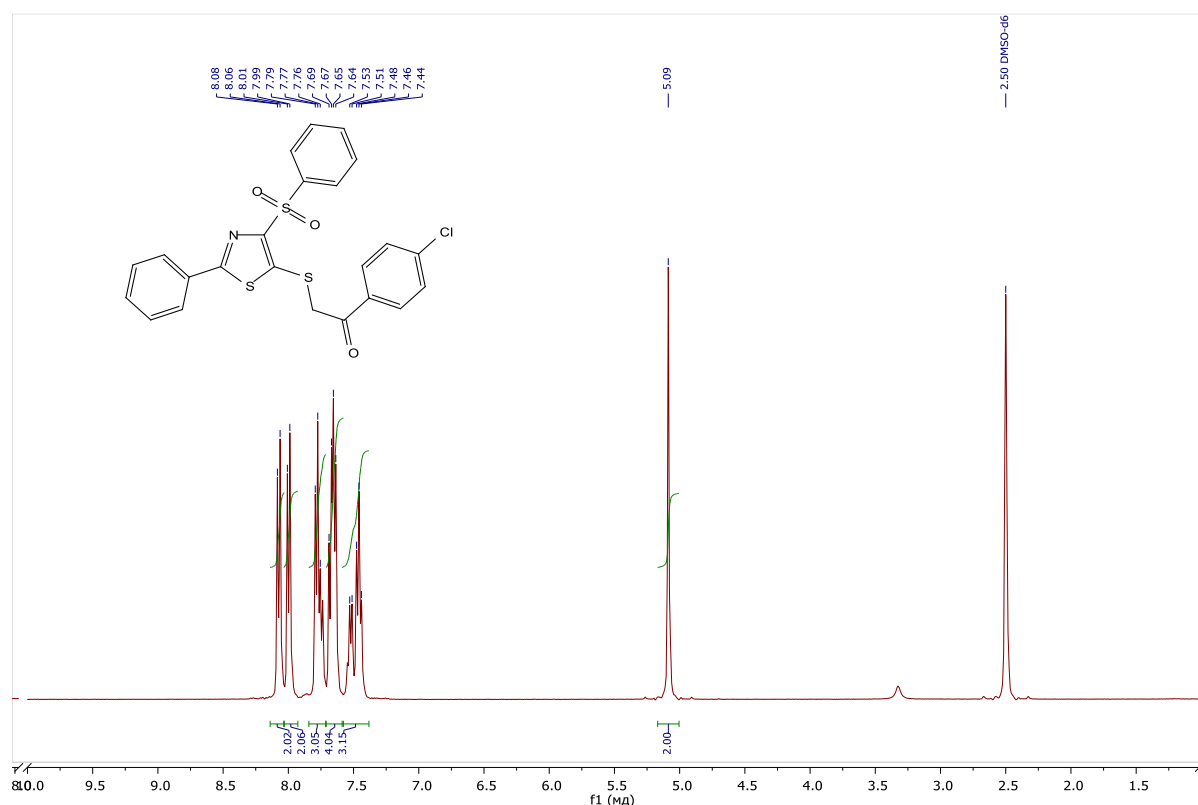


Figure S6. ^{13}C NMR spectrum of 4-(benzenesulfonyl)-5-[(4-fluorophenyl)methylsulfanyl]-2-phenyl-1,3-oxazole (**D3**).



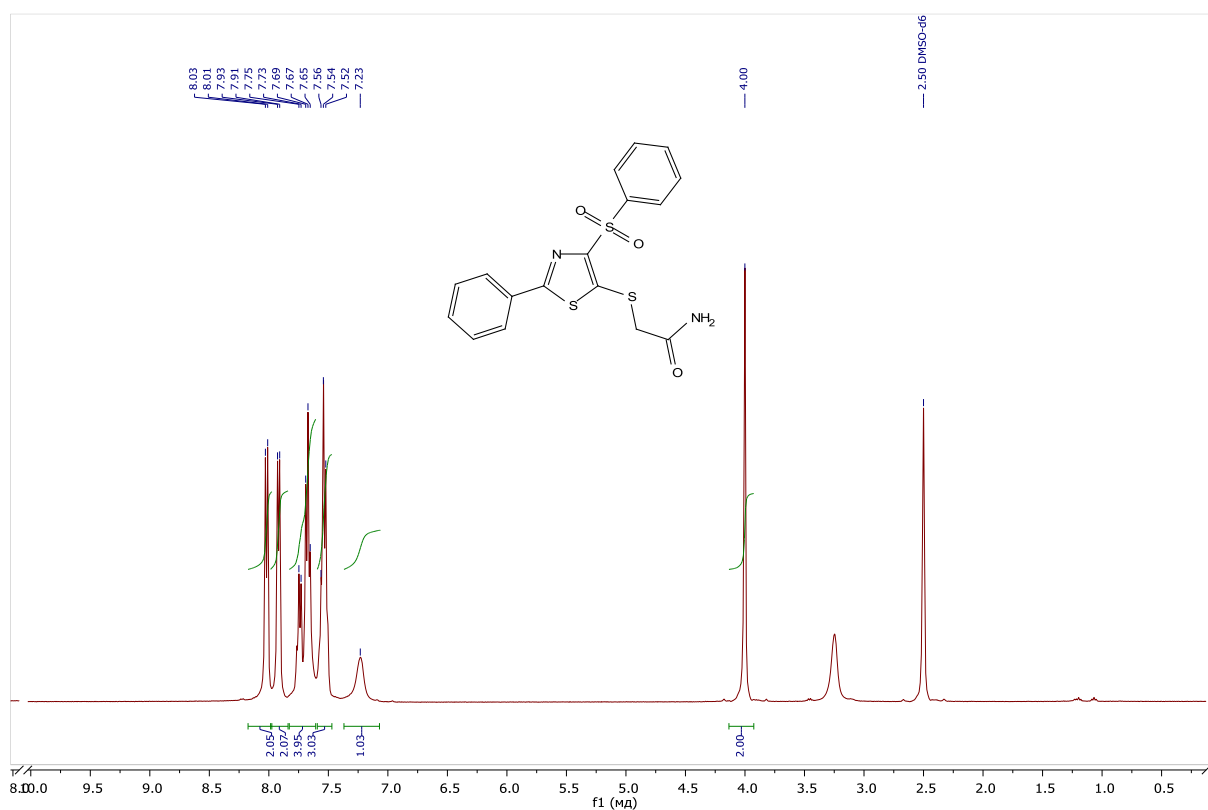


Figure S9. ¹H NMR spectrum of 2-[4-(benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (**D5**)

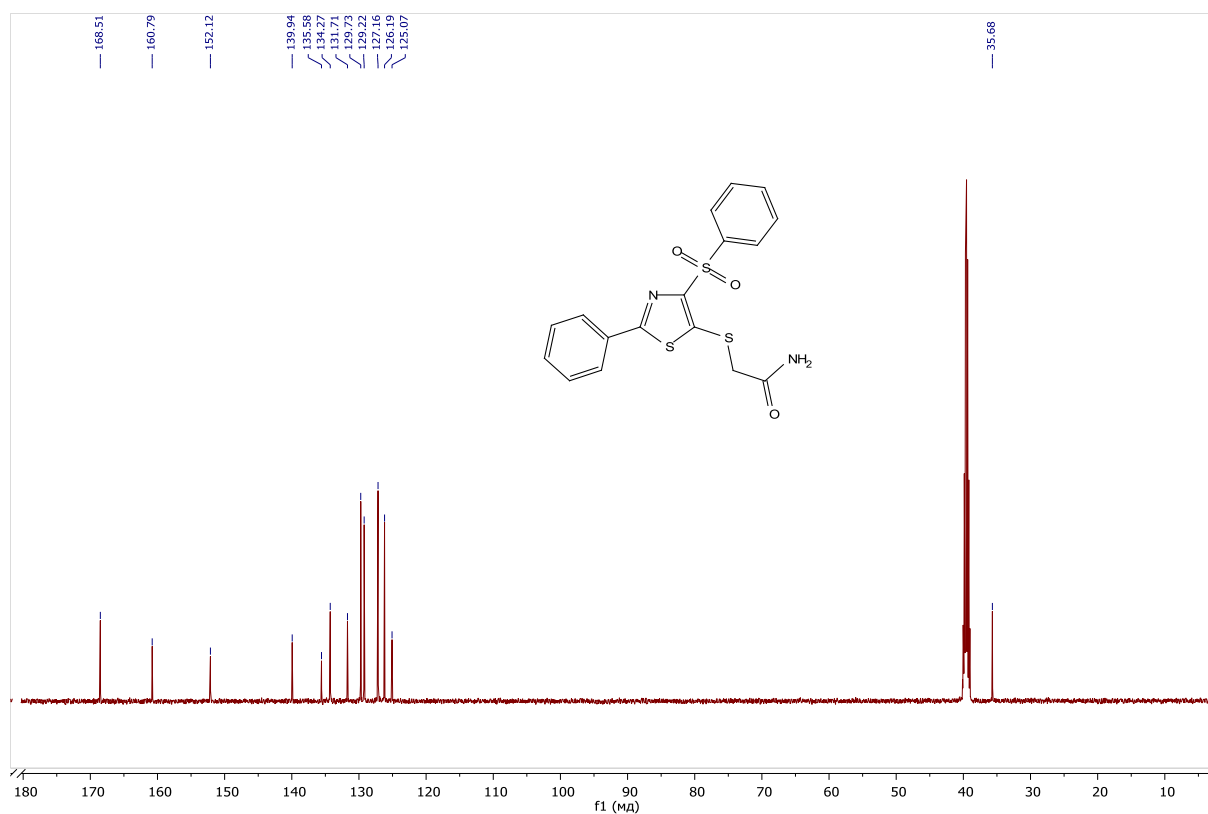
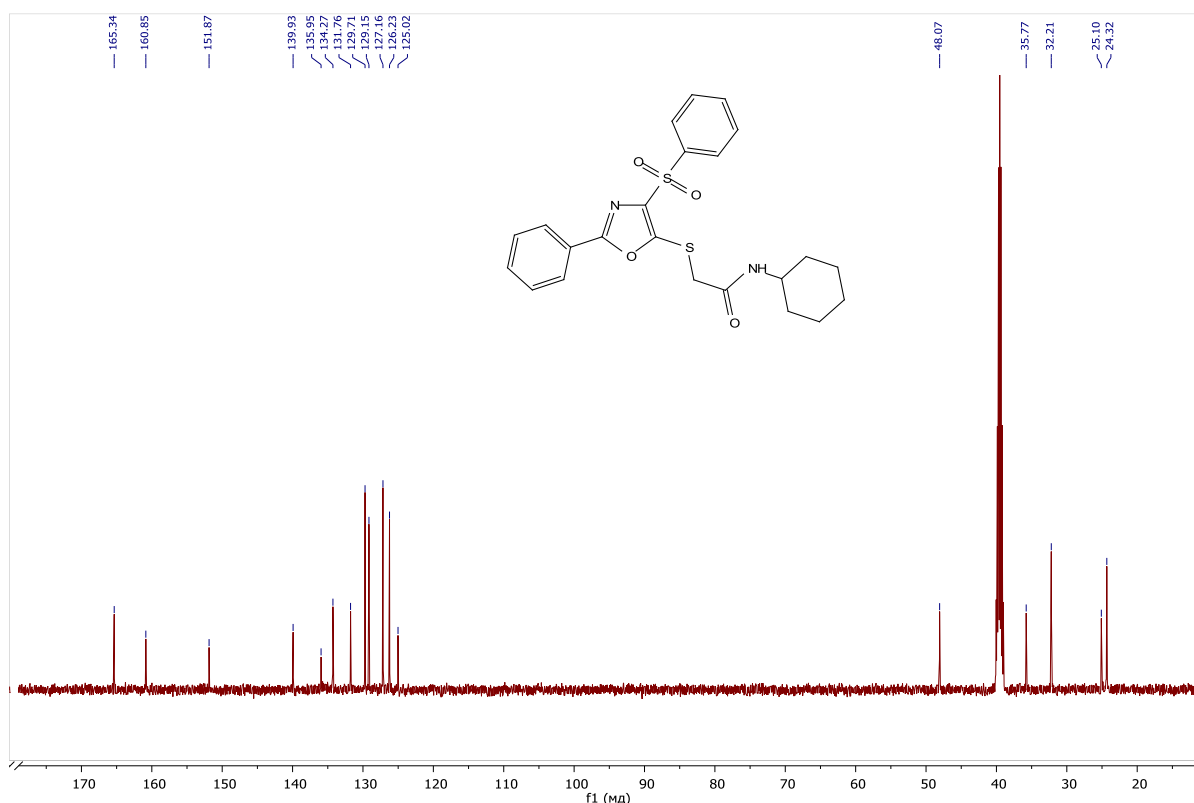
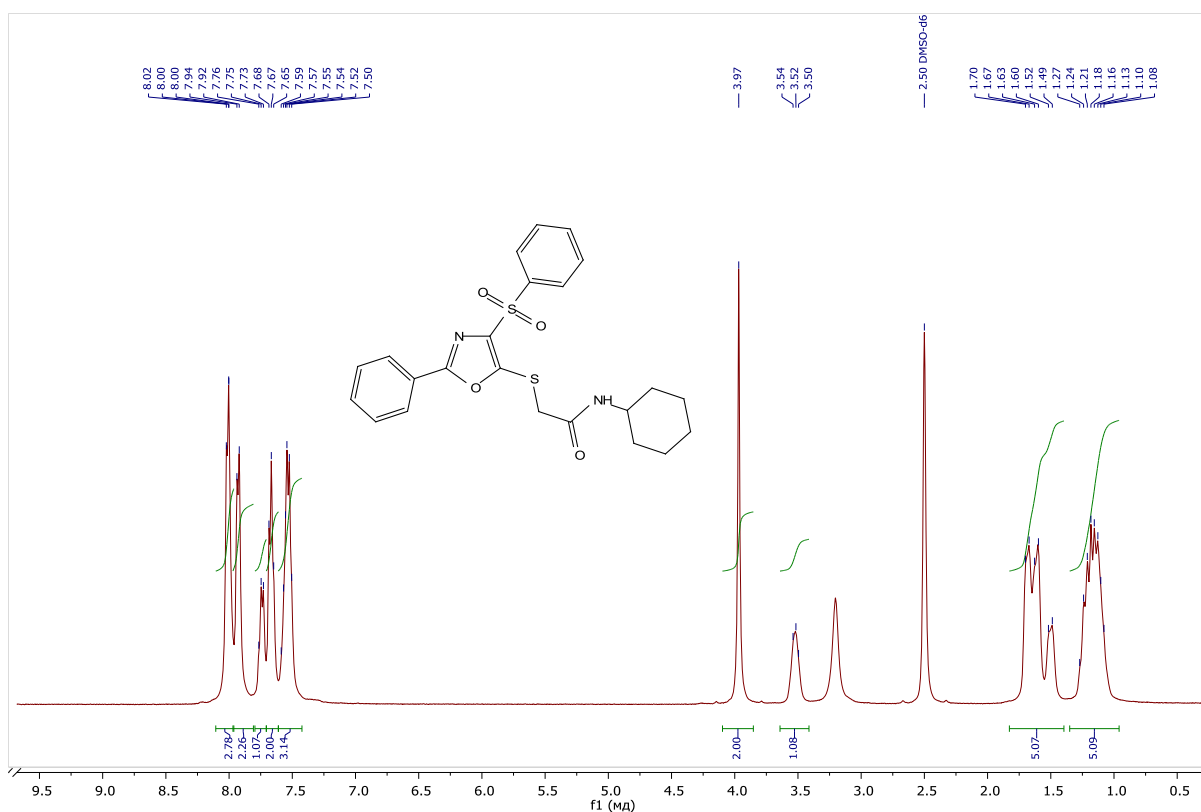


Figure S10. ¹³C NMR spectrum of 2-[4-(benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (**D5**).



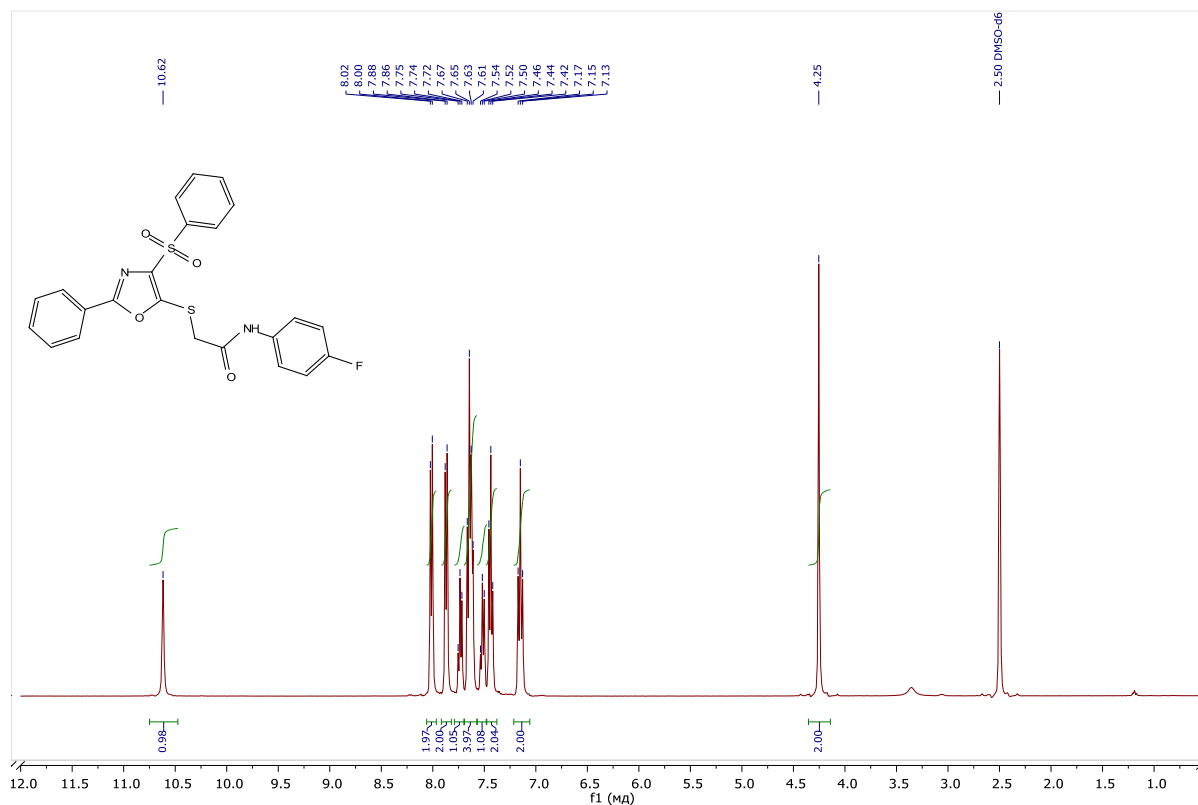


Figure S13. ¹H NMR spectrum of 2-[4-(benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-fluorophenyl)acetamide (**D7**).

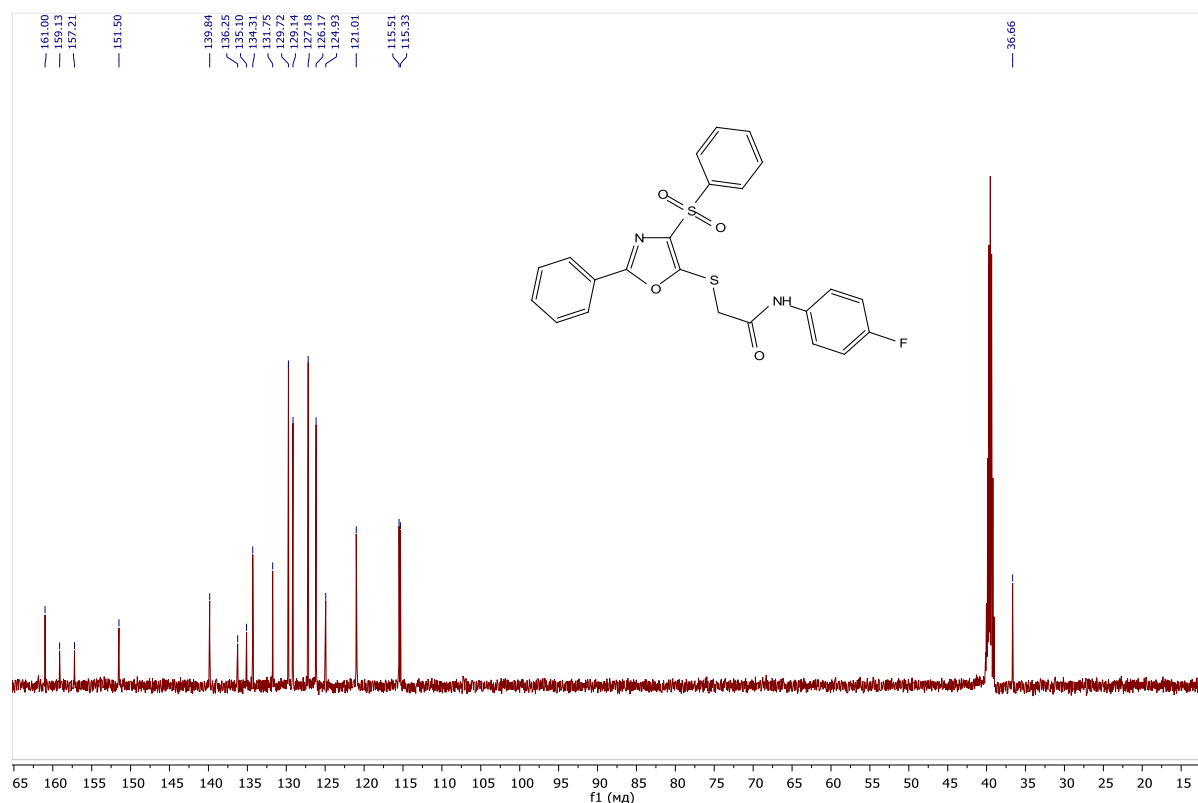


Figure S14. ¹³C NMR spectrum of 2-[4-(benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-fluorophenyl)acetamide (**D7**).

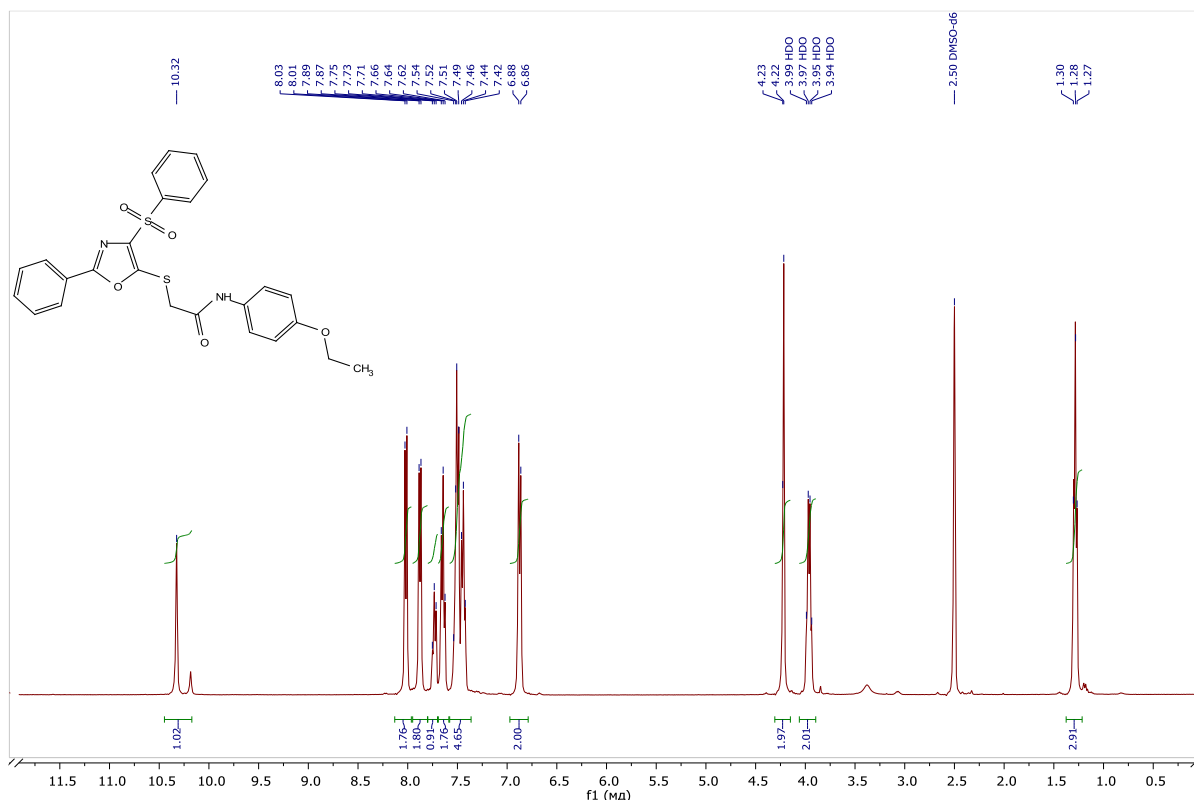


Figure S15. ¹H NMR spectrum of 2-[4-(benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-ethoxyphenyl)acetamide (**D8**).

