

Synthesis and Antitumor Activity of 5-Phenyl-1,3-thiazole-4-sulfonamide Derivatives

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Abstract—A method for the synthesis of 5-phenyl-1,3-thiazole-4-sulfonyl chloride was developed based on the cyclization of ethyl 2-{{[1-(benzylsulfanyl)-2-oxo-2-phenylethyl]amino}-2-oxoacetate obtained from available reagents under the action of the Lawesson's reagent and oxidative chlorination of the intermediate benzyl 5-phenyl-1,3-thiazol-4-ylsulfide. The resulting sulfonyl chloride was converted into a series of 5-phenyl-1,3-thiazole-4-sulfonamide derivatives for which *in vitro* antitumor activity screening studies were performed on 60 cancer cell lines.

Keywords: 1,3-thiazole, sulfonyl chloride, sulfonamide, antitumor activity

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Malignant diseases are widespread. They are considered as the main problem of this century, which worries the medical community around the world [1]. The development of resistance to anticancer drugs, leading to their inefficiency, necessitates the search for new highly active and less toxic chemotherapeutic agents. Among drug development strategies, special attention is paid to molecules containing heterocycles with a sulfur atom in their structure, and, in particular, a thiazole ring, since its derivatives have excellent pharmacological characteristics [2–4]. The thiazole ring is present in more than 18 FDA-approved drugs [4].

Modification of a thiazole scaffold with carboxyl, sulfonyl, or sulfonamide pharmacophores significantly expands the spectrum of biological activity, making such hybrids ideal candidates for the development of more effective and safer drugs. Among them, the most studied are thiazole-4- and thiazole-5-carboxylic acid derivatives [2, 5, 6], which include the well-known antitumor drugs bleomycin **1** and dasatinib **2** (Scheme 1). Among thiazole-2-carboxylic acid amides **3**, effective inhibitors of ubiquitin-specific peptidase 7 (USP7) were found [7].

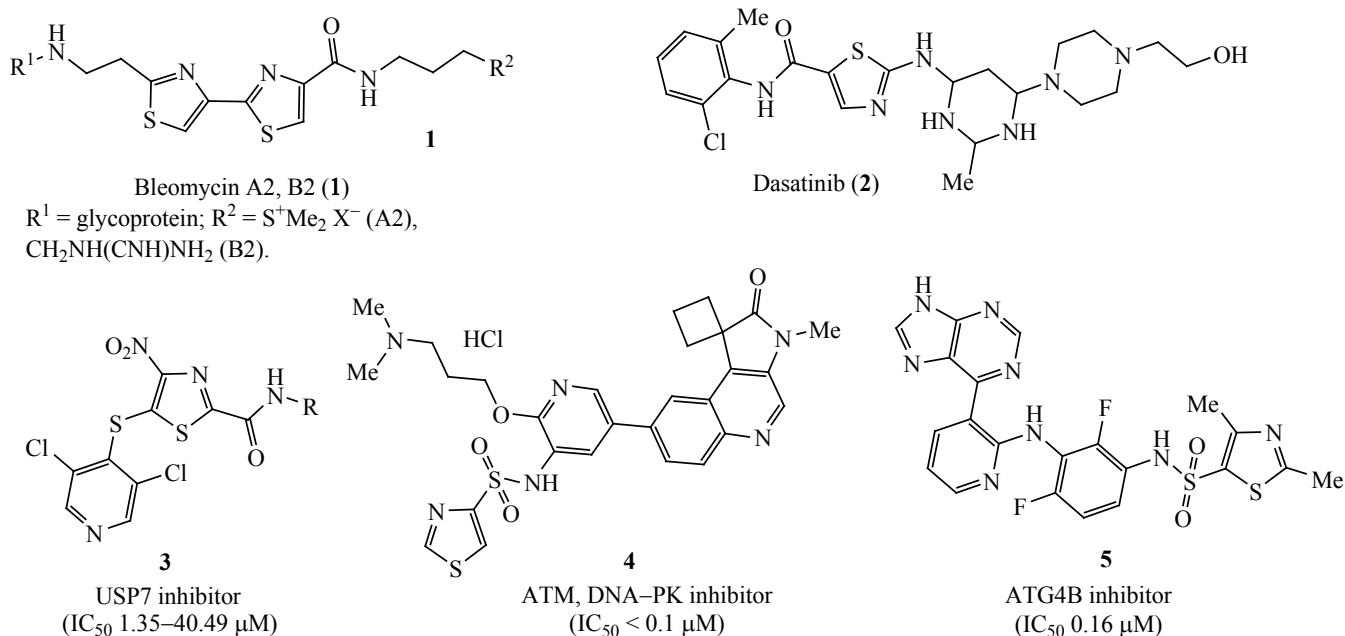
Sulfonyl hybrids are widely studied for their anticancer activity, as they are characterized by minimal side effects along with encouraging indicators of the