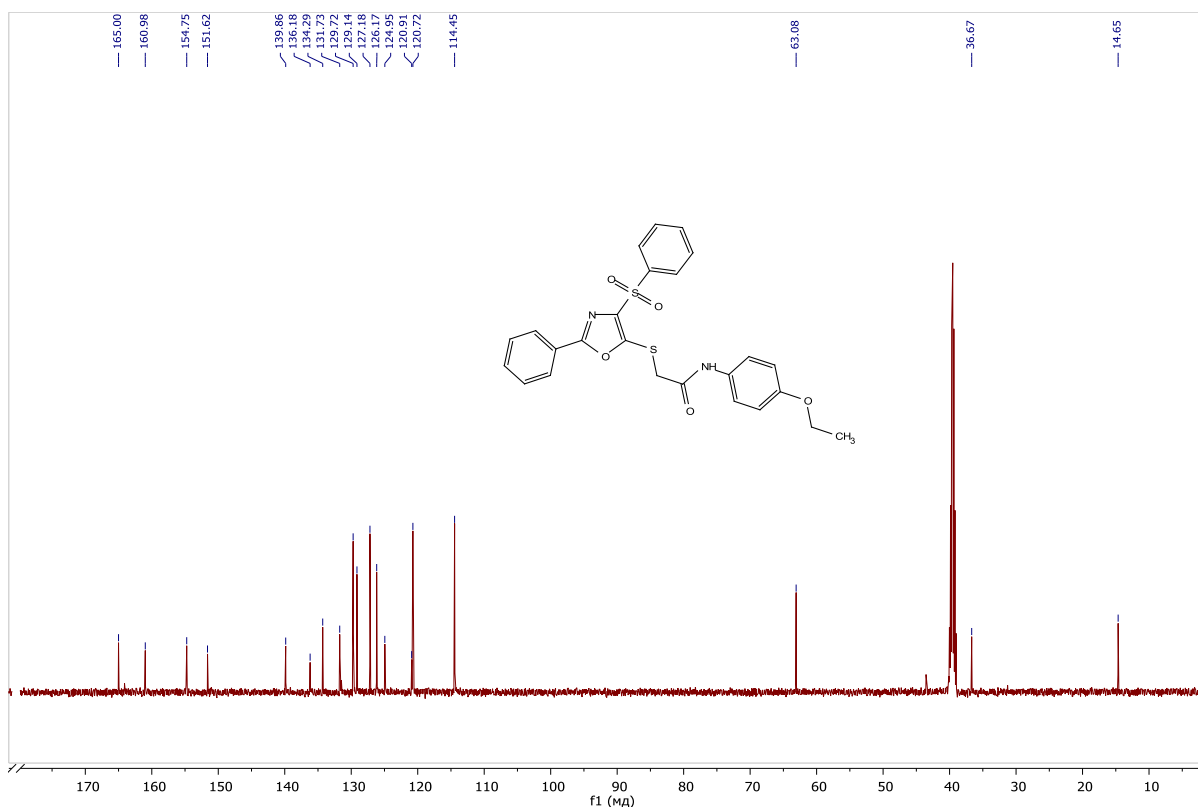


Figure S16. ¹³C NMR spectrum of 2-[4-(benzenesulfonyl)-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-ethoxyphenyl)acetamide (**D8**).

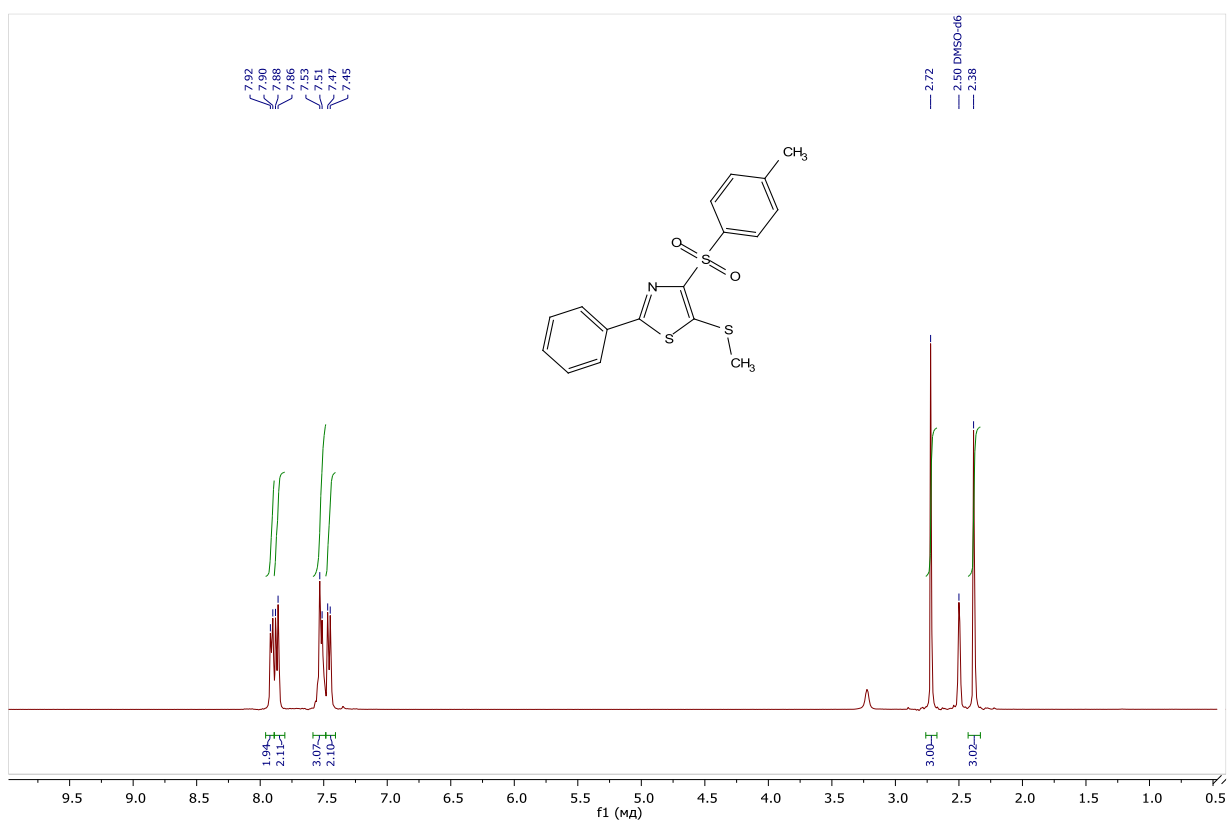


Figure S17. ¹H NMR spectrum of 2-phenyl-5-methylsulfanyl-4-(4-tolylsulfonyl)-1,3-oxazole (D9).

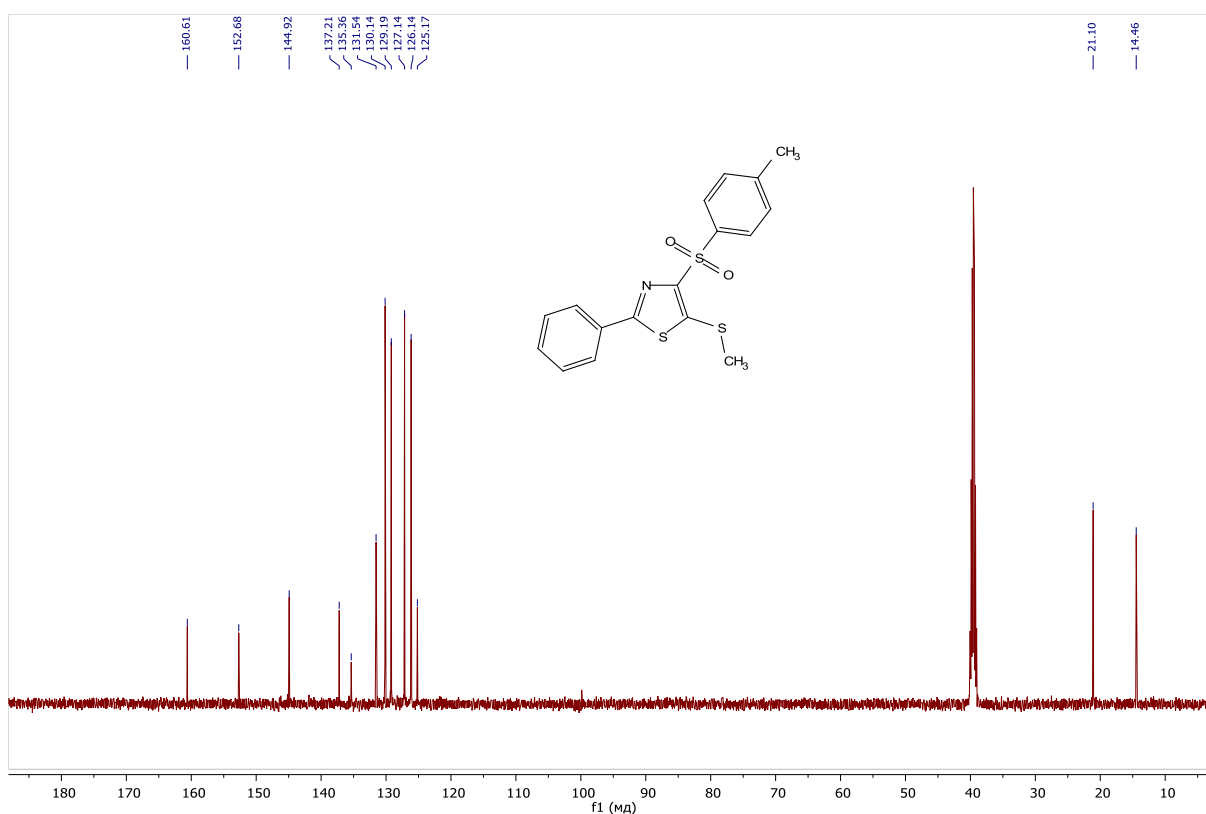


Figure S18. ¹³C NMR spectrum of 2-phenyl-5-methylsulfanyl-4-(4-tolylsulfonyl)-1,3-oxazole (D9).

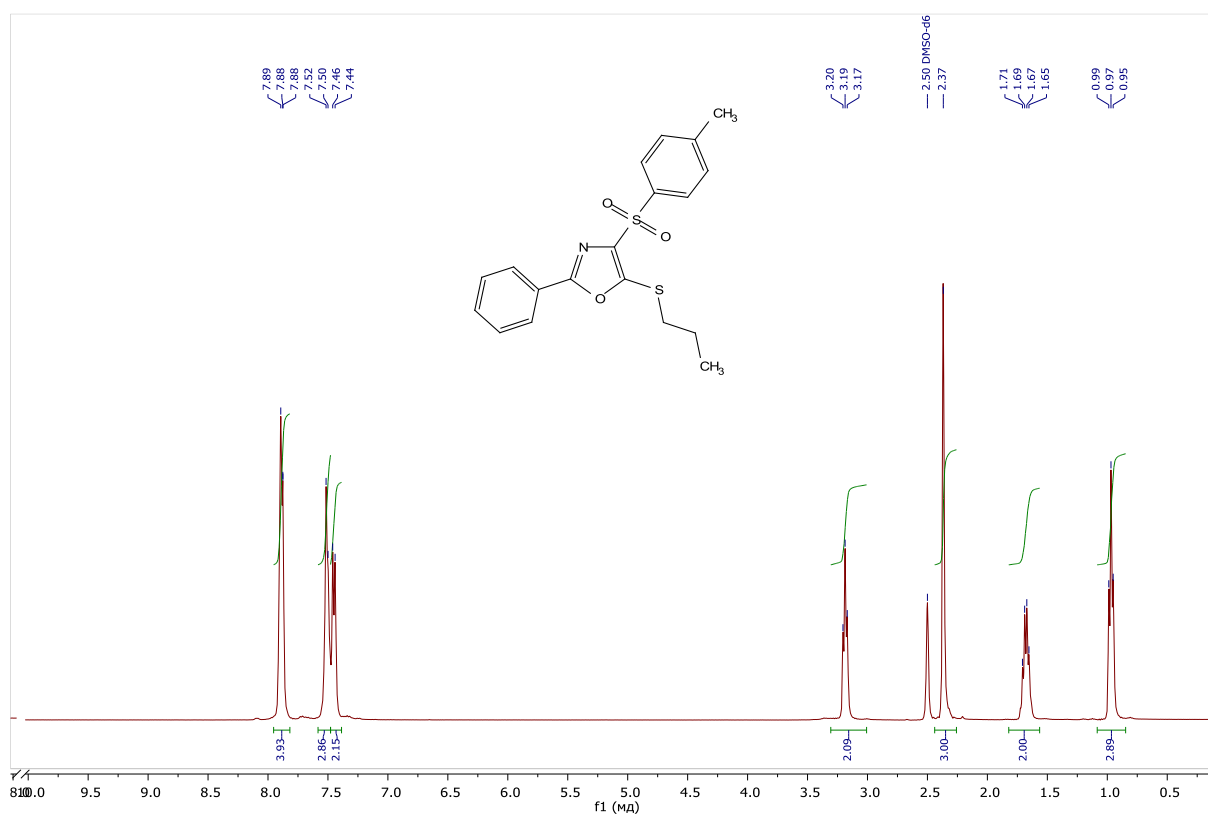


Figure S19. ¹H NMR spectrum of 2-phenyl-5-propylsulfanyl-4-(4-tolylsulfonyl)-1,3-oxazole (D10).

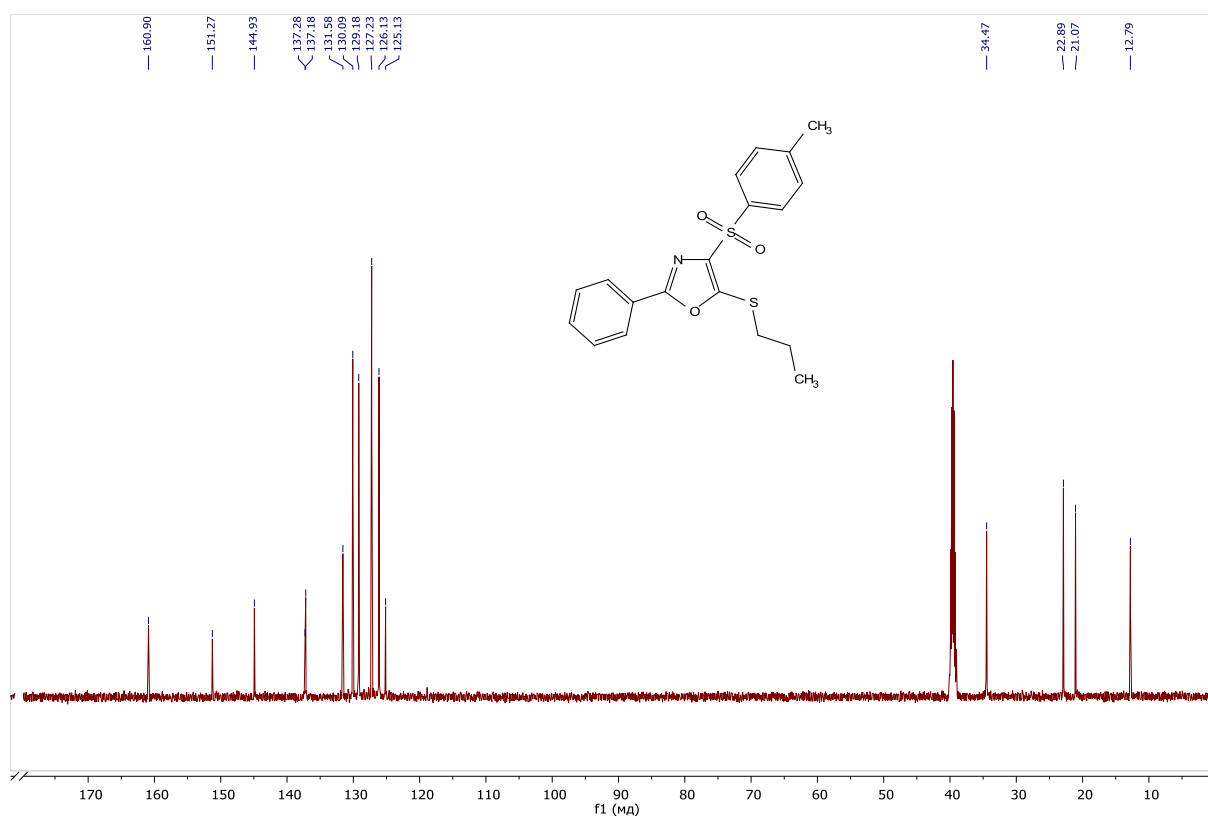


Figure S20. ¹³C NMR spectrum of 2-phenyl-5-propylsulfanyl-4-(4-tolylsulfonyl)-1,3-oxazole (D10).

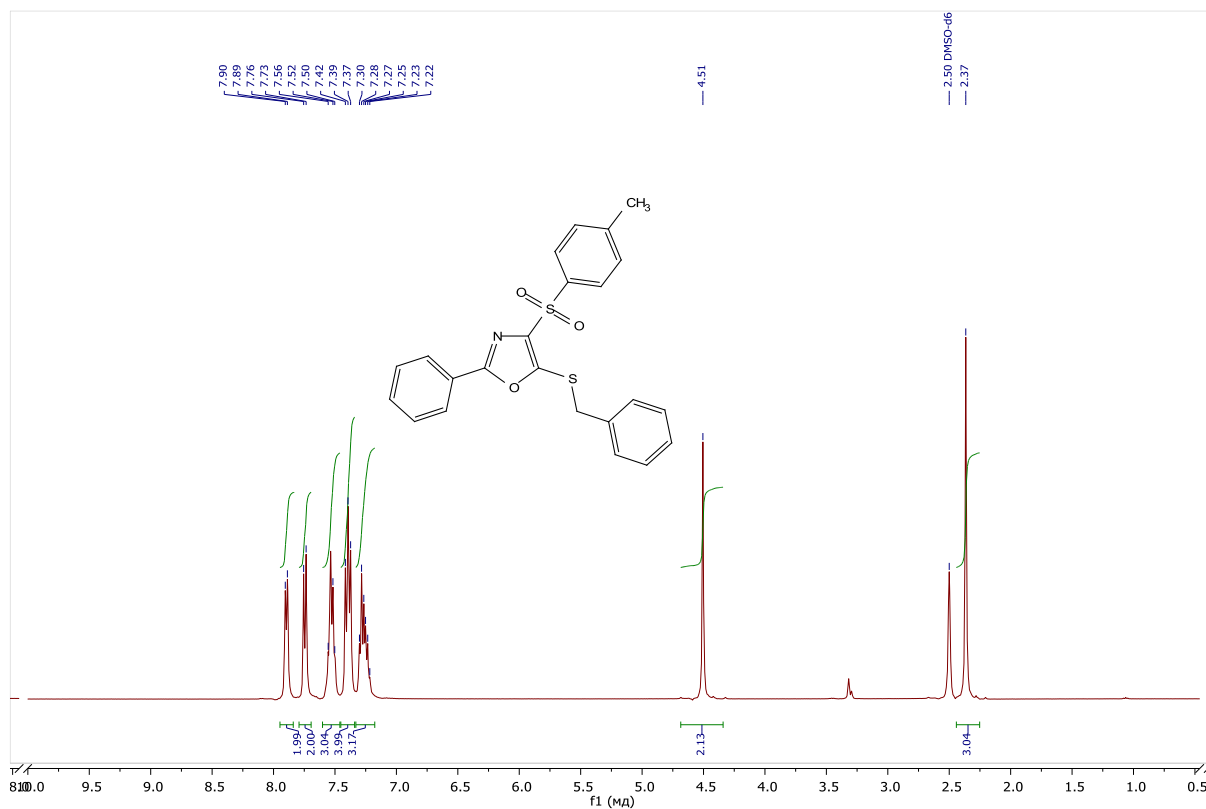


Figure S21. ¹H NMR spectrum of 5-benzylsulfanyl-2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazole (**D11**).

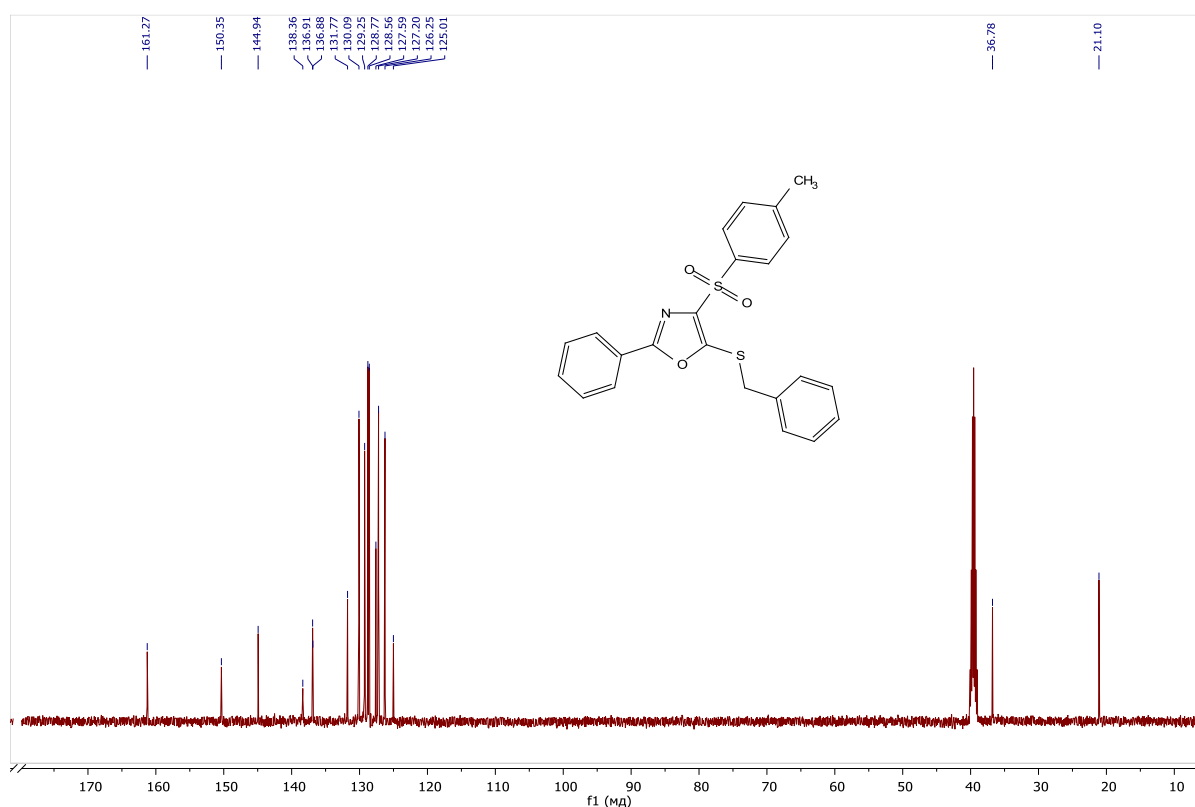
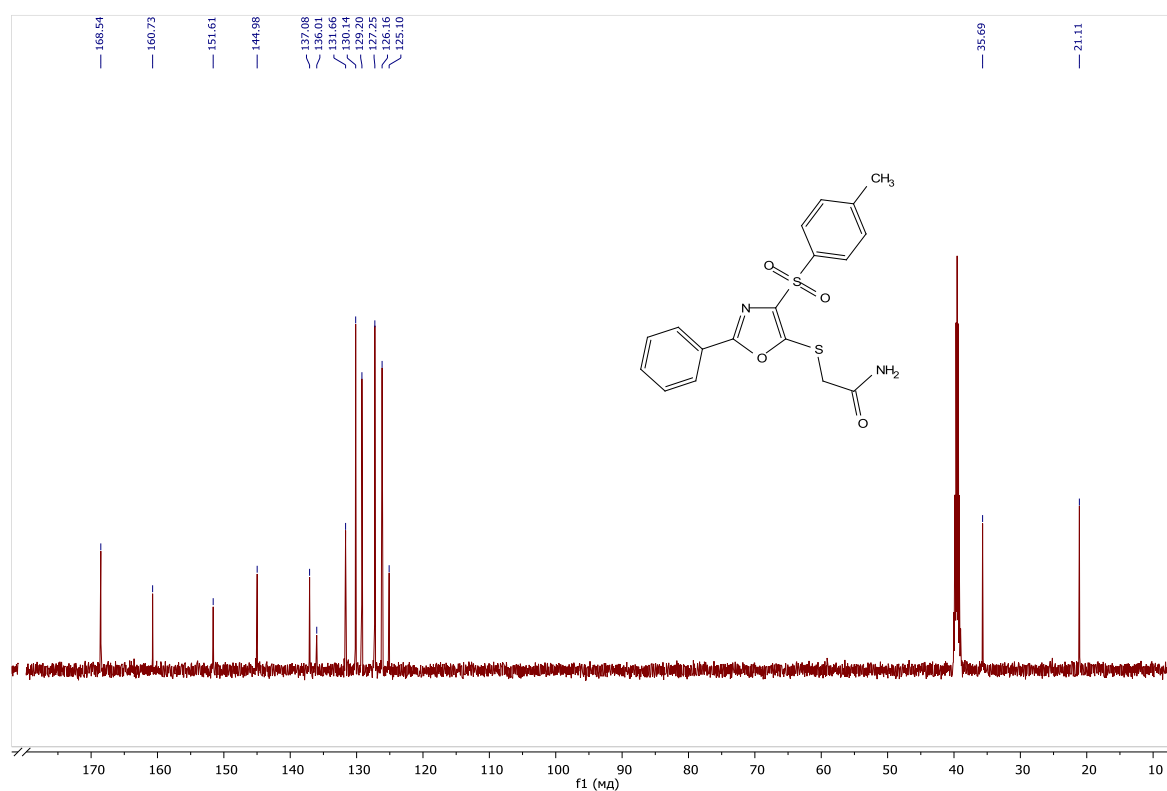
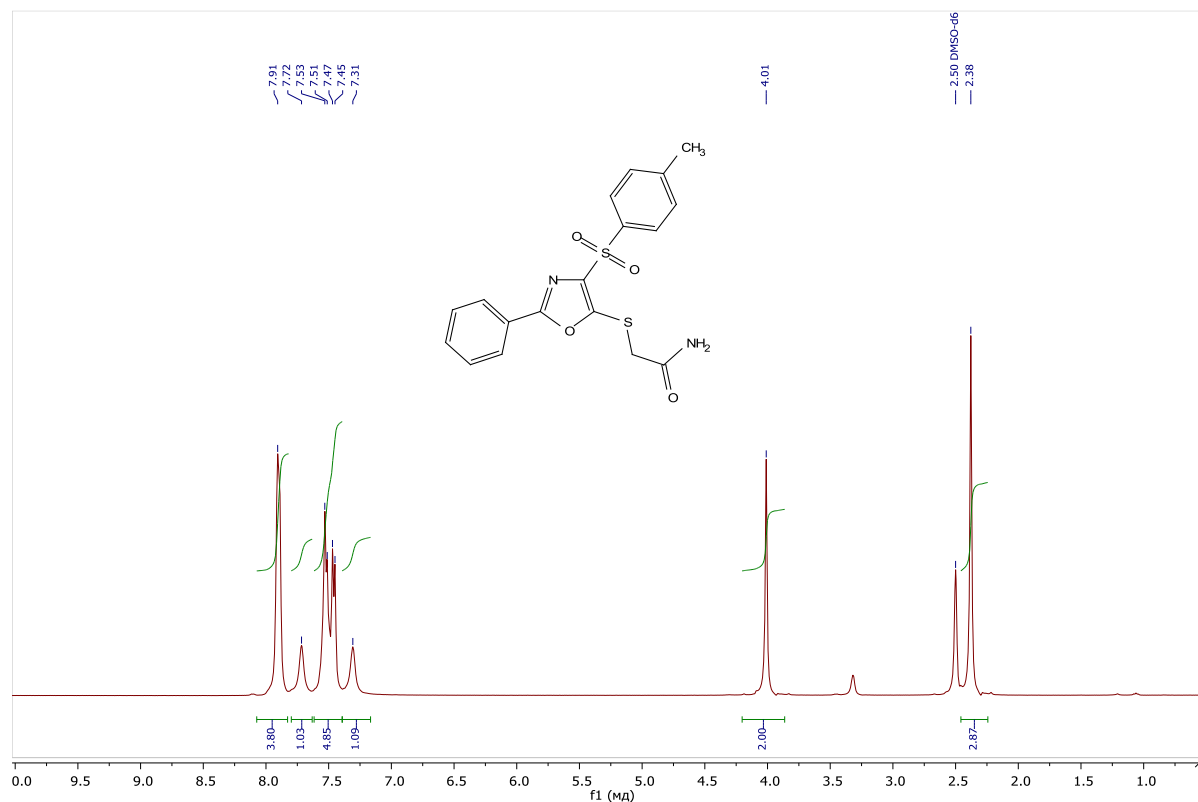


Figure S22. ¹³C NMR spectrum of 5-benzylsulfanyl-2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazole (**D11**).



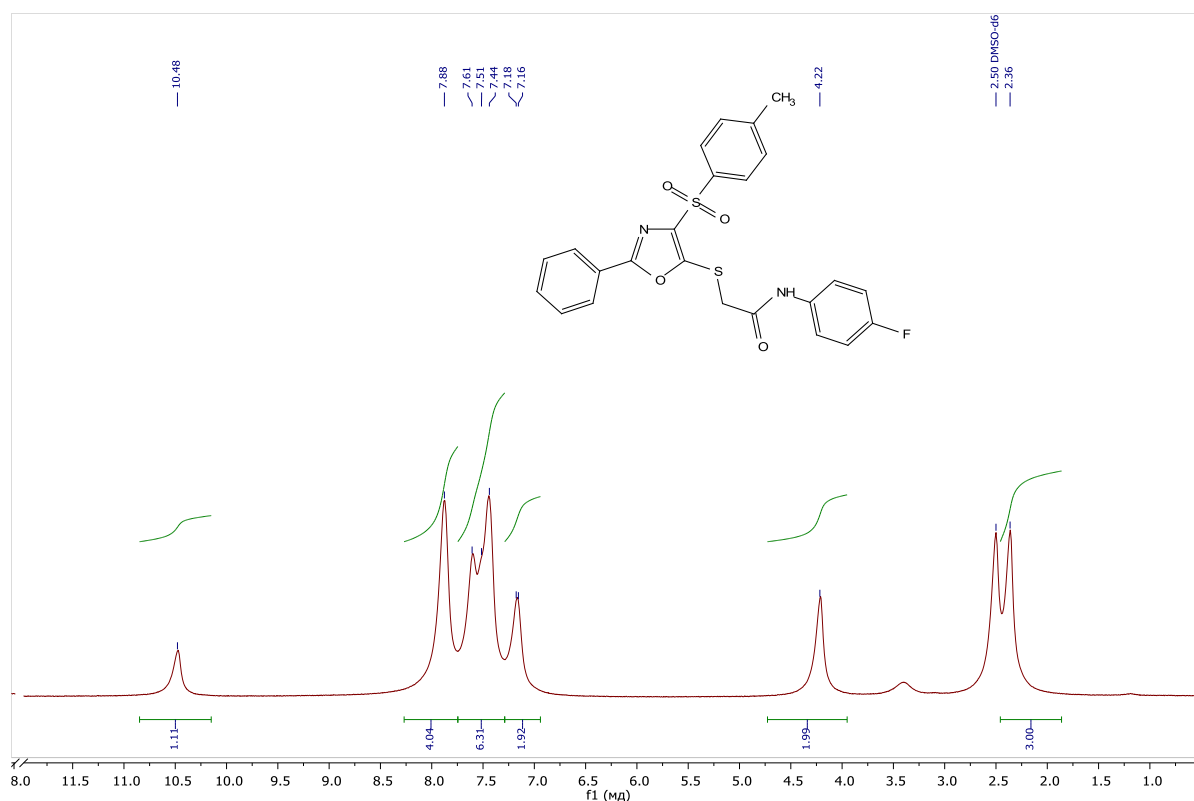


Figure S25. ¹H NMR spectrum of N-(4-fluorophenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)1,3-oxazol-5-yl]sulfanylacetamide (**D13**).

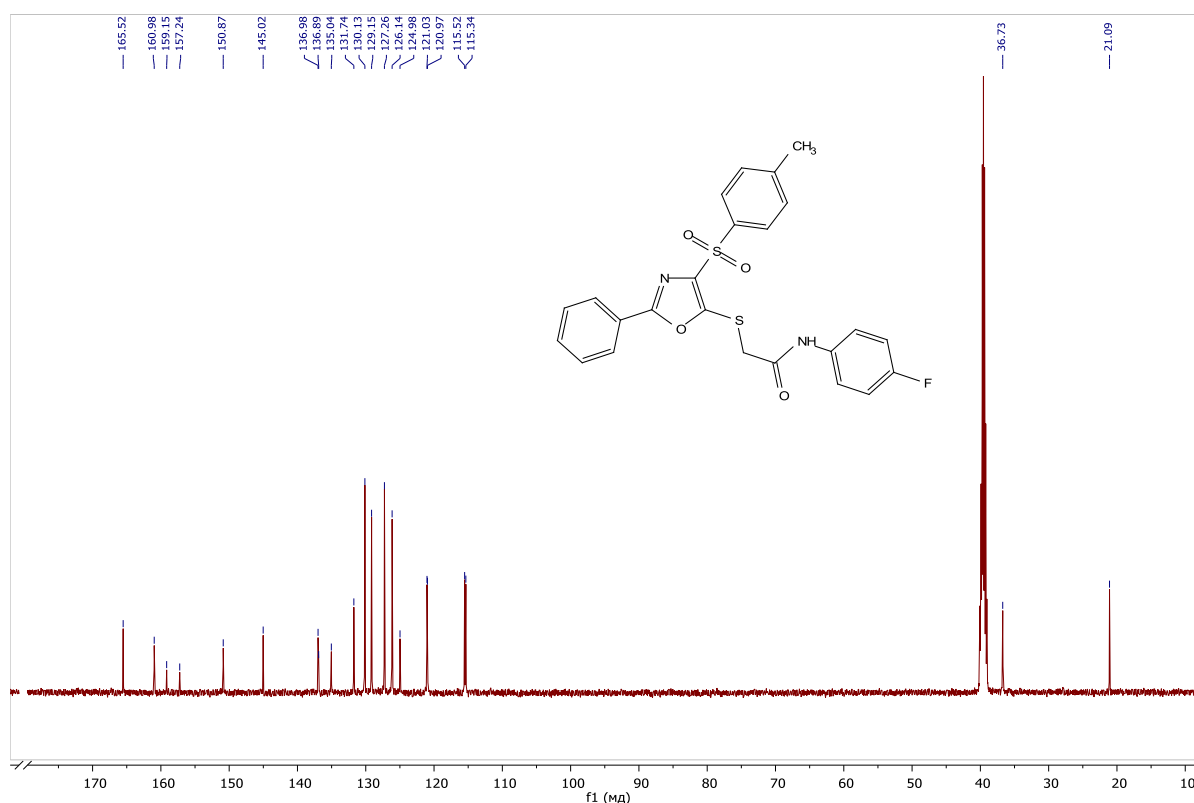
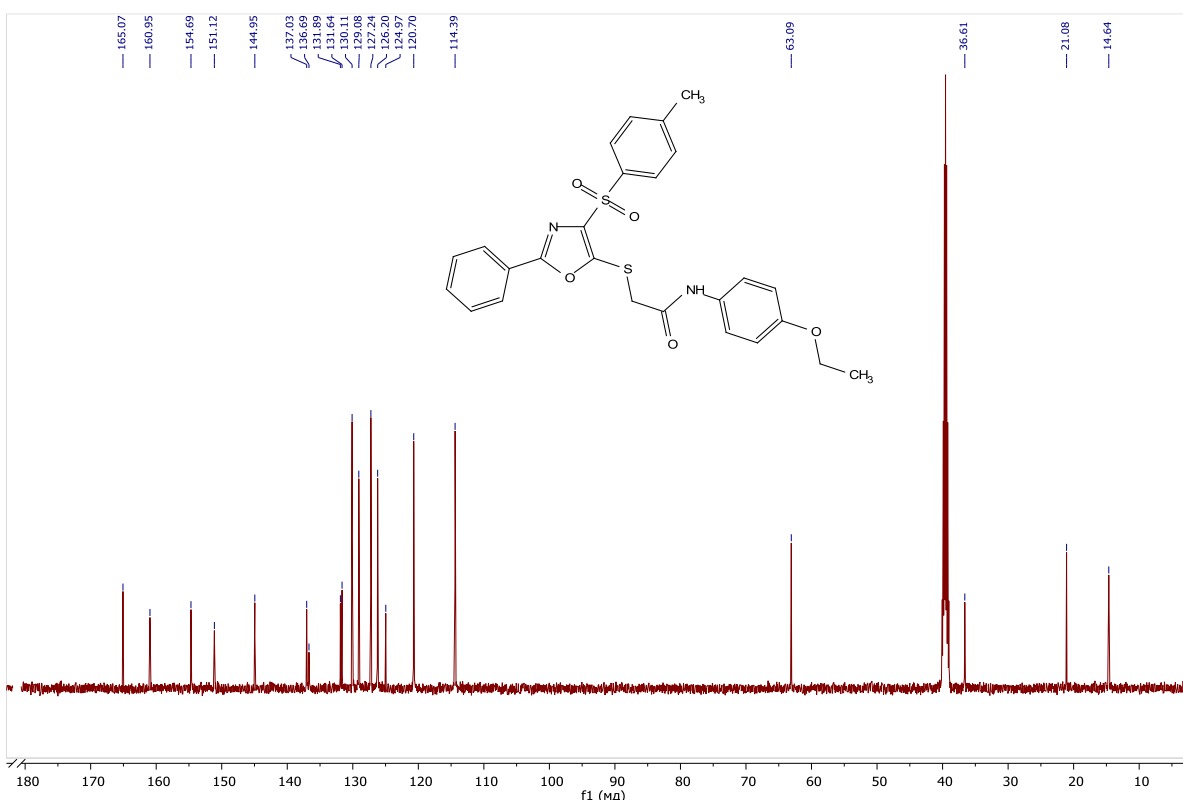
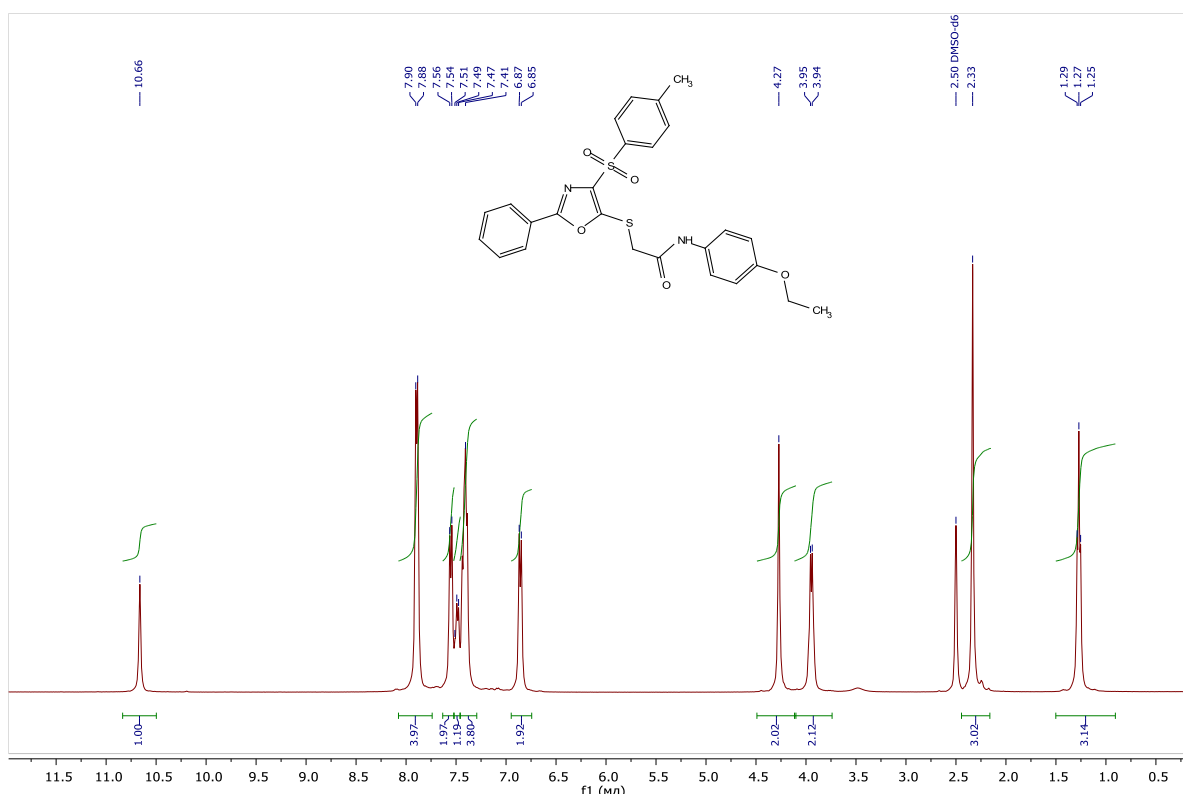


Figure S26. ¹³C NMR spectrum of N-(4-fluorophenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)1,3-oxazol-5-yl]sulfanylacetamide (**D13**).



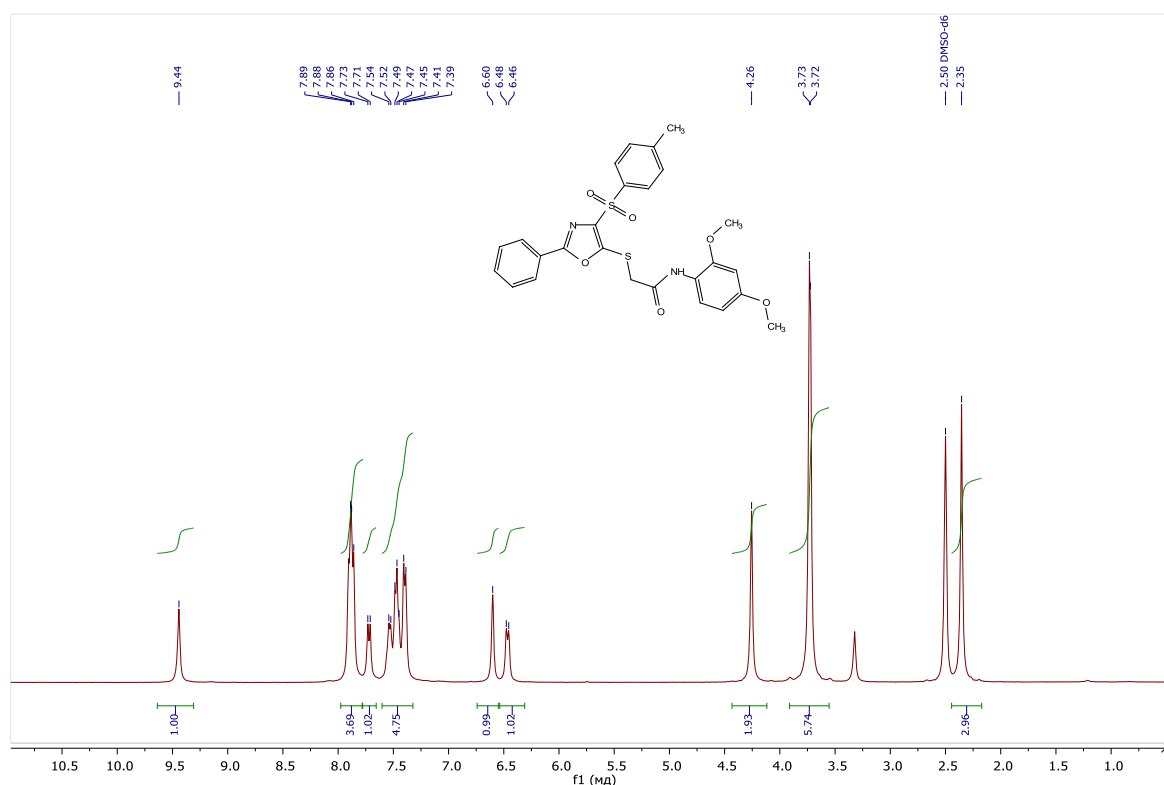


Figure S29. ^1H NMR spectrum of N-(2,4-dimethoxyphenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazol-5-yl]sulfanyl-acetamide (**D15**).

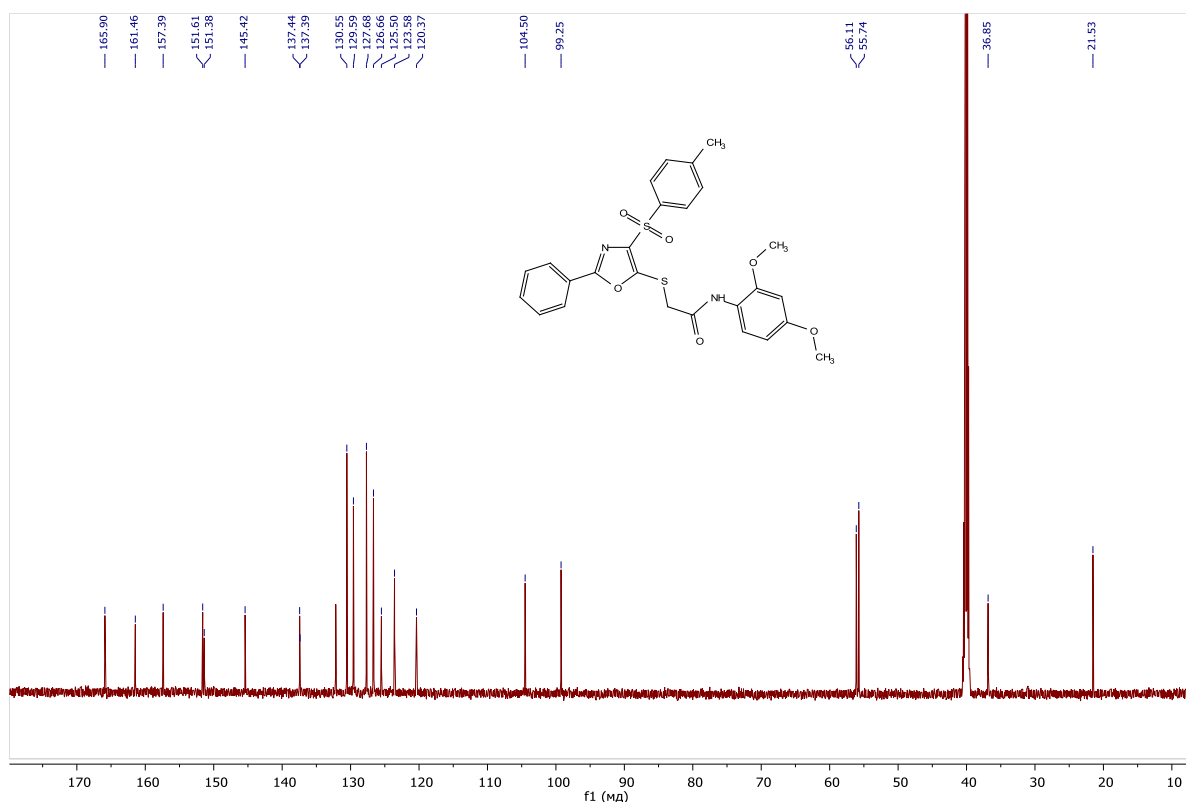


Figure S30. ^{13}C NMR spectrum of N-(2,4-dimethoxyphenyl)-2-[2-phenyl-4-(4-tolylsulfonyl)-1,3-oxazol-5-yl]sulfanyl-acetamide (**D15**).

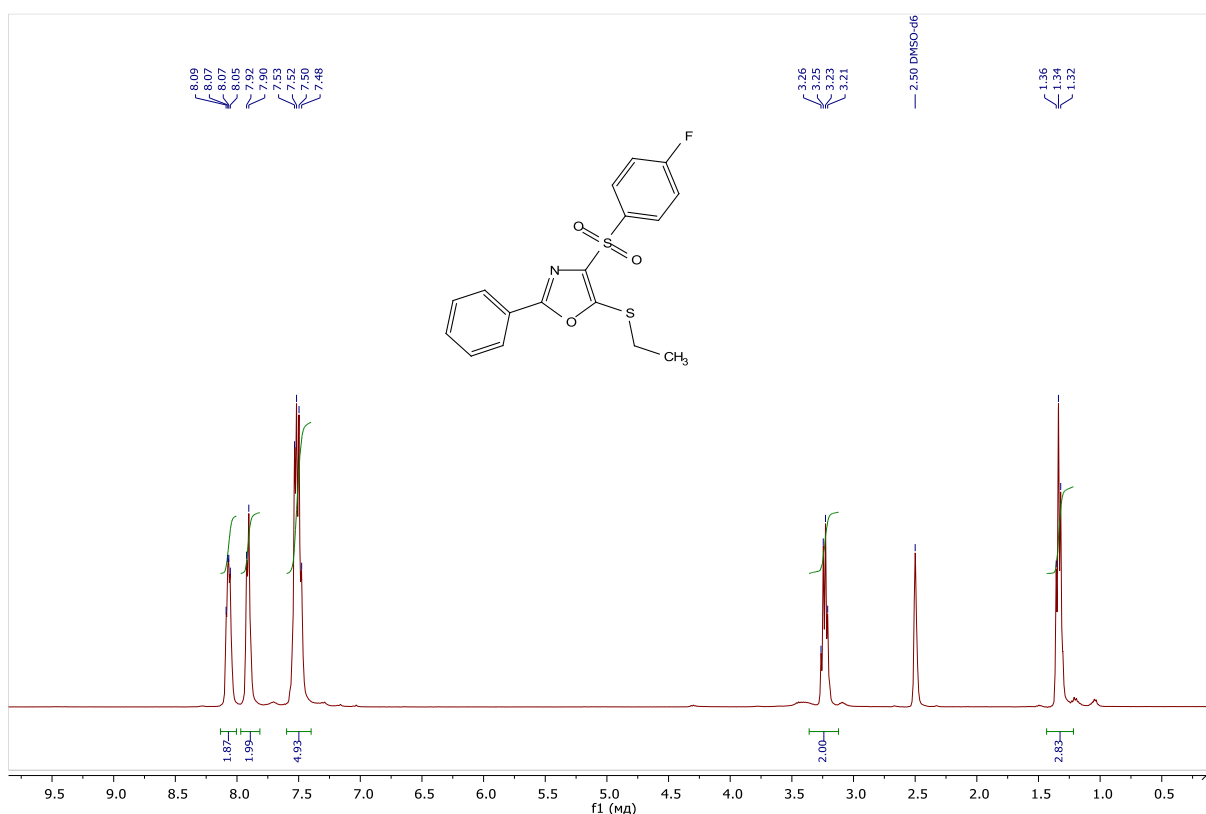


Figure S31. ¹H NMR spectrum of 5-ethylsulfanyl-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (**D16**).