possible development of drug resistance associated with their repeated use [8–10]. Thiazolesulfonamides have a wide spectrum of pharmacological activity, among which a number of thiazole-4- (**4**) and thiazole-5-sulfonamides (**5**) have been proposed for the prevention or treatment of cancer as inhibitors of ATM and DNA-PK [11], PI3K α [12], Raf [13] kinases and ATG4B protease [14].

This work is a continuation of our research on the synthesis of thiazole-4-sulfonamides [15] in order to search for effective anticancer agents, and is based on the idea of creating previously unknown sulfonyl hybrids of thiazolecarboxylic acids.

To implement this task, we used an approach developed by us earlier [15–17] based on the cyclization of *N*-(2-oxo-2-arylethyl)amides under the action of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetan-2,4-dithione (Lawesson's reagent) and oxidative chlorination of benzylsulfanyl-1,3-thiazoles. Ethyl 2-[(1-hydroxy-2-oxo-2-phenylethyl)amino]-2-oxoacetate **6** obtained by heating a mixture of reagents in tetrahydrofuran (Scheme 2). Further, using a simple sequence **6**→**7**→**8**, carbinol **6** was converted into ethyl 2-{{[1-(benzylsulfanyl)-2-oxo-2-phenylethyl]amino}-2-oxoacetate **8**. 1-Substituted 2-[(2-phenyl-2-oxoethyl)amino]-2-oxoacetates **6**–**8** were obtained for the first time. Their spectral

Scheme 1.



characteristics fully correspond to the expected ones and agree with the data for the previously described *N*-(2-aryl-1-*R*-2-oxoethyl)carboxamides with similar structures [15, 17].

Thionization of oxoacetate **8** with Lawesson's reagent was carried out in anhydrous dioxane, resulting in cyclization to the 1,3-thiazole derivative. To isolate product **9**, we applied a procedure previously used in the synthesis of 4-substituted 1,3-thiazoles: treatment of the reaction mixture with an aqueous NaOH solution followed by extraction of the product with chloroform [15–17]. However, according to IR spectroscopy data (the absence of strong stretching vibrations of the CO₂Et group), the decarboxylation product—benzyl-5-phenyl-1,3-thiazol-4-ylsulfide **10**—was isolated instead of the expected ethyl 4-(benzylsulfanyl)-5-phenyl-1,3-thiazole-2-carboxylate **9**. It should be noted that the synthesis of 4-unsubstituted ethyl 5-aryl-1,3-thiazol-2-carboxylates has been successfully carried out earlier under similar conditions [18].

Since compound **10** could not be isolated in pure form, we tried to obtain it in another way, starting from the adduct of formamide and phenylglyoxal. However, unlike 4-chlorophenyl- and 4-methylphenylglyoxals, for which adducts with formamide have been successfully