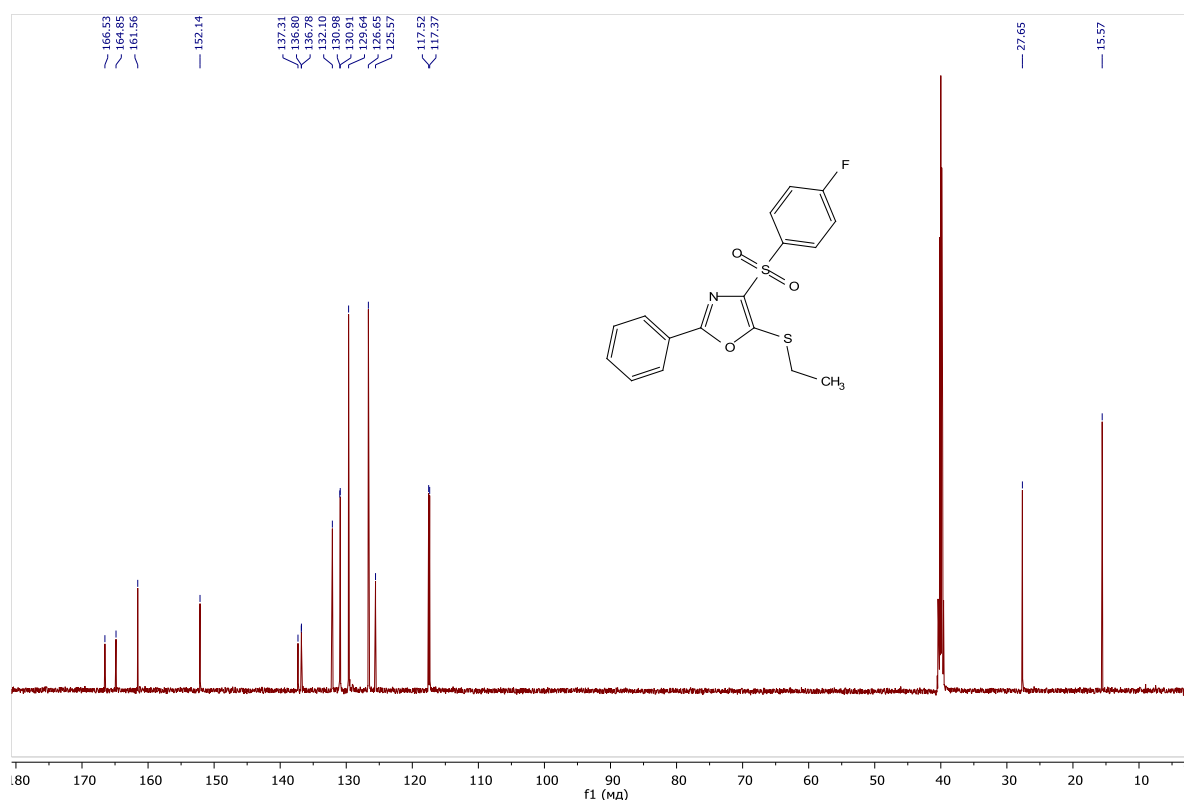


Figure S32. ¹³C NMR spectrum of 5-ethylsulfanyl-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (**D16**).

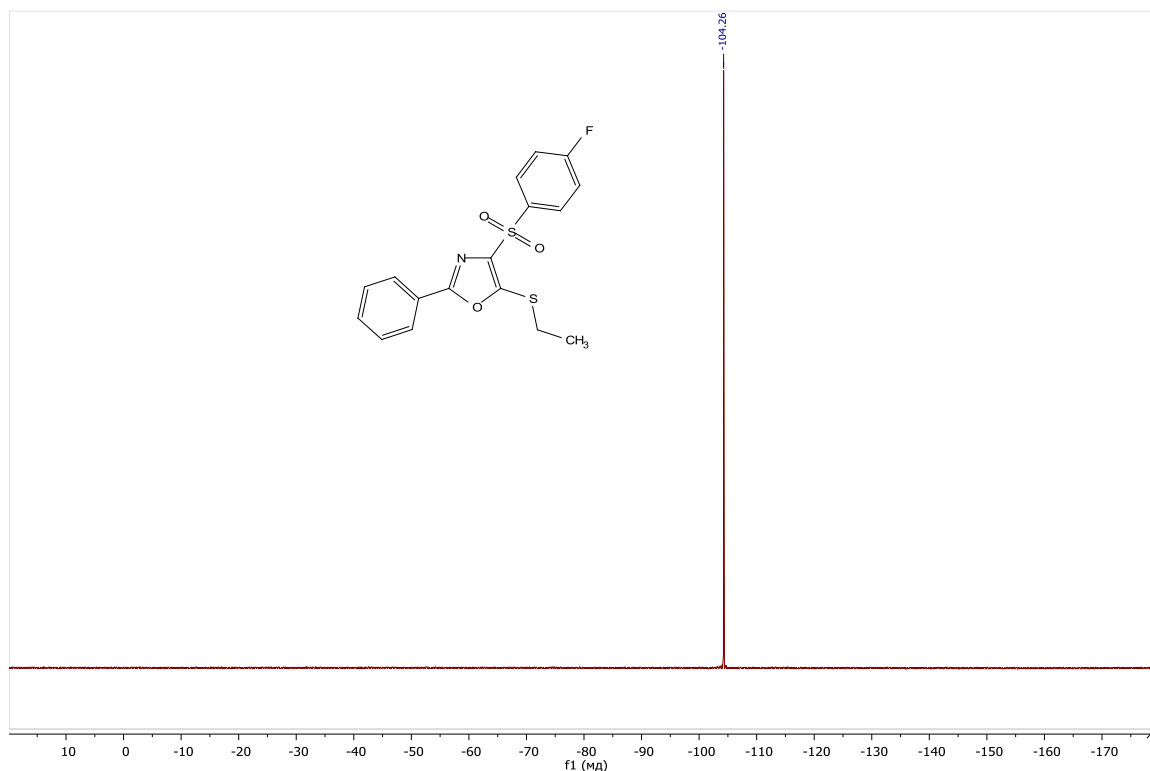


Figure S33. ¹⁹F NMR spectrum of 5-ethylsulfanyl-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (**D16**).

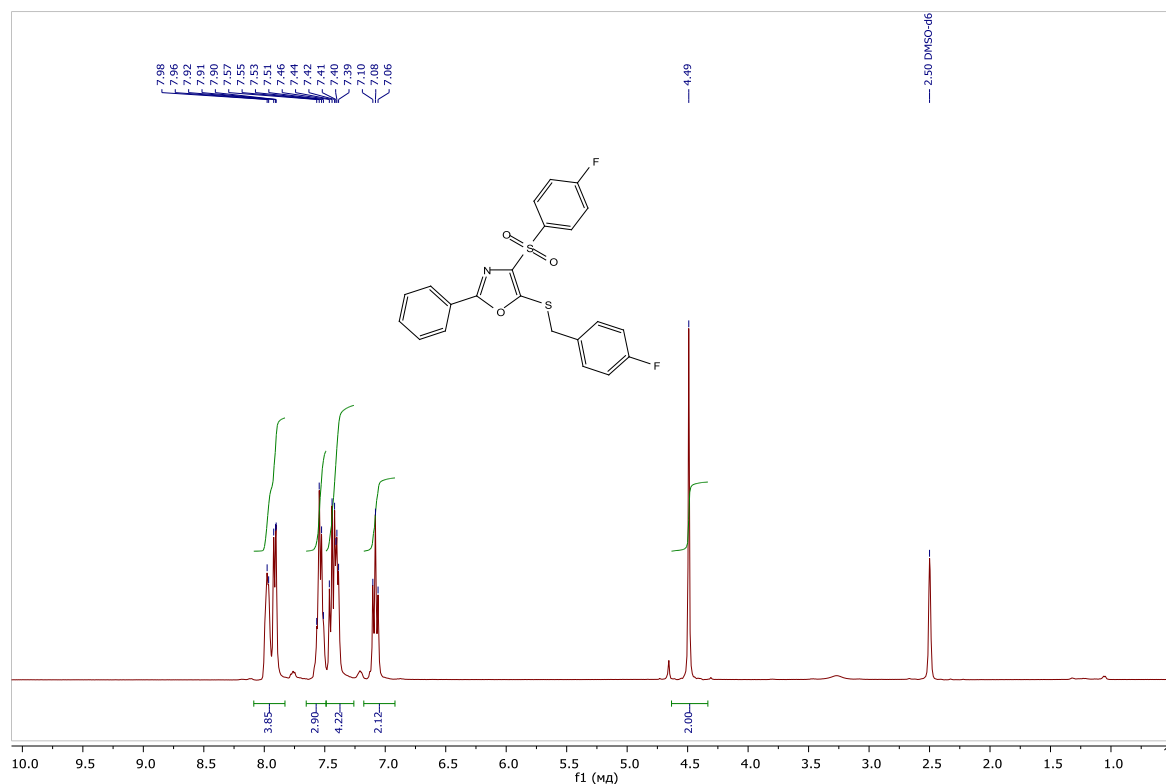


Figure S34. ¹H NMR spectrum of 5-[(4-fluorophenyl)methylsulfanyl]-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (**D17**).

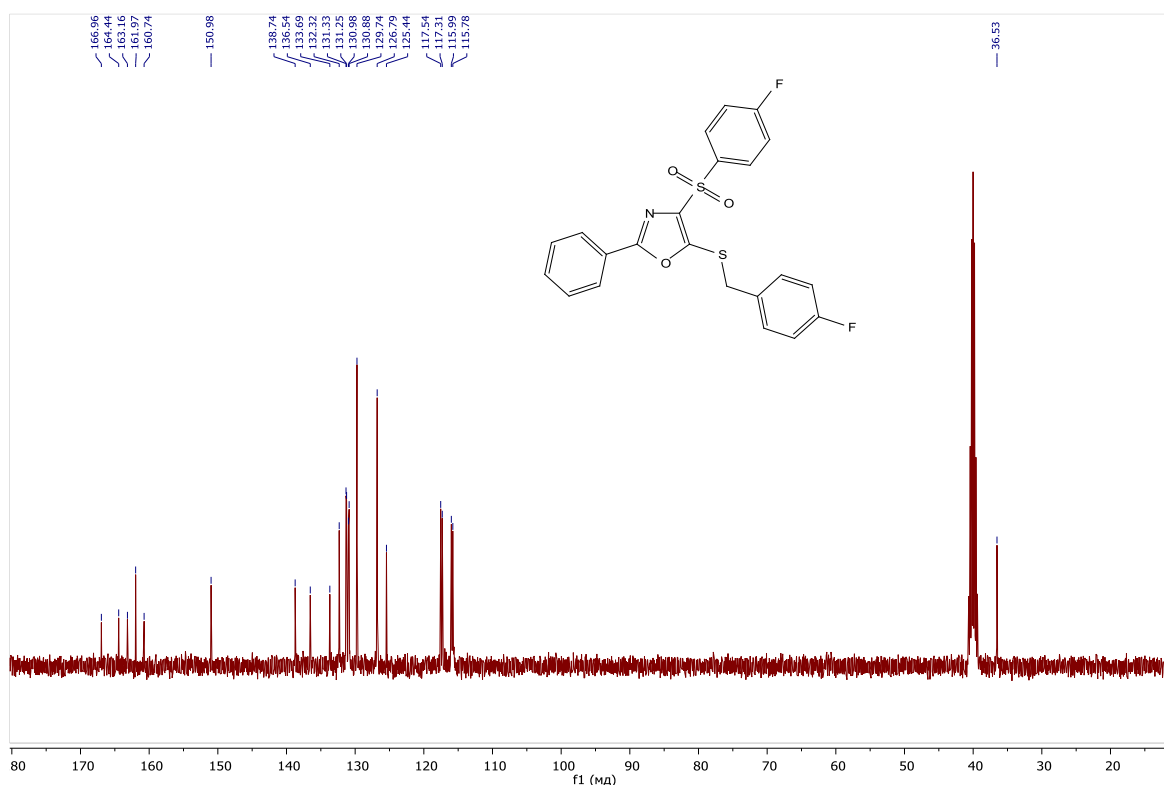


Figure S35. ¹³C NMR spectrum of 5-[(4-fluorophenyl)methylsulfanyl]-4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazole (**D17**).

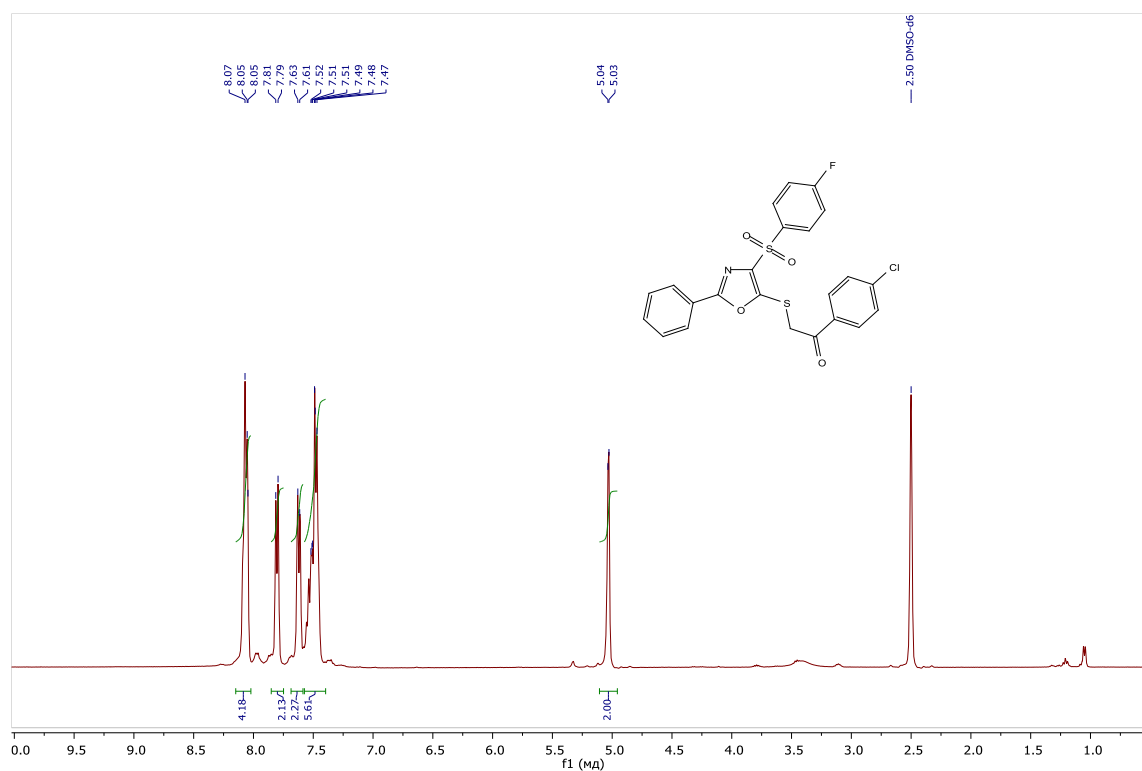


Figure S36. ¹H NMR spectrum of 1-(4-chlorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-ethanone (**D18**).

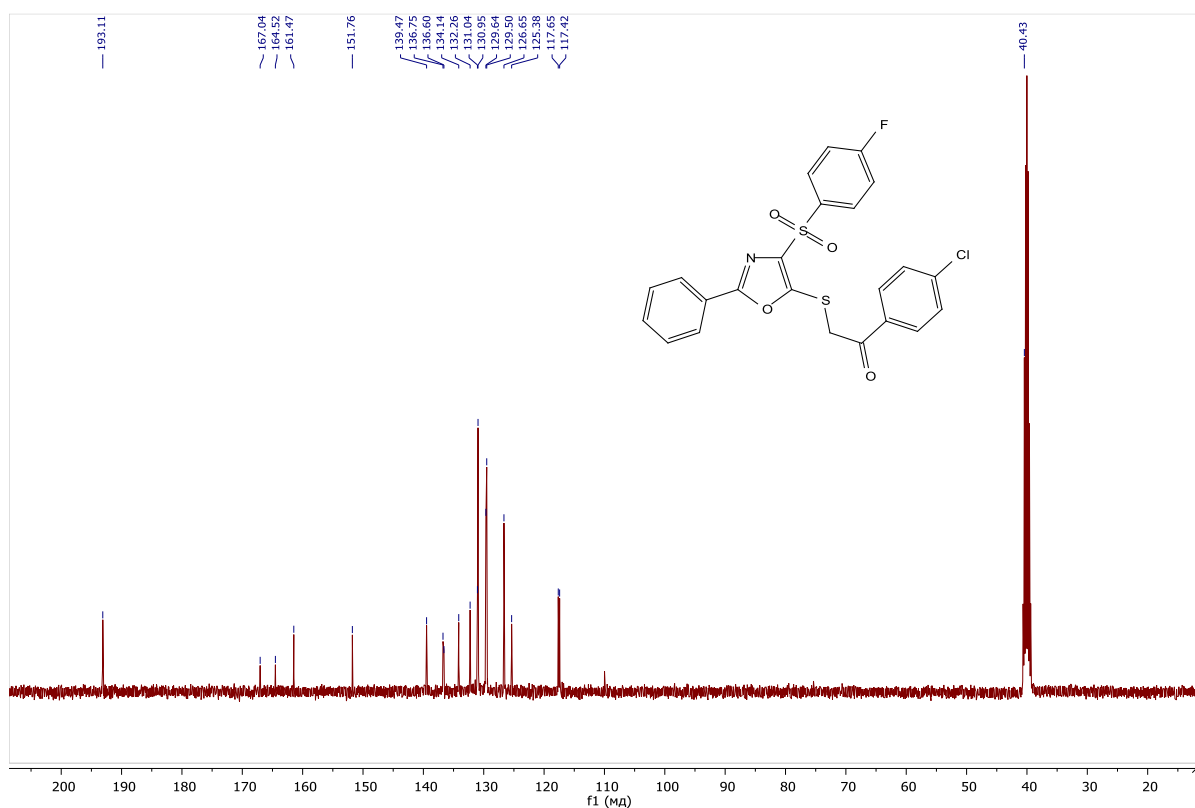


Figure S37. ¹³C NMR spectrum of 1-(4-chlorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-ethanone (D18).

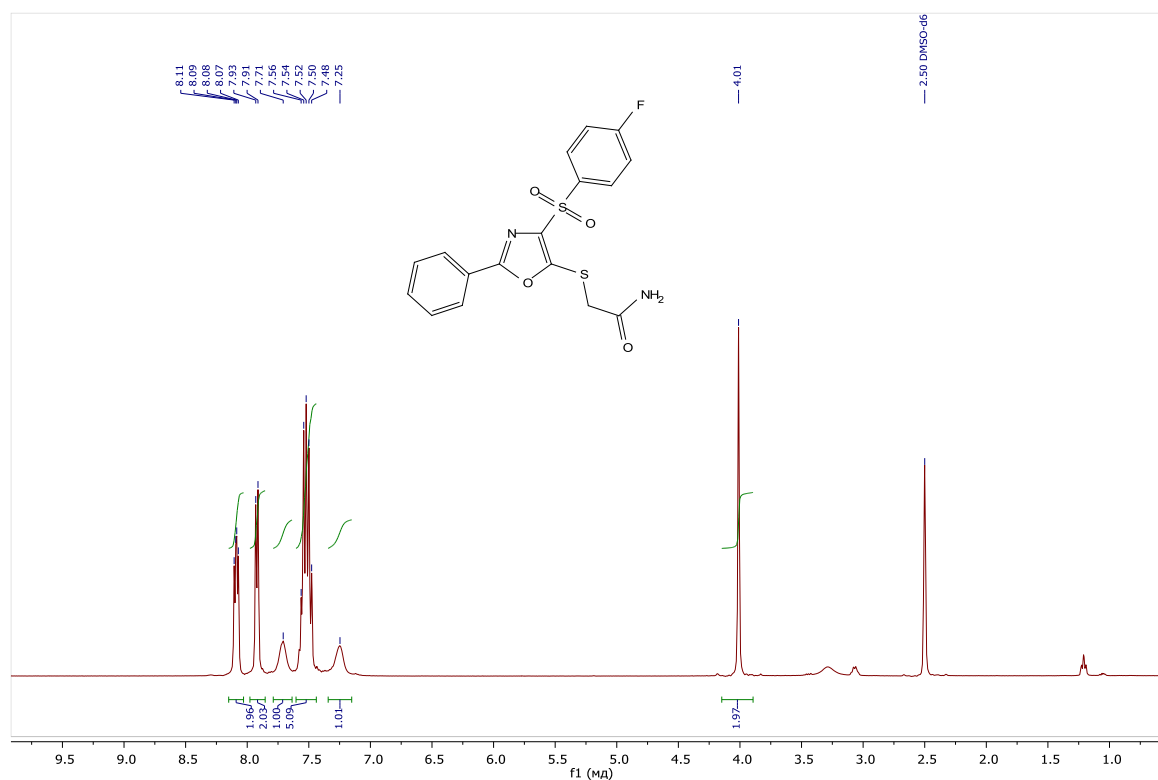


Figure S38. ¹H NMR spectrum of 2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (D19).

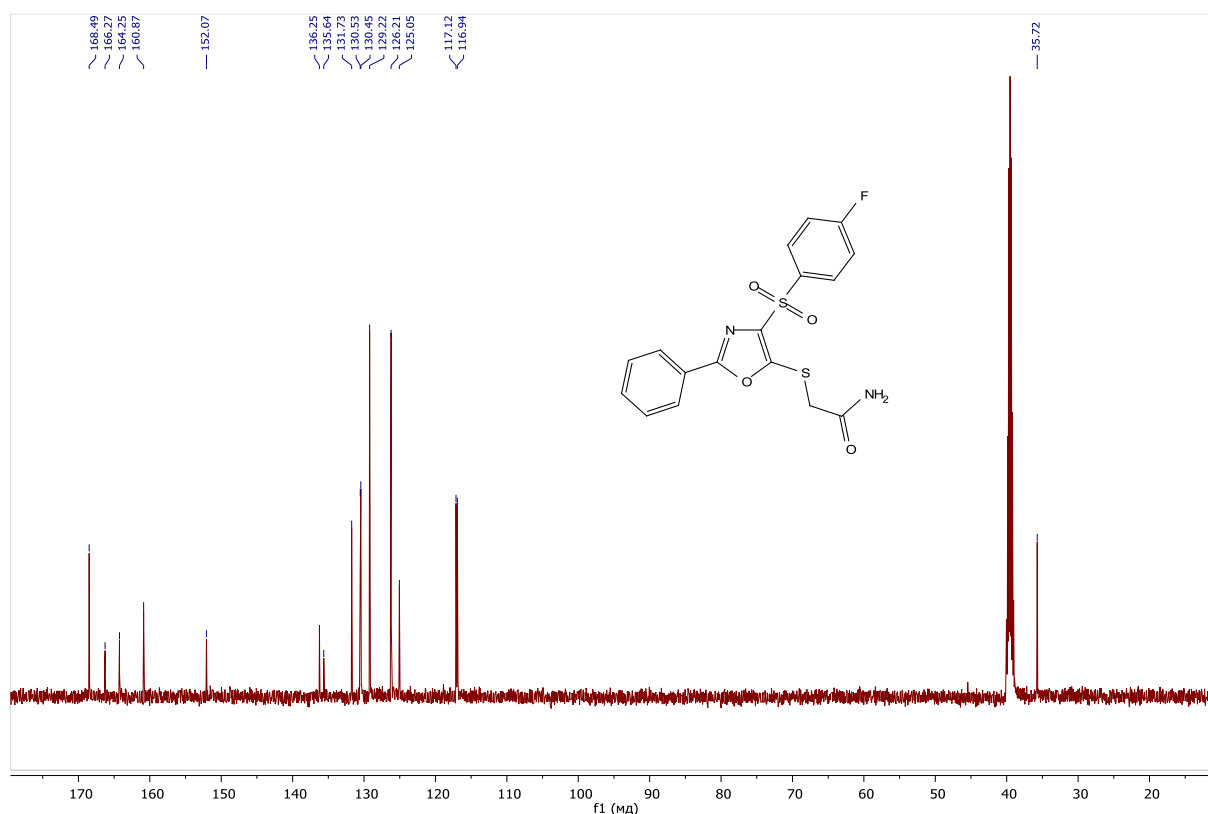


Figure S39. ^{13}C NMR spectrum of 2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (**D19**).

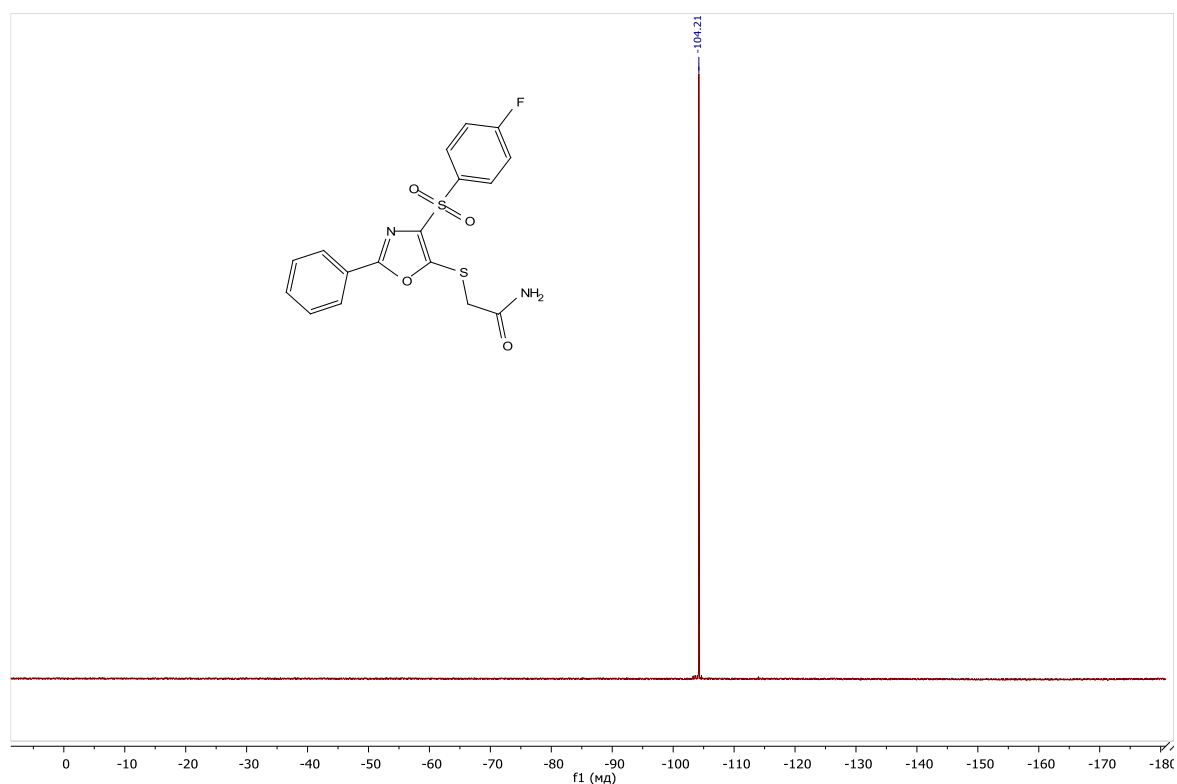


Figure S40. ^{19}F NMR spectrum of 2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (**D19**).

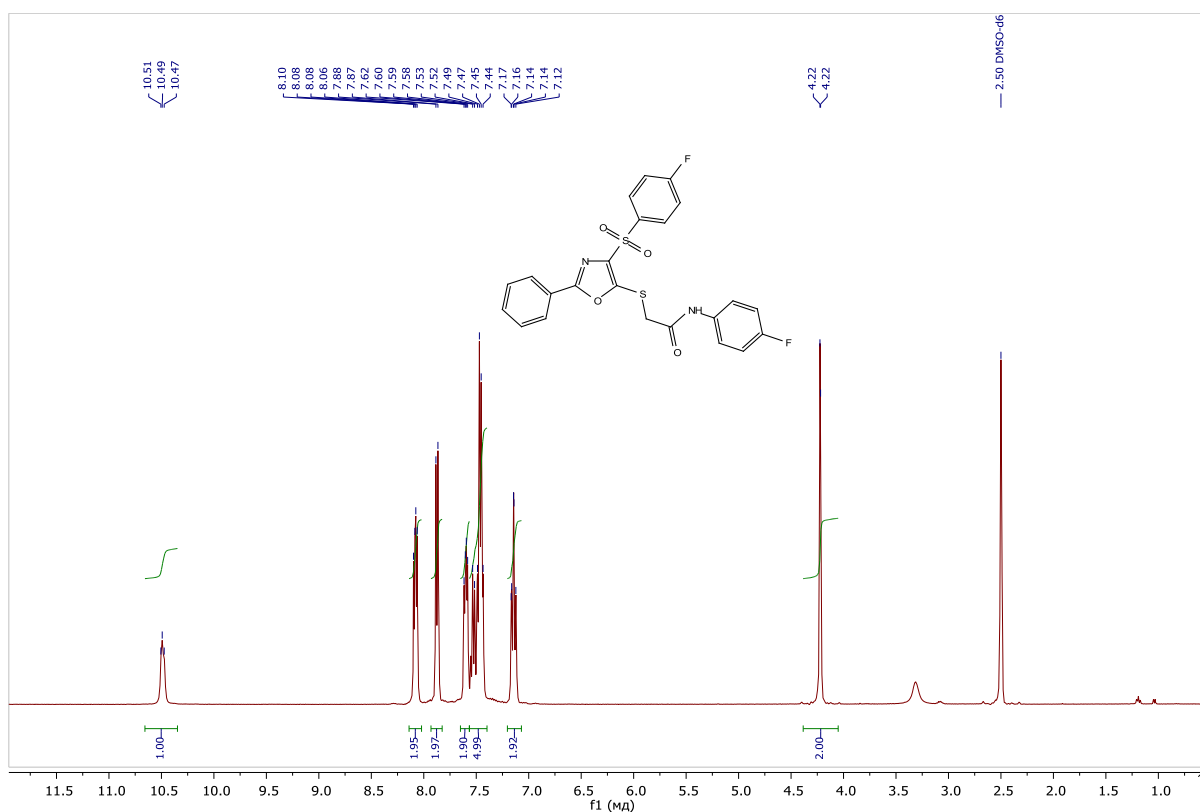


Figure S41. ¹H NMR spectrum of N-(4-fluorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D20).

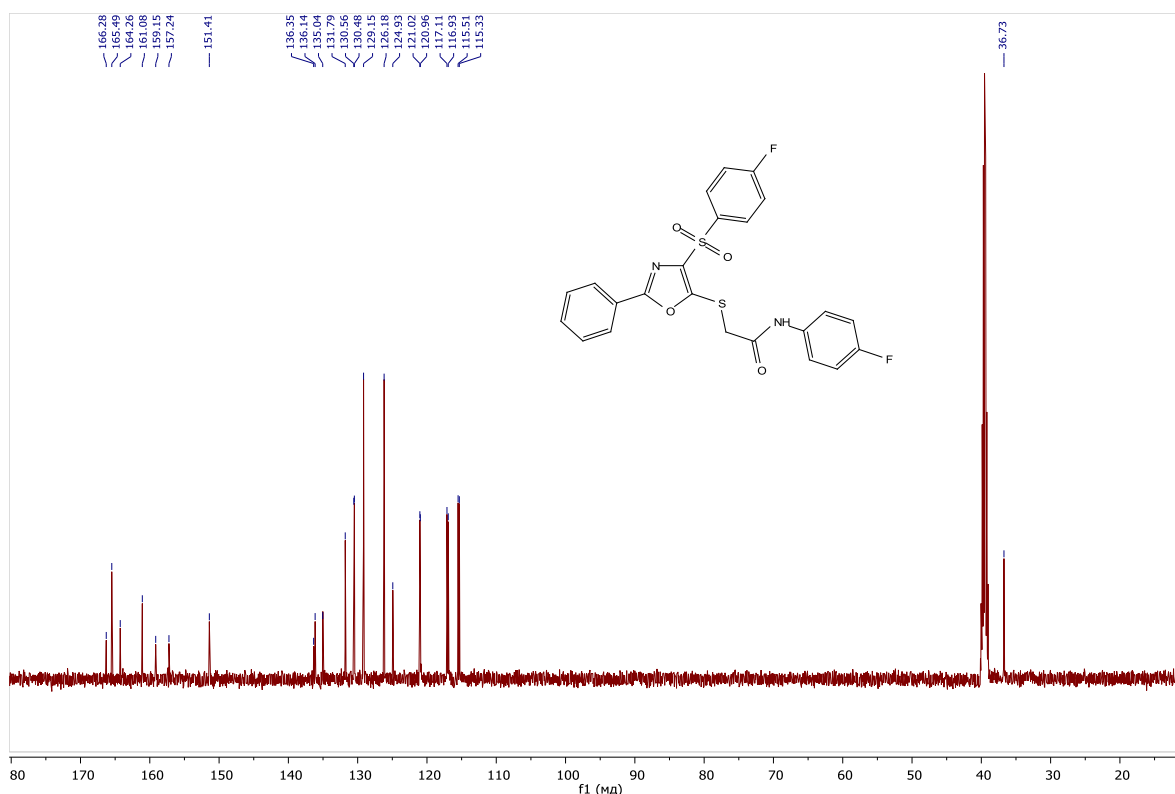


Figure S42. ¹³C NMR spectrum of N-(4-fluorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D20).

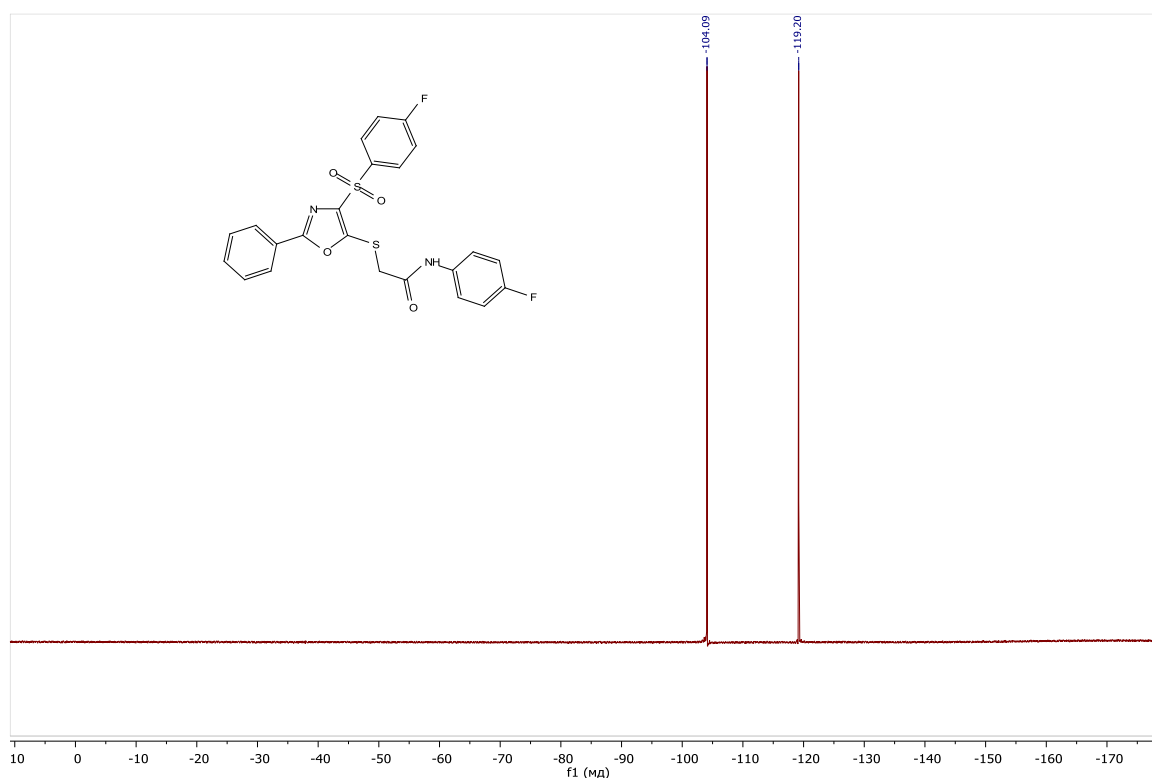


Figure S43. ^{19}F NMR spectrum of N-(4-fluorophenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D20).

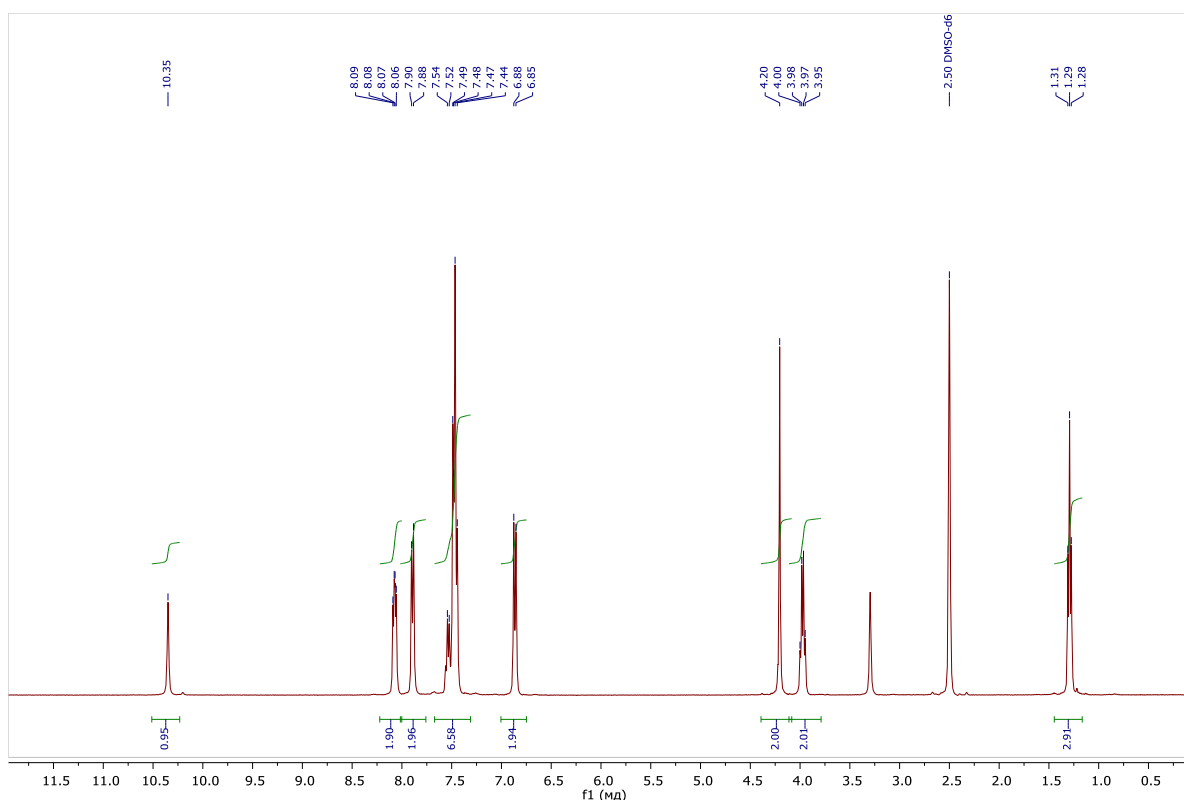


Figure S44. ^1H NMR spectrum of N-(4-ethoxyphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (D21).

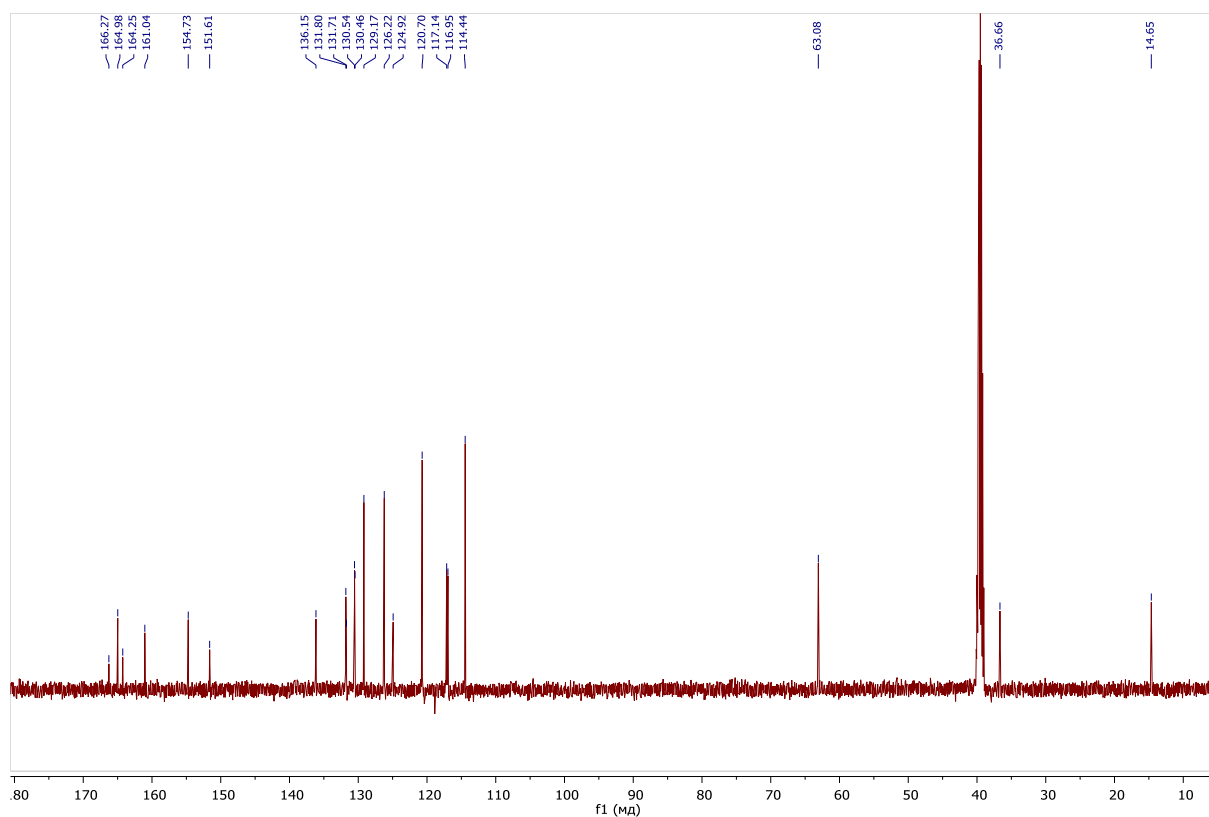


Figure S45. ^{13}C NMR spectrum of N-(4-ethoxyphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (**D21**).

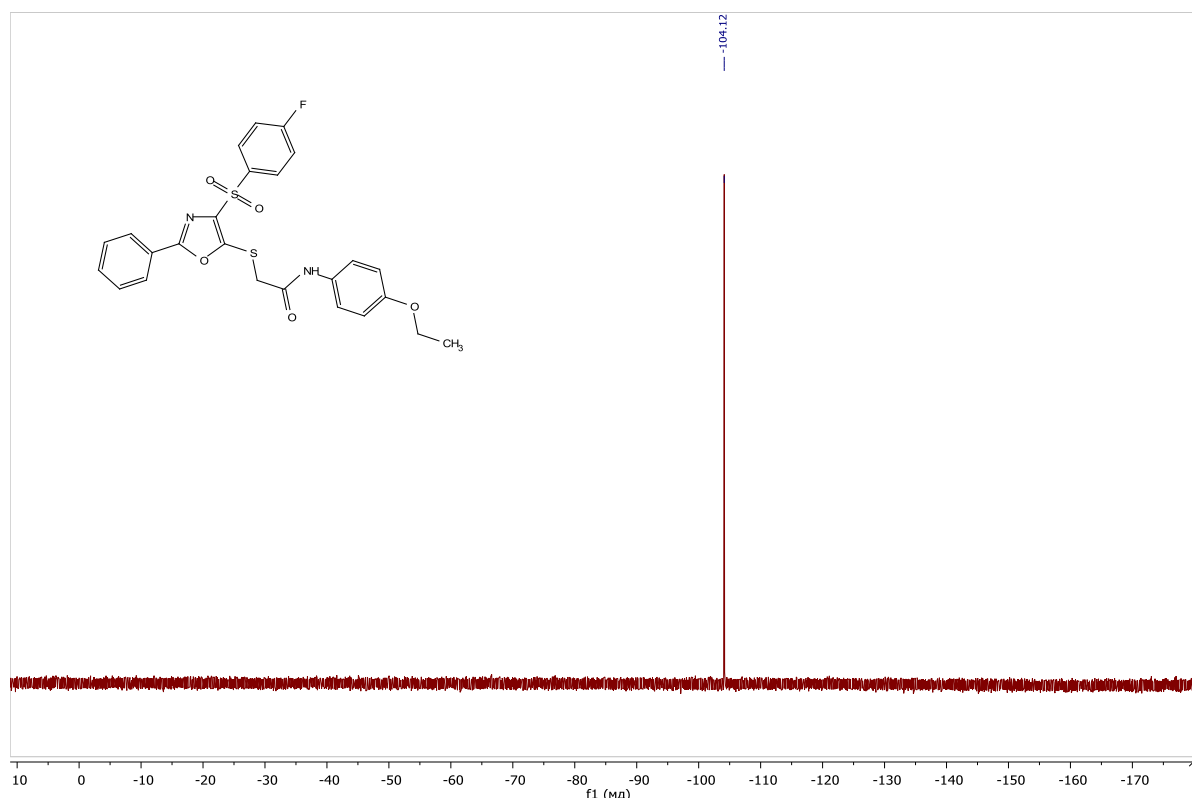


Figure S46. ^{19}F NMR spectrum of N-(4-ethoxyphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (**D21**).

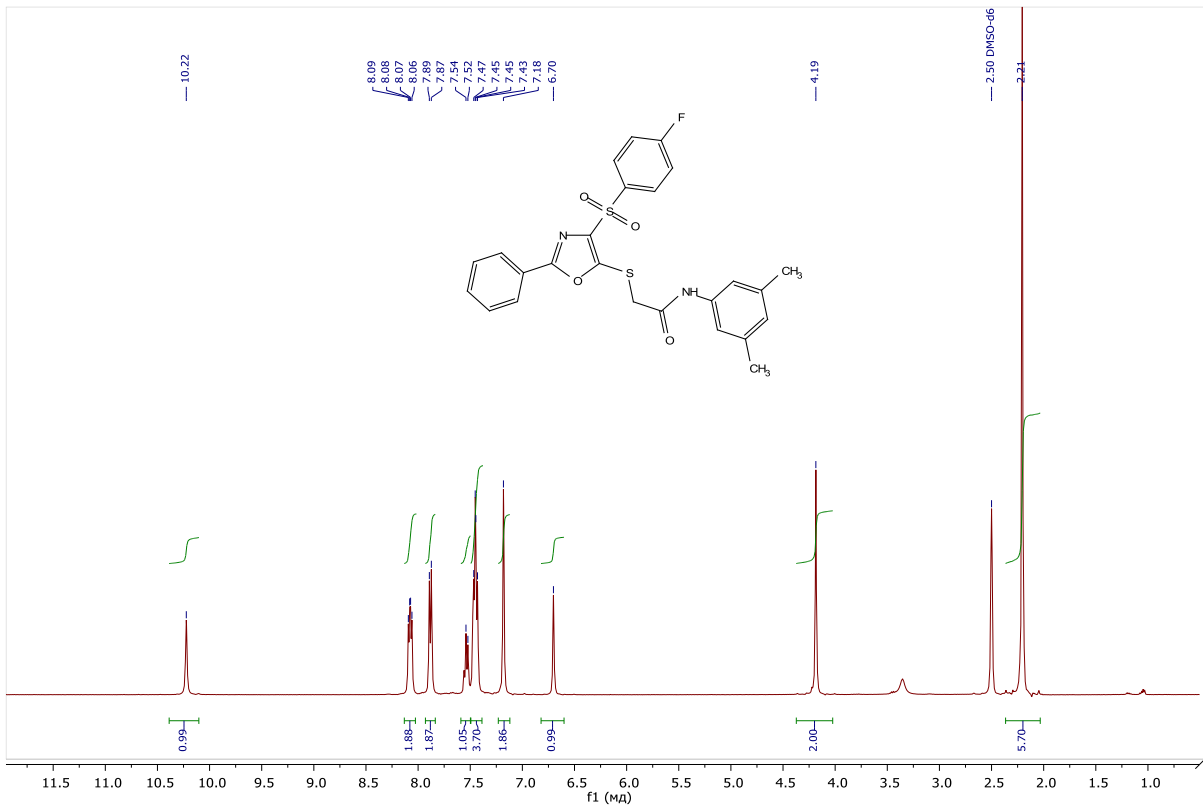


Figure S47. ¹H NMR spectrum of N-(3,5-dimethylphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (**D22**).