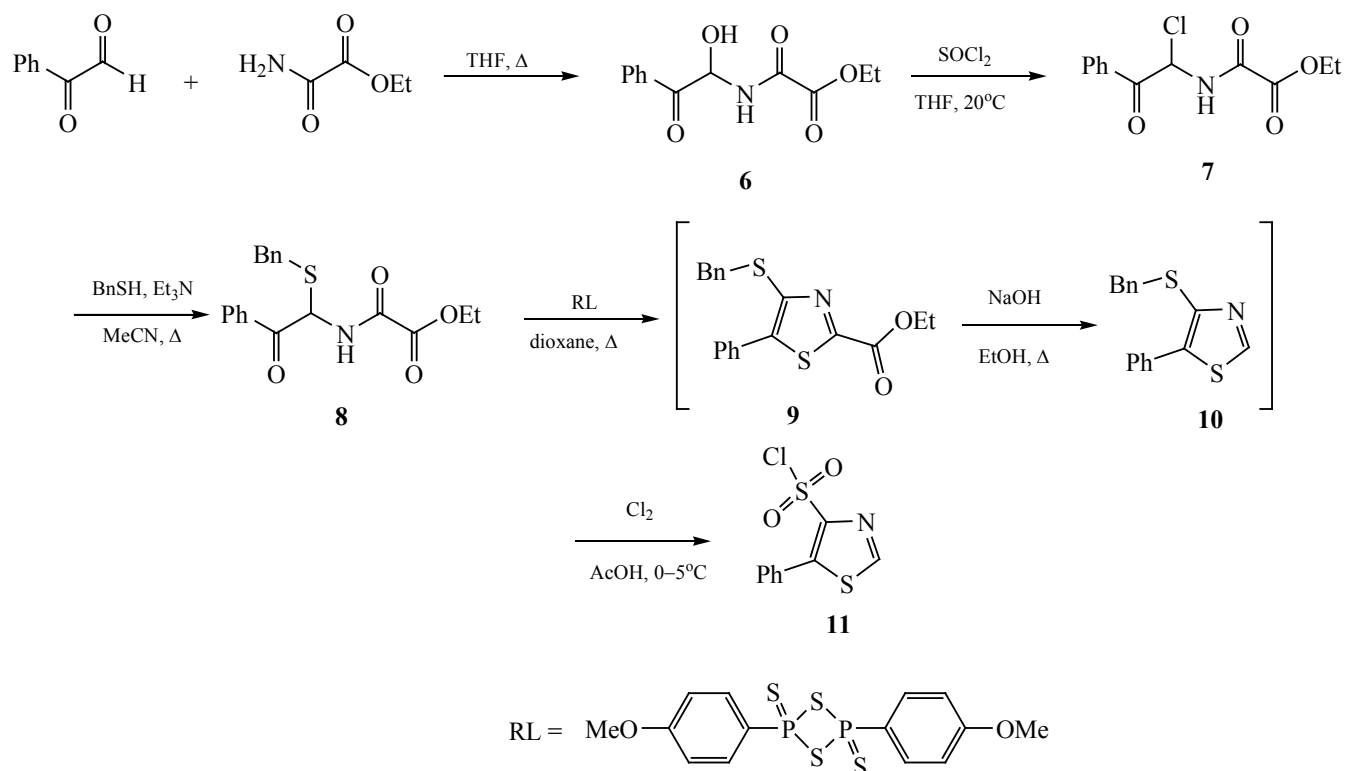
synthesized [17, 19], the reaction of phenylglyoxal with formamide was accompanied by significant resin formation, regardless of conditions (when heated or at room temperature, in benzene or THF).

The crude product **10** was used to obtain 5-phenyl-1,3-thiazole-4-sulfonyl chloride **11**. Compound **11** was synthesized by oxidative chlorination in acetic acid.

Amination of sulfonyl chloride **11** with ammonia and amines was carried out by heating in dioxane (Scheme 3), which made it possible to obtain a series of sulfonamides **12–15** for further testing for anticancer activity. It should be noted that the list of 2-unsubstituted 1,3-thiazole-4-sulfonyl chlorides and 4-sulfonamides described earlier is limited to 5-unsubstituted derivatives and compounds with non-aromatic substituents in position 5 [11, 20, 21]. For reactions, amines containing pharmacophore fragments (piperidine, morpholine, piperazine or tetrahydrothiophene-1,1-dione) were chosen, since such structural fragments are present in a number ofazole sulfonamides, which exhibit a high level of anticancer activity [22, 23].

Amination product **12** was formed by the reaction of sulfonyl chloride **11** with aqueous ammonia at room temperature. *N*-Substituted sulfonamides **13–15** were obtained by heating a reactants mixture with triethylamine

Scheme 2.



in dioxane. The yields of amination products are practically independent of the amine structure; all sulfonamides were obtained in high yields (70–85%).