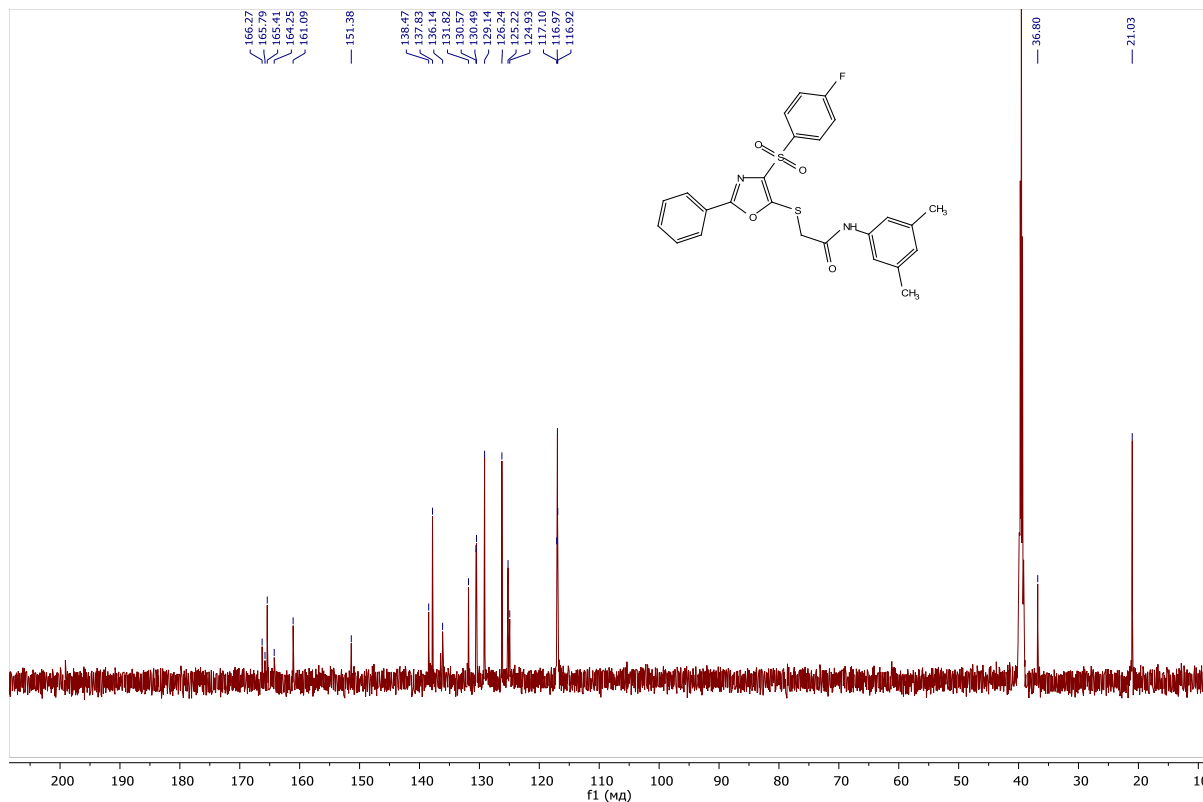


Figure S48. ¹³C NMR spectrum of N-(3,5-dimethylphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (**D22**).

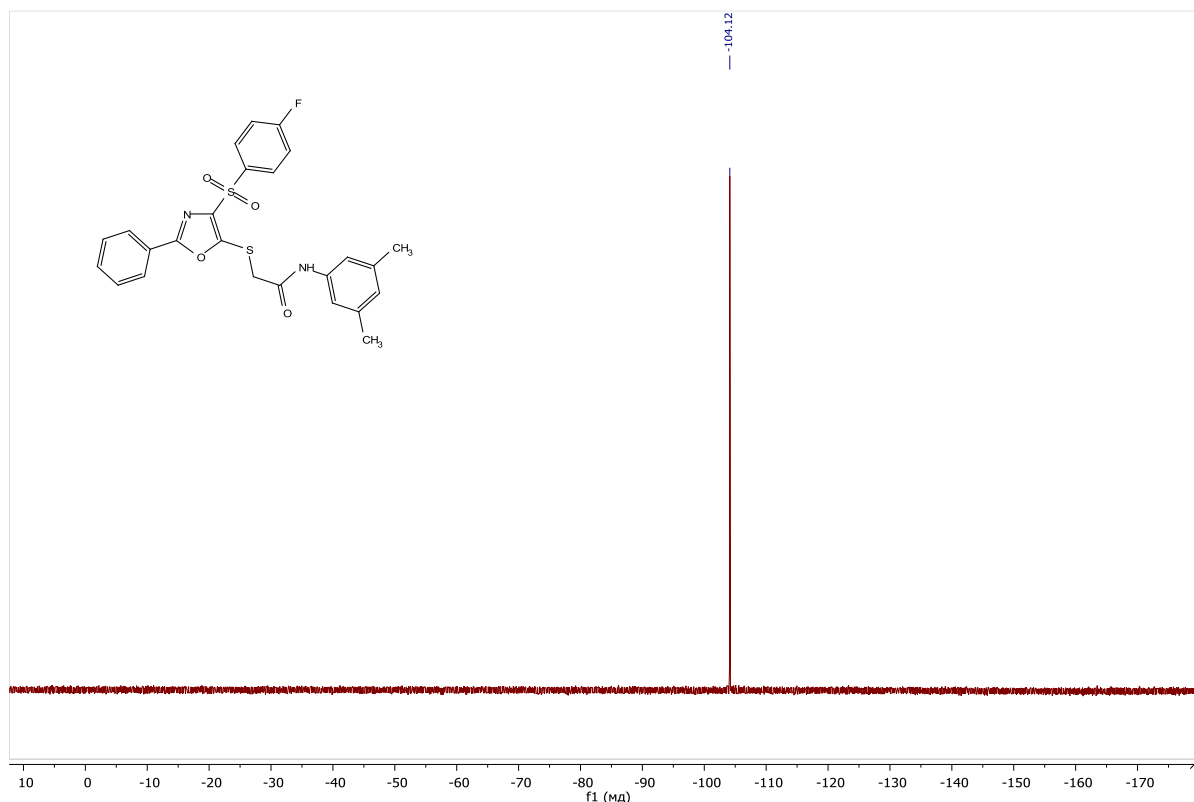


Figure S49. ^{19}F NMR spectrum of N-(3,5-dimethylphenyl)-2-[4-(4-fluorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-acetamide (**D22**).

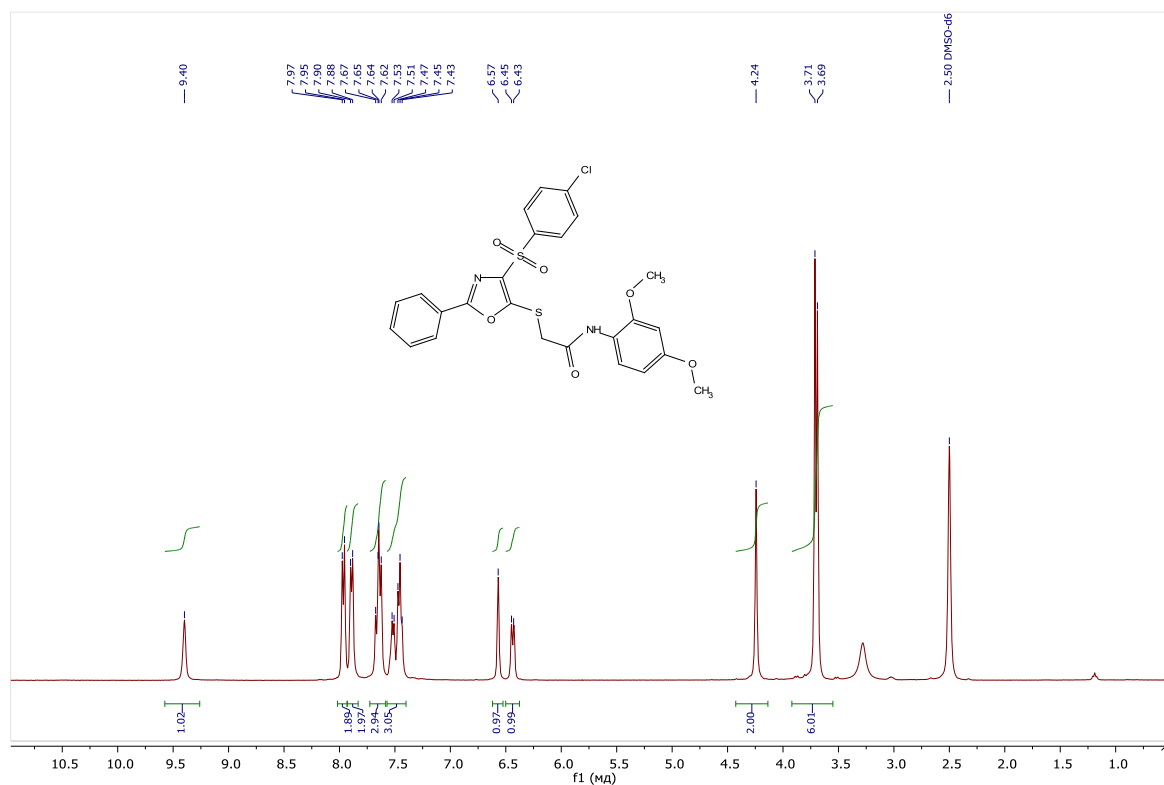


Figure S50. ^1H NMR spectrum of 2-[4-(4-chlorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)-acetamide (**D23**).

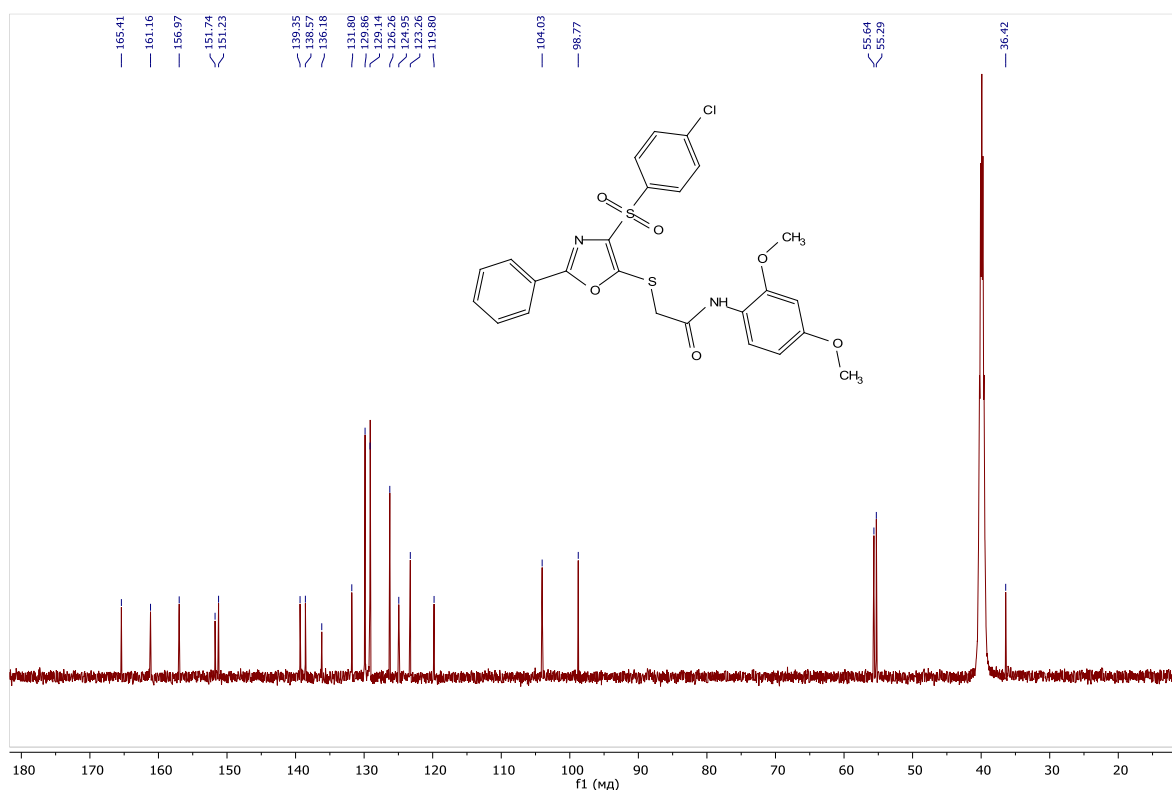


Figure S51. ¹³C NMR spectrum of 2-[4-(4-chlorophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)-acetamide (D23).

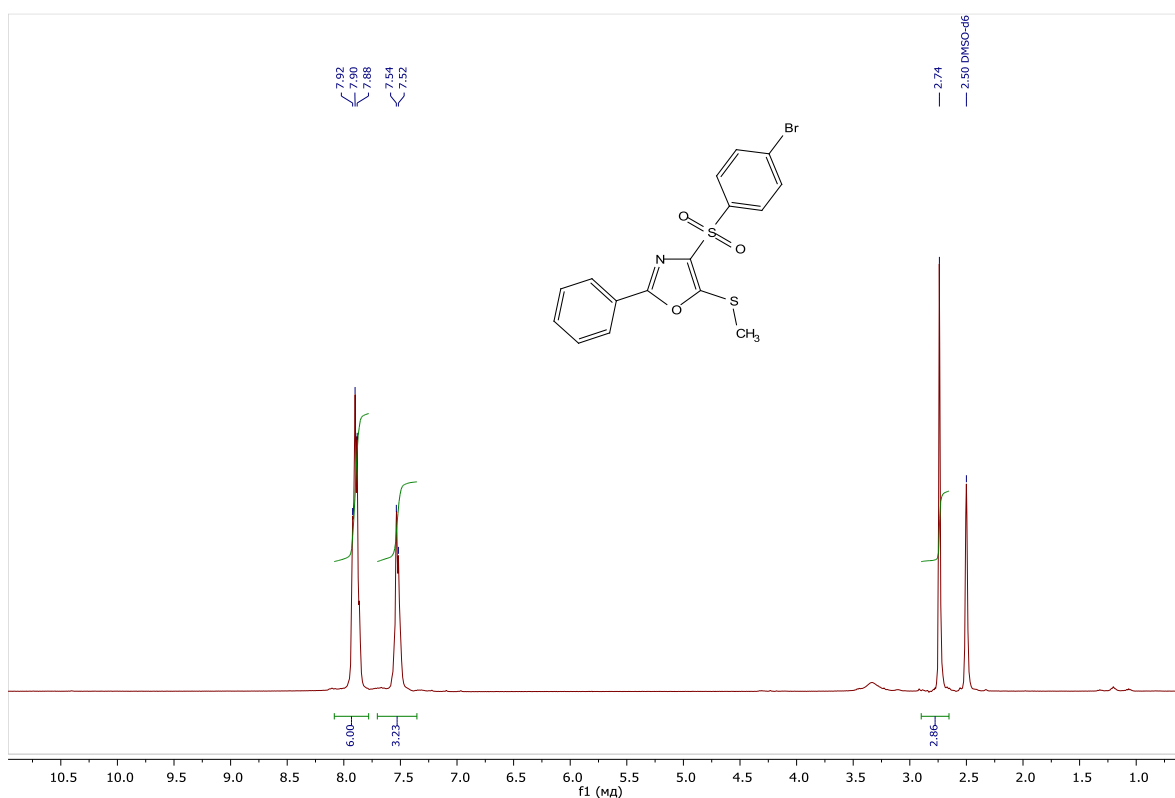
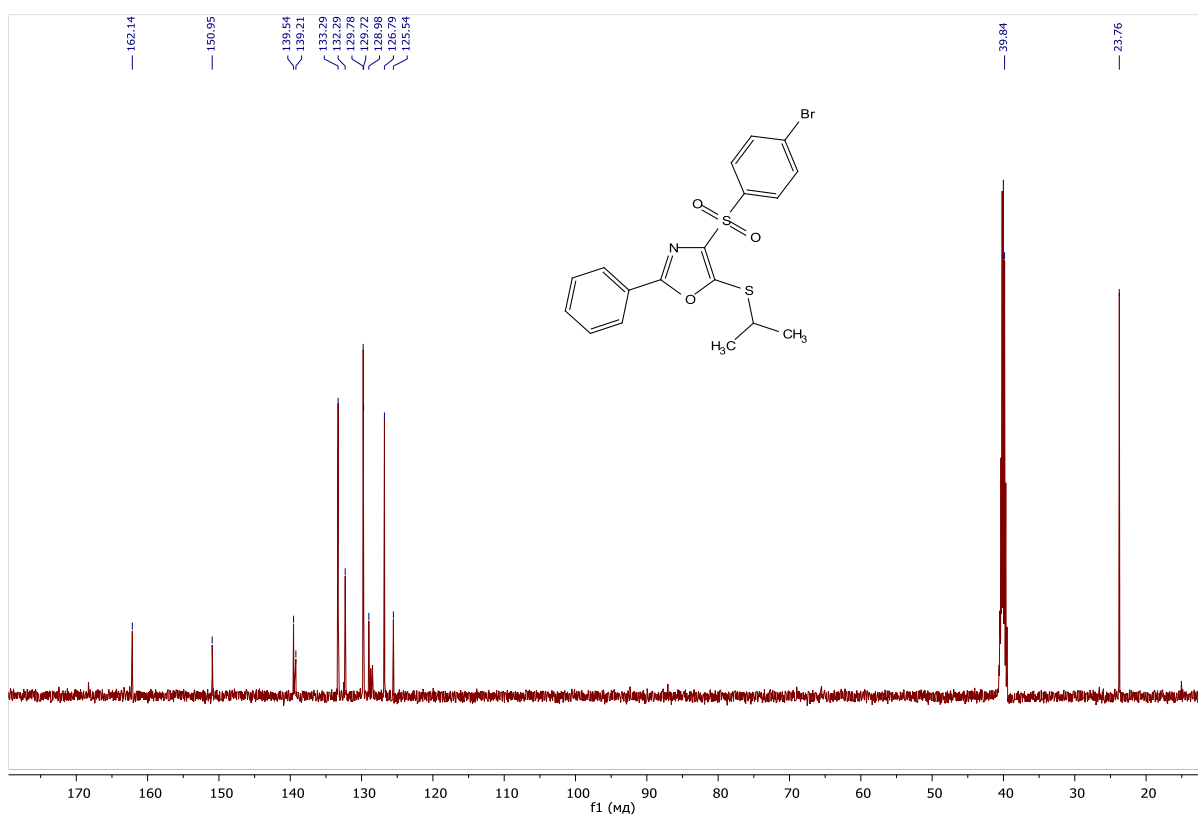
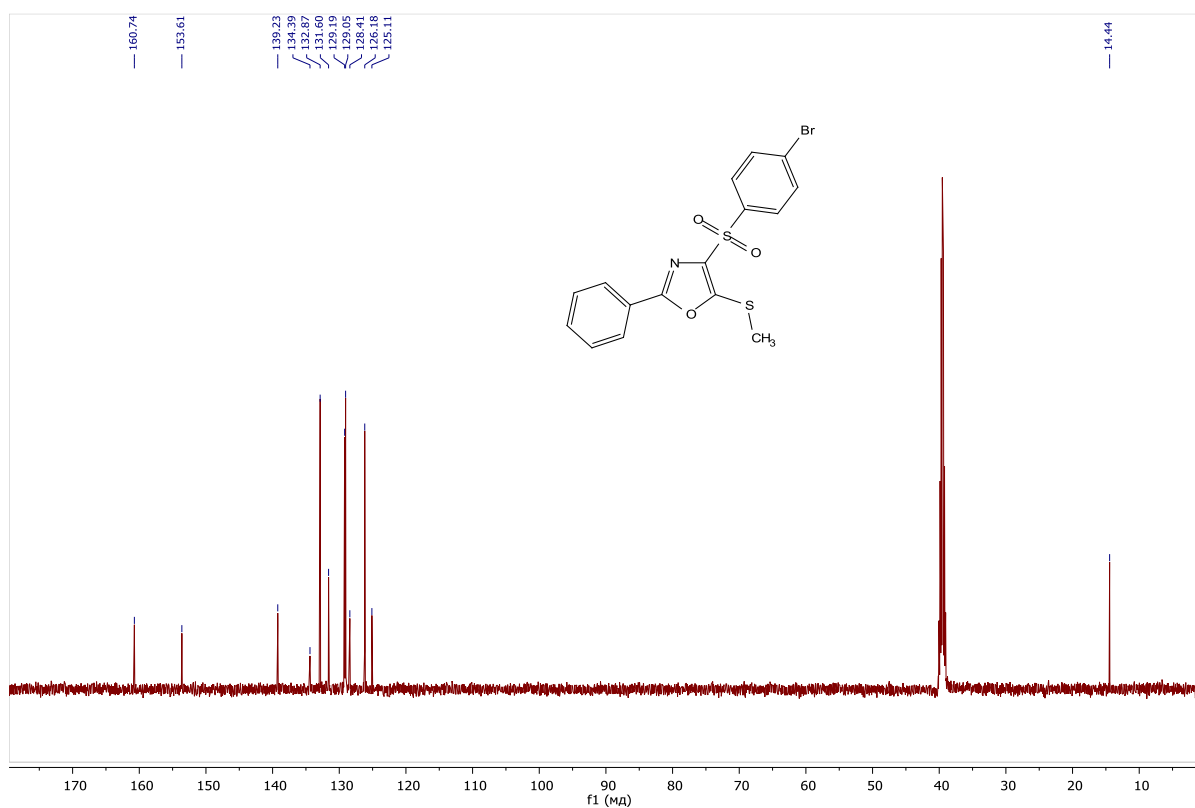


Figure S52. ¹H NMR spectrum of 4-(4-bromophenyl)sulfonyl-5-methylsulfanyl-2-phenyl-1,3-oxazole (D24).



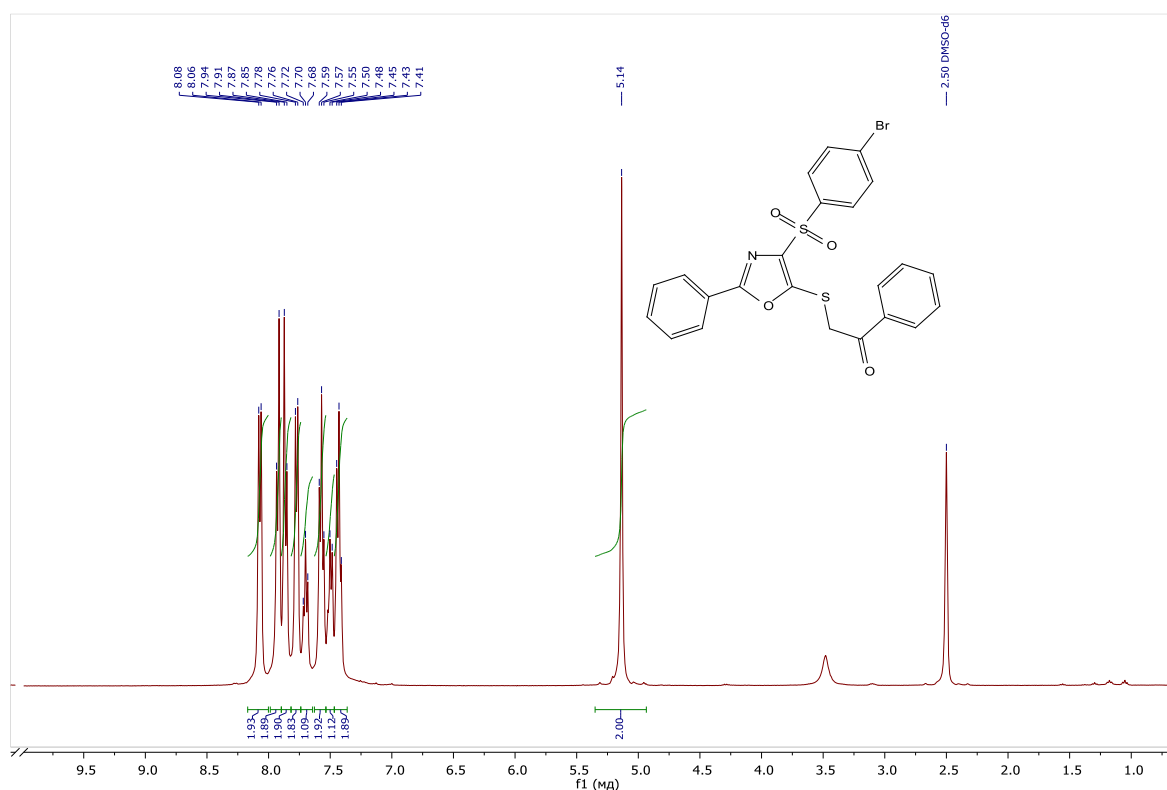


Figure S55. ^1H NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-1-phenylethanone (**D26**).

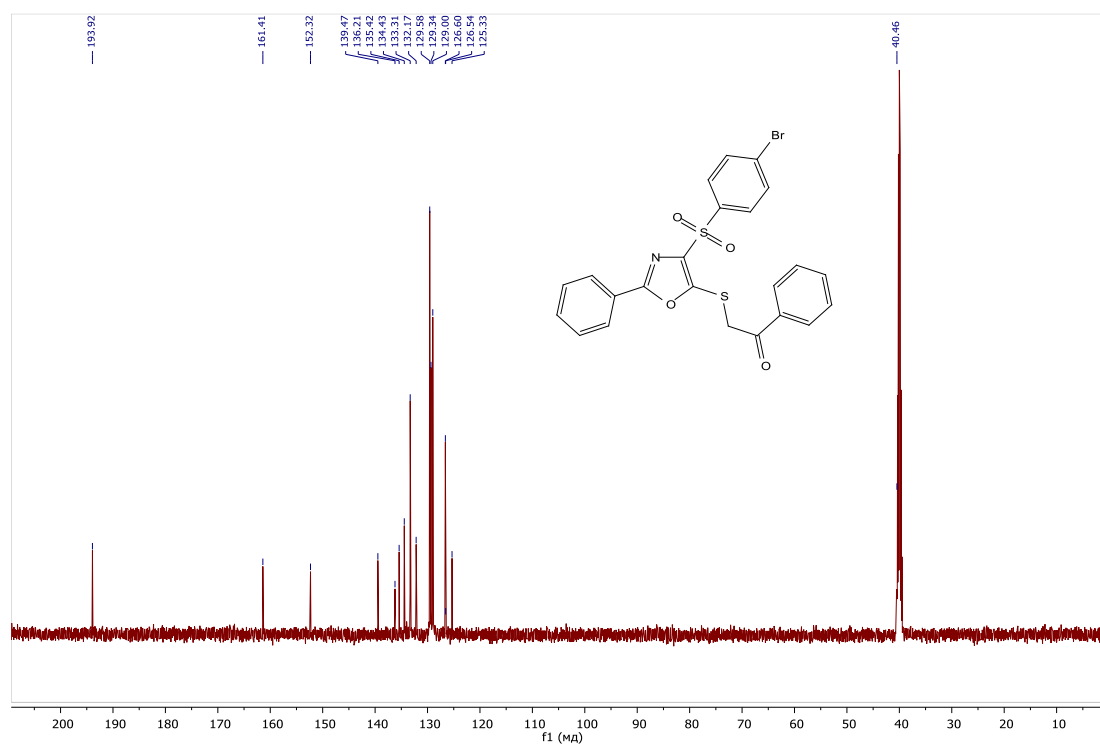


Figure S56. ^{13}C NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-1-phenylethanone (**D26**).

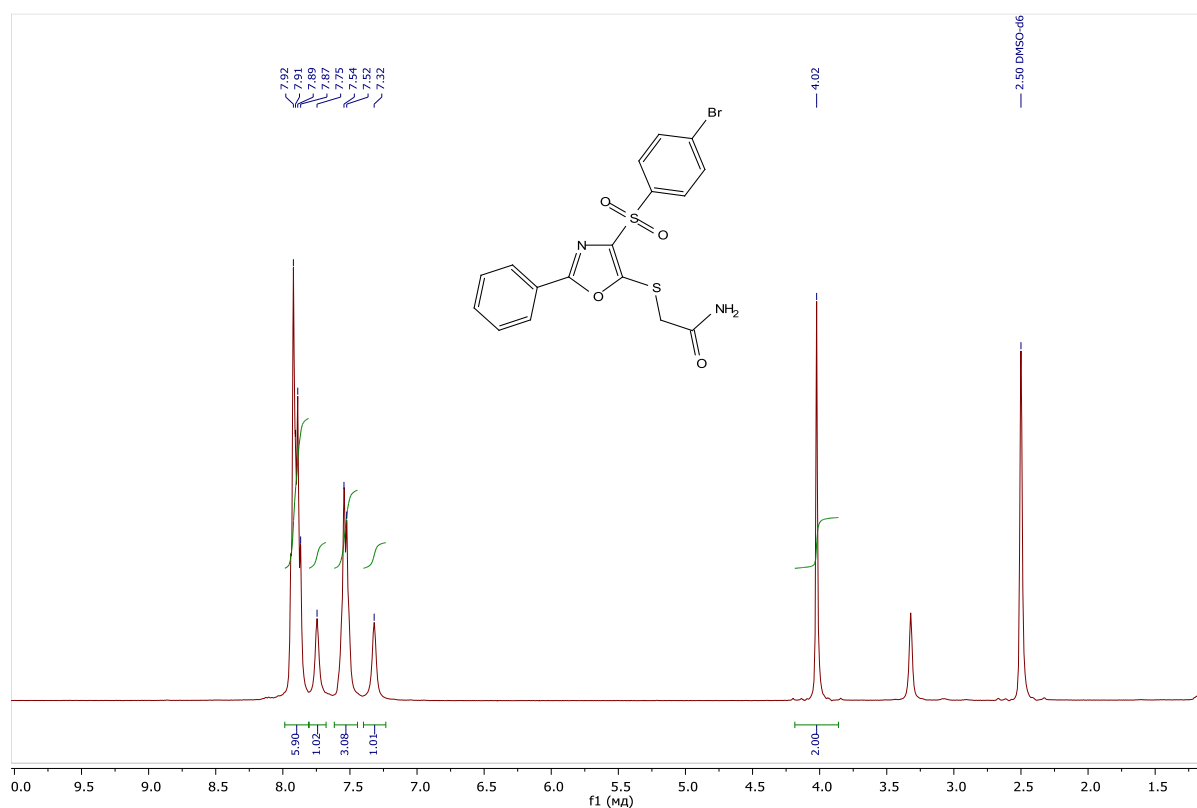


Figure S57. ¹H NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (D27).

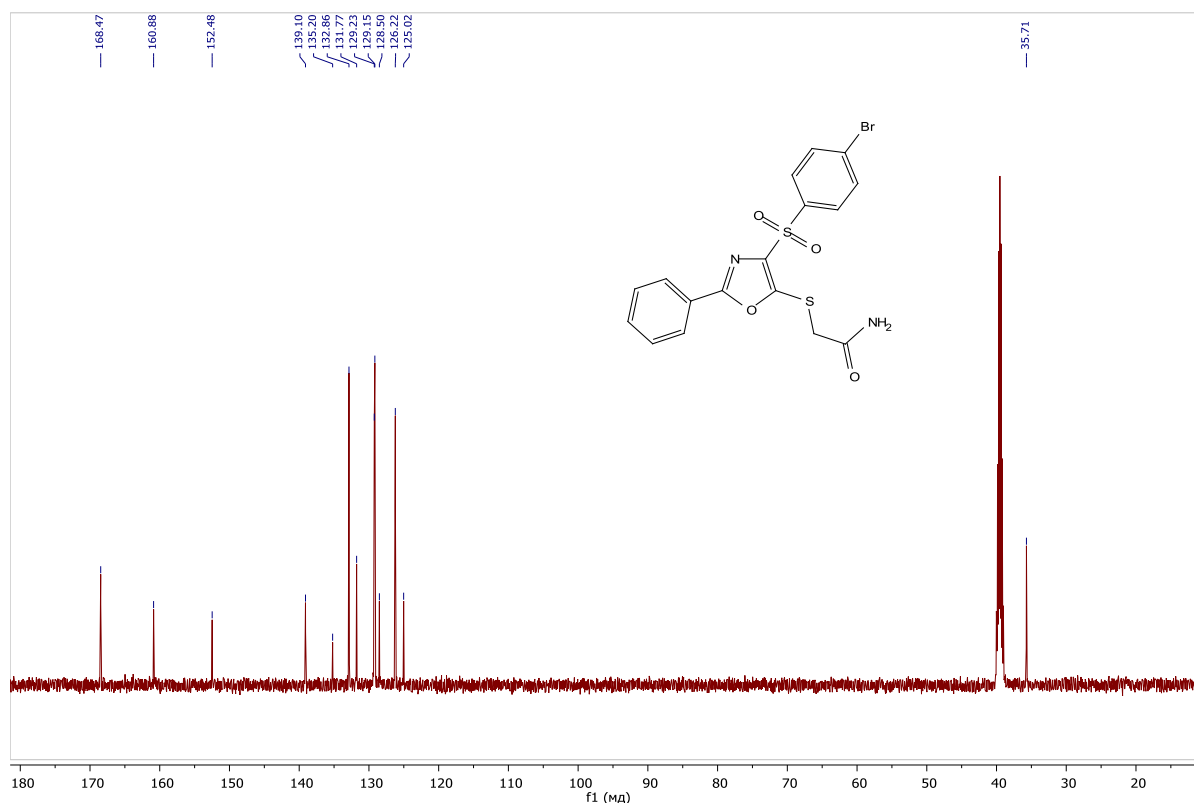


Figure S58. ¹³C NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanylacetamide (D27).

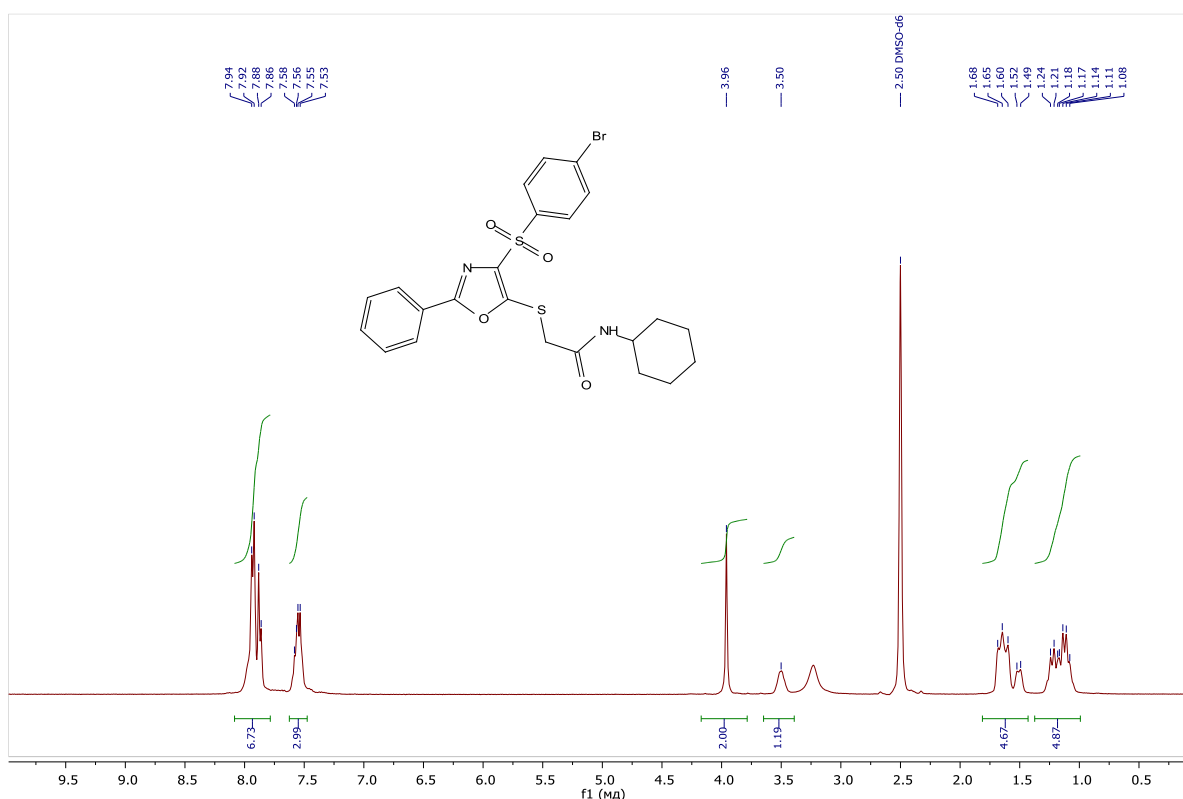


Figure S59. ^1H NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-cyclohexyl-acetamide (D28).

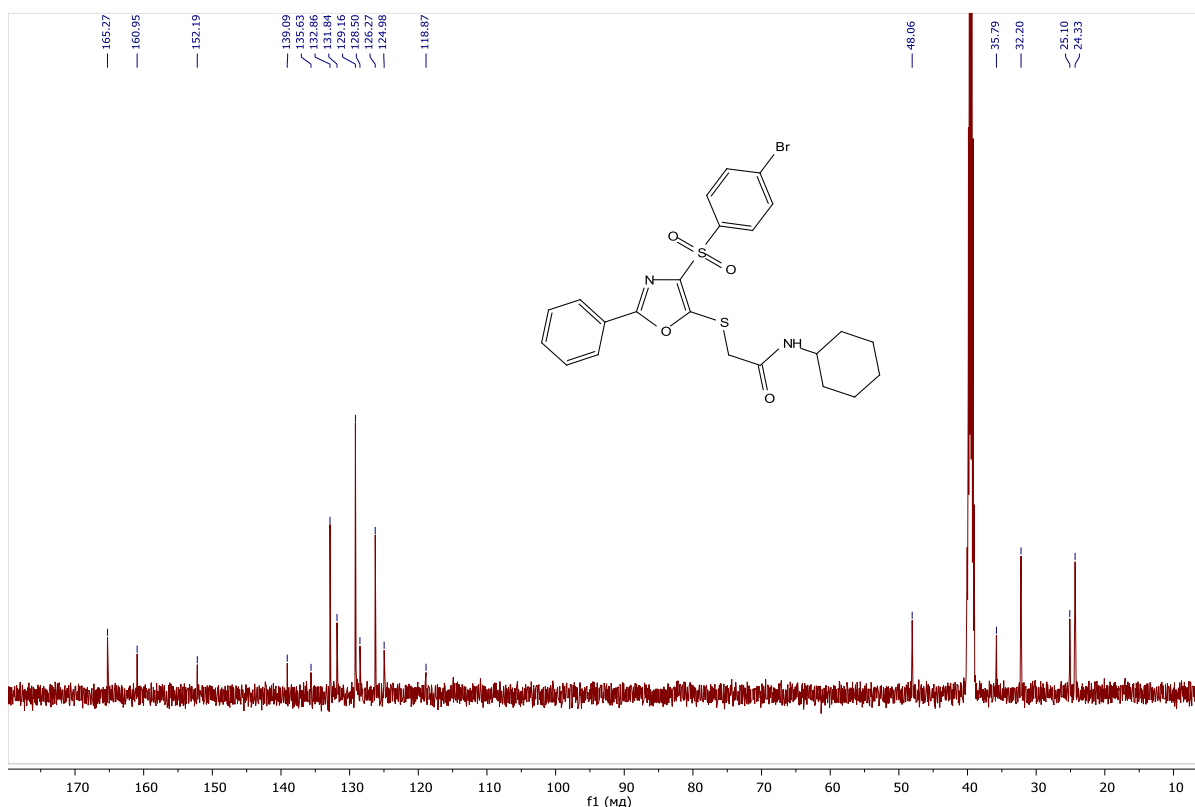
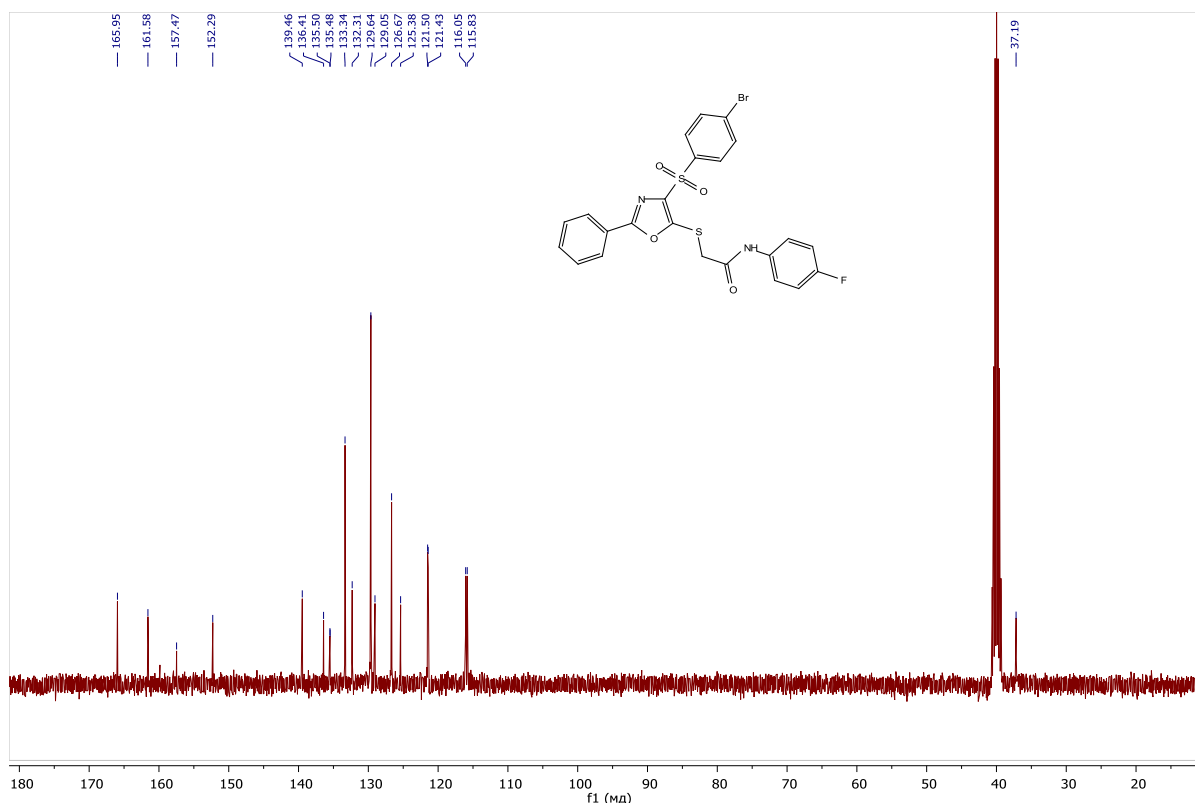
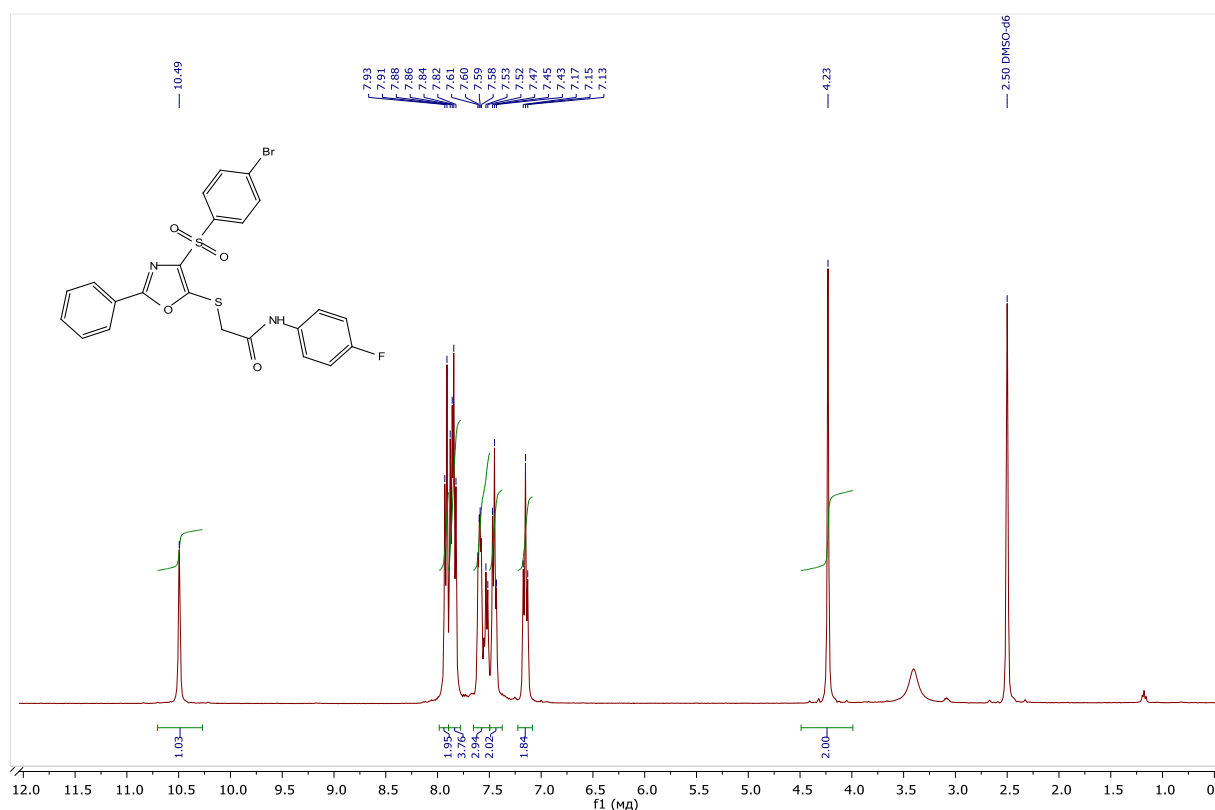


Figure S60. ^{13}C NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-cyclohexyl-acetamide (D28).



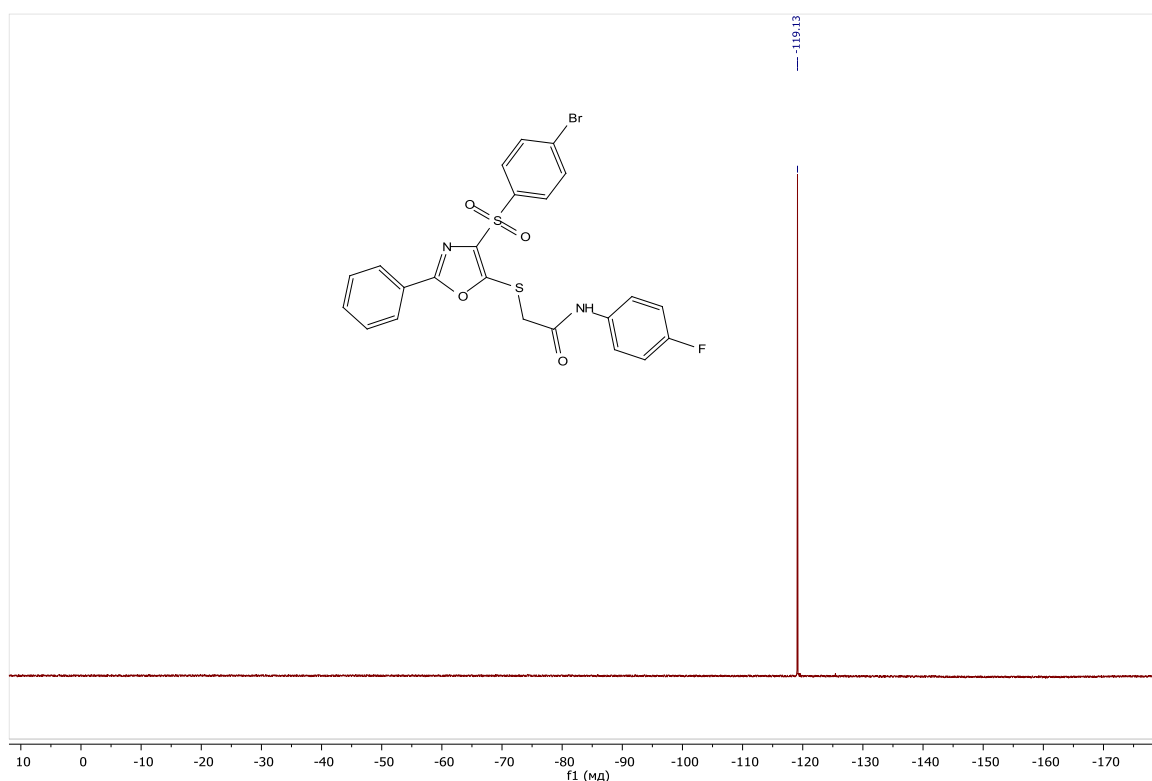


Figure S63. ¹⁹F NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-fluorophenyl)-acetamide (**D29**).

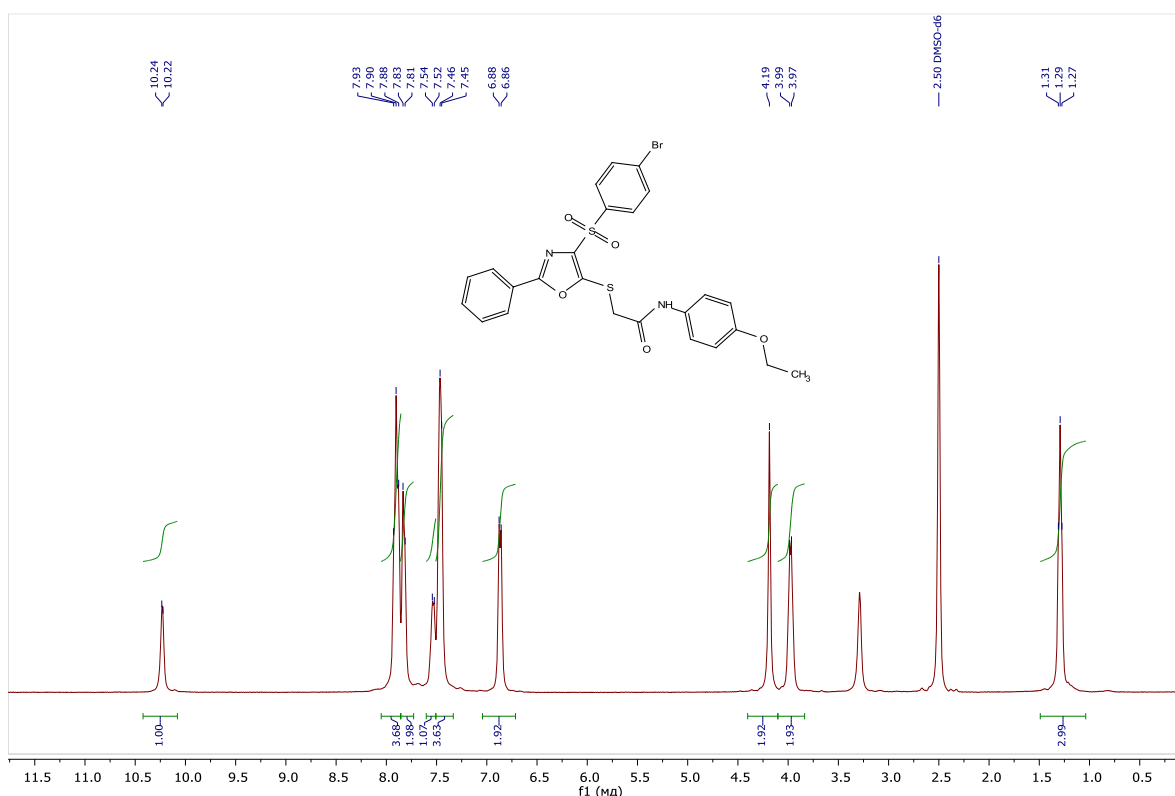


Figure S64. ¹H NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-ethoxyphenyl)-acetamide (**D30**).

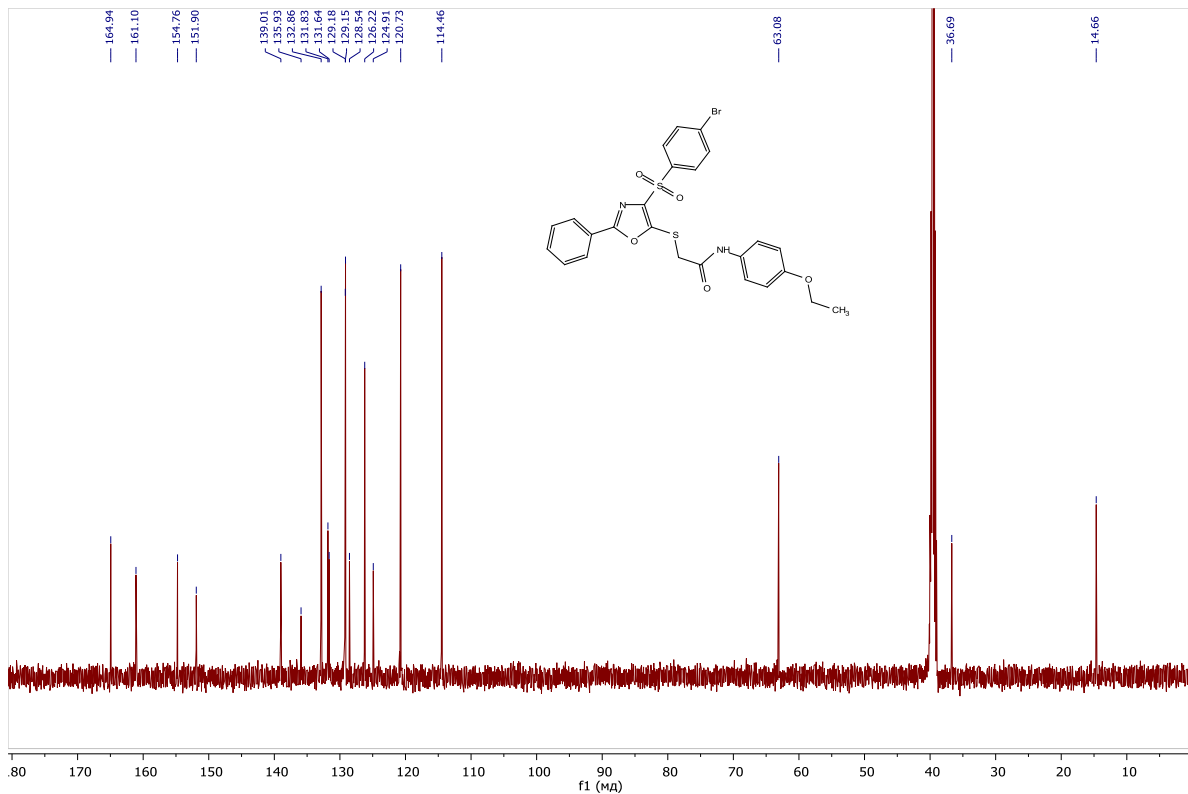


Figure S65. ^{13}C NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(4-ethoxyphenyl)-acetamide (**D30**).

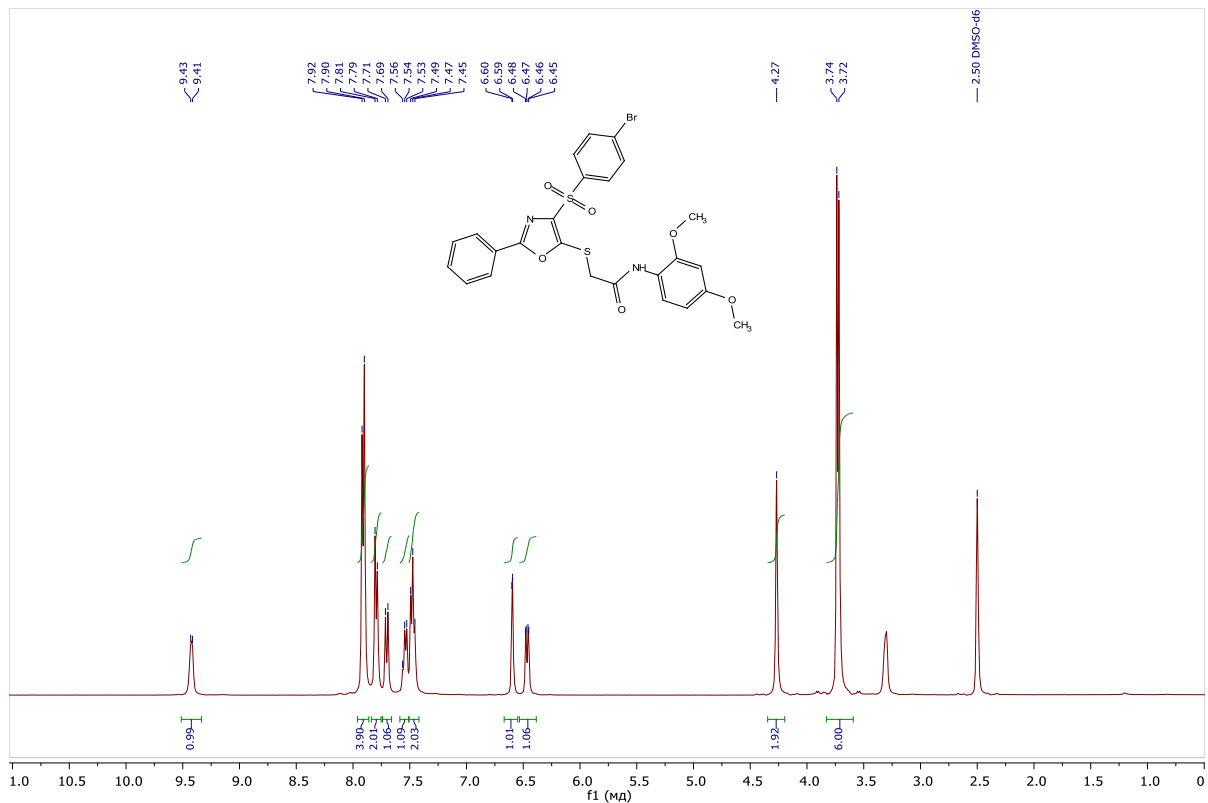


Figure S66. ^1H NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)-acetamide (**D31**).

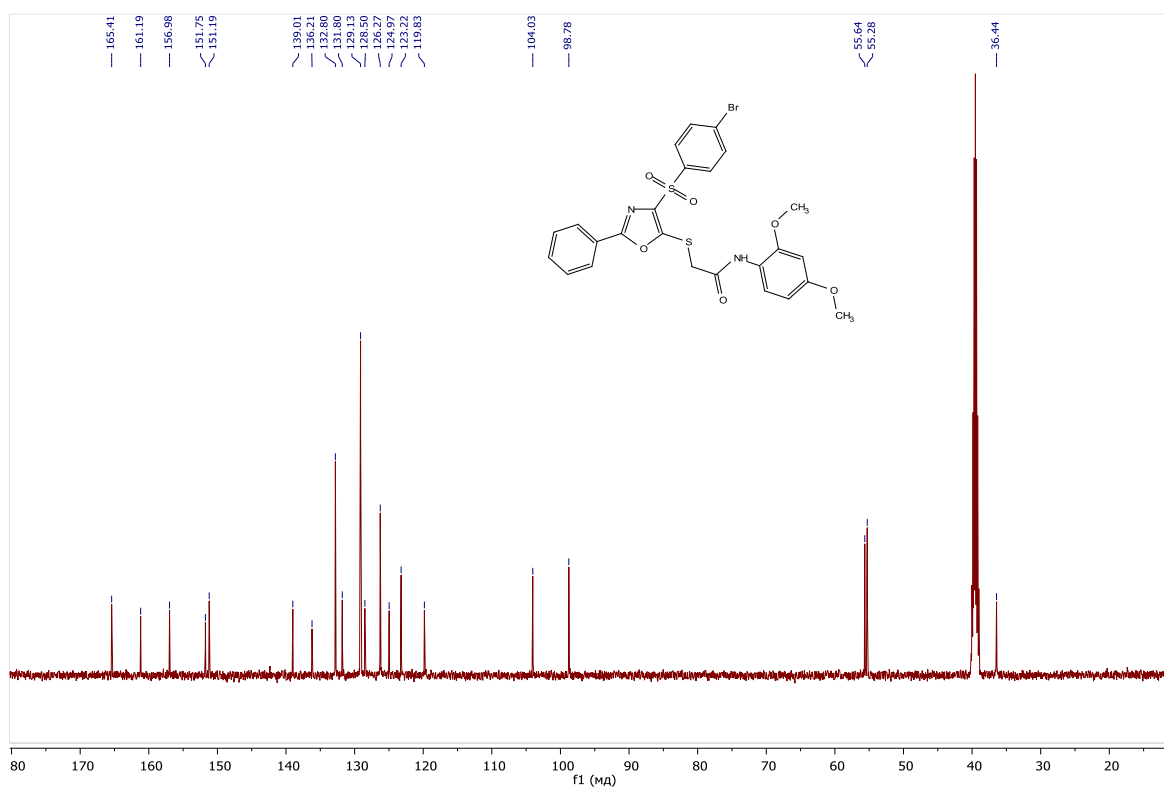


Figure S67. ^{13}C NMR spectrum of 2-[4-(4-bromophenyl)sulfonyl-2-phenyl-1,3-oxazol-5-yl]sulfanyl-N-(2,4-dimethoxyphenyl)-acetamide (**D31**).

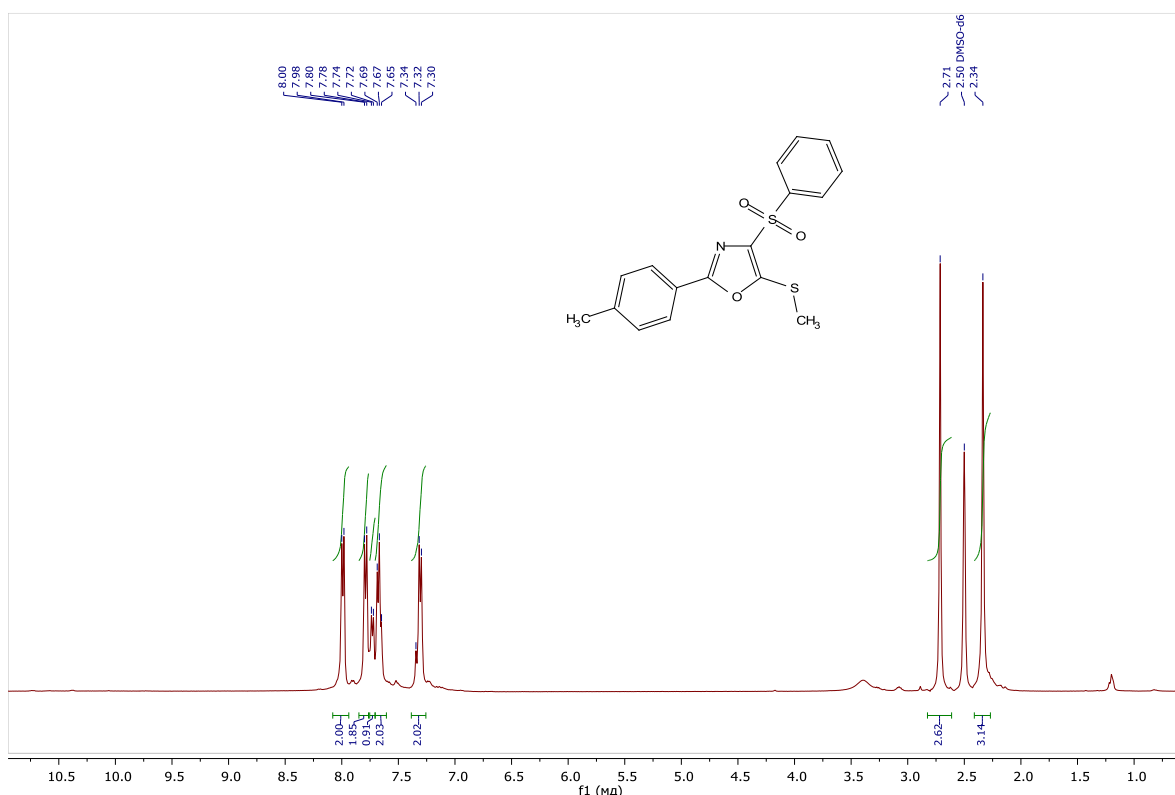


Figure S68. ^1H NMR spectrum of 4-(benzenesulfonyl)-5-methylsulfanyl-2-(4-tolyl)-1,3-oxazole (**D32**).

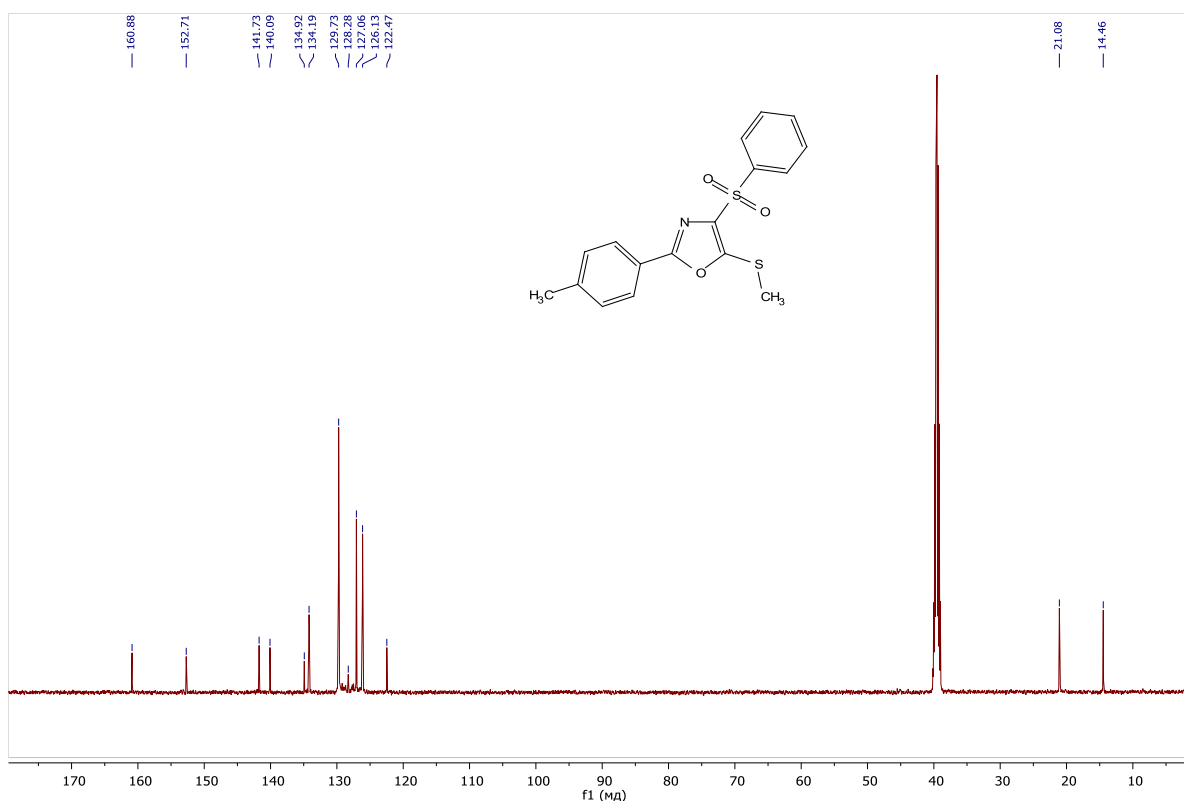


Figure S69. ^{13}C NMR spectrum of 4-(benzenesulfonyl)-5-methylsulfanyl-2-(4-tolyl)-1,3-oxazole (**D32**).

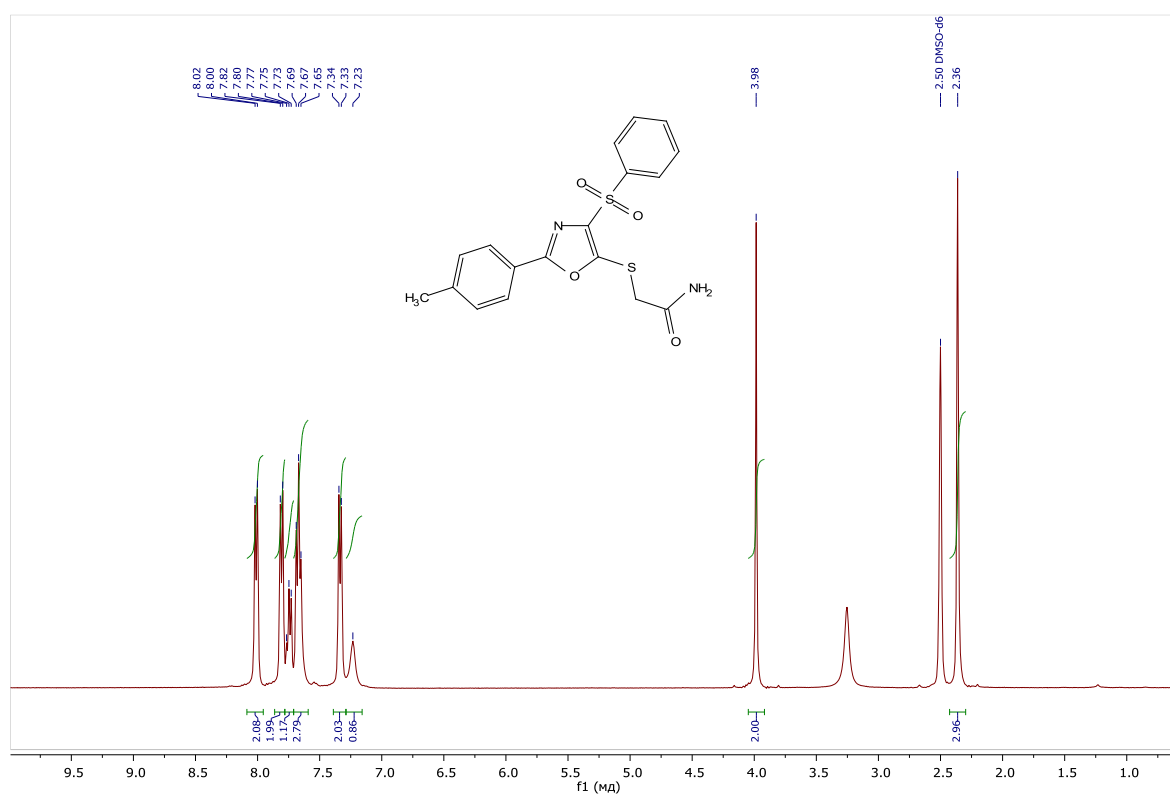


Figure S70. ^1H NMR spectrum of 2-[4-(benzenesulfonyl)-2-(4-tolyl)-1,3-oxazol-5-yl]sulfanylacetamide (**D33**).

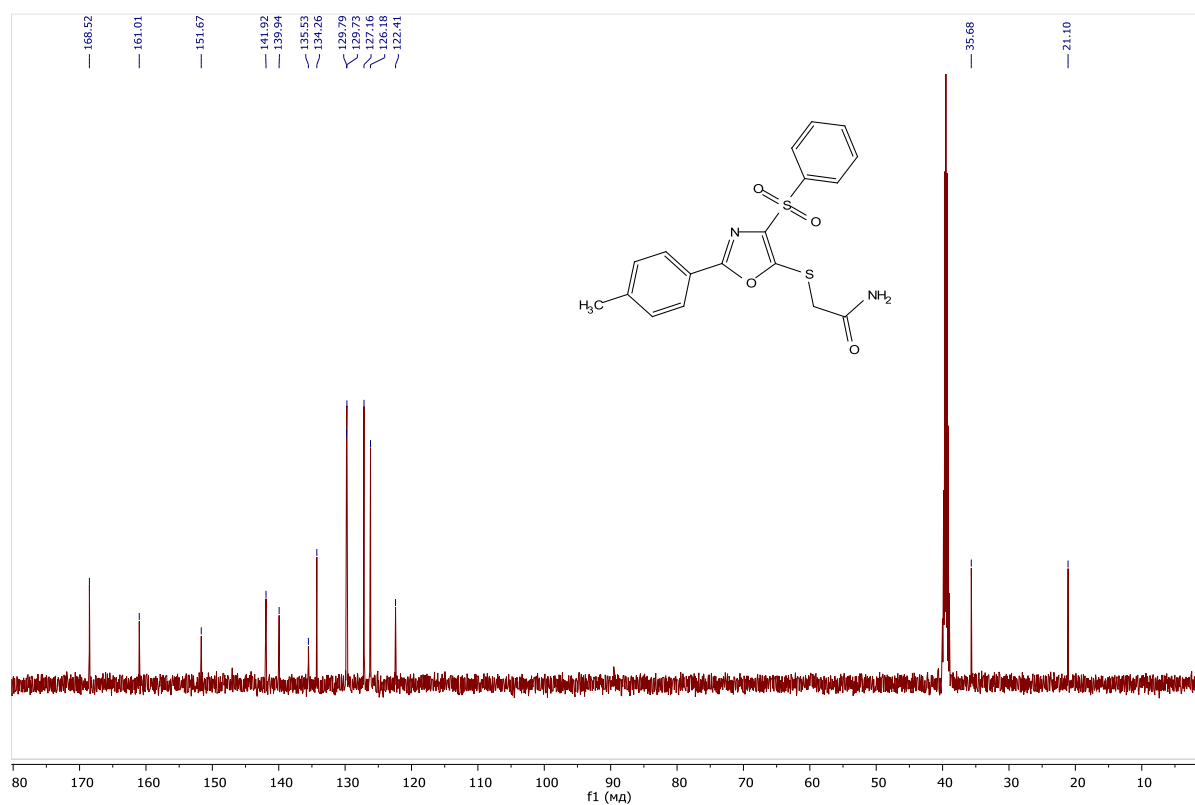


Figure S71. ¹³C NMR spectrum of 2-[4-(benzenesulfonyl)-2-(4-tolyl)-1,3-oxazol-5-yl]sulfanylacetamide (**D33**).