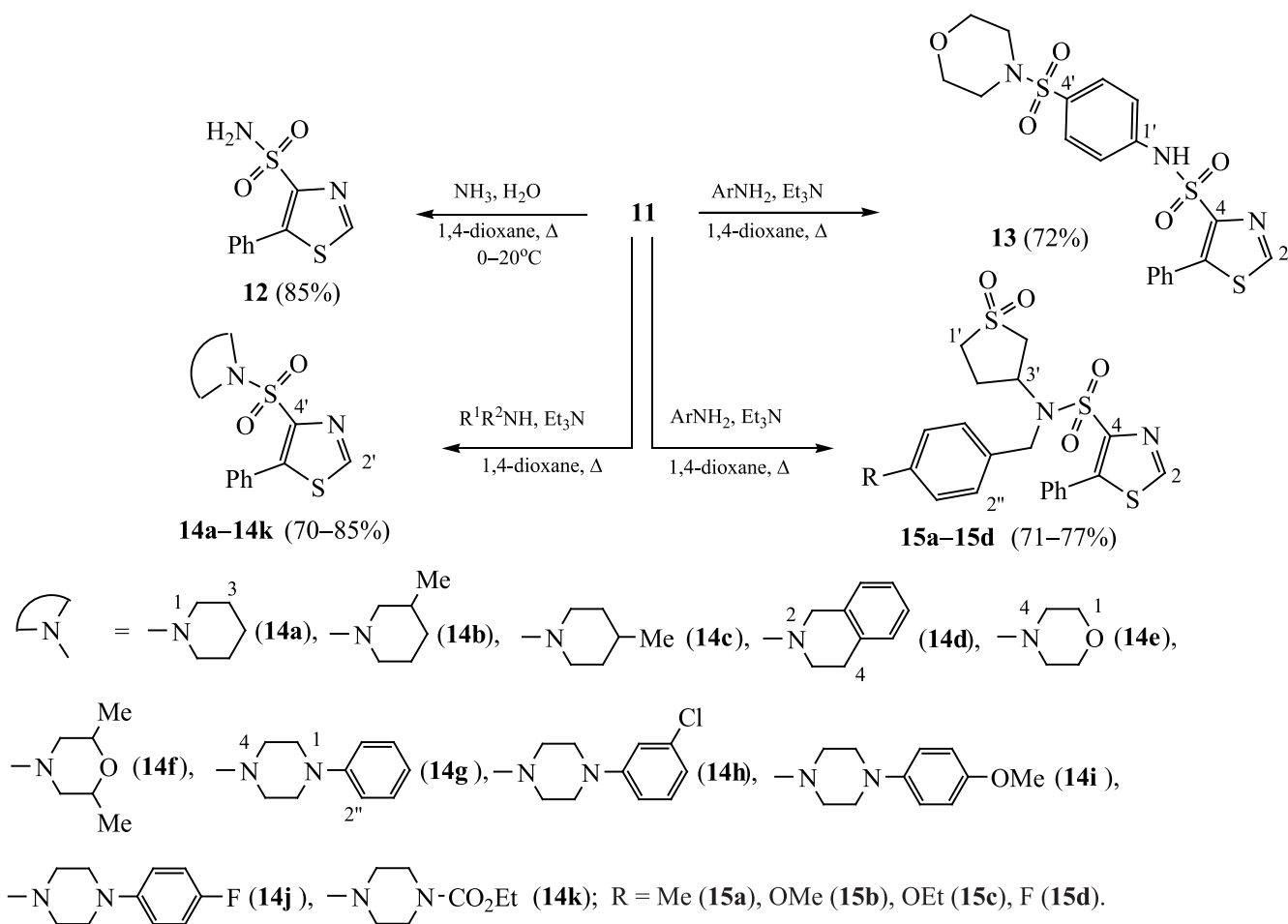
Composition and structure of new thiazole derivatives **11–15** were confirmed by elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry methods. The formation of an azole ring is indicated by the absence in the IR and NMR spectra of the NH signals and carbonyl groups characteristic of the starting acyclic compound **9**. Stretching vibrations of the SO_2 group in the IR spectra of compounds **11–15** are observed in the form of two strong bands in the 1143–1193 and 1332–1382 cm^{-1} regions. A characteristic feature of the ^1H NMR spectra of thiazoles **11–15** is the presence of a singlet of the aromatic proton of the C^2H thiazole ring in a downfield (9.11–9.29 ppm). In the ^{13}C NMR spectra, the resonance of the tertiary carbon C^2 of the thiazole ring is observed in a lower field (153.5–155.1 ppm) than the signal of the quaternary carbon C^4 (143.6–150.1 ppm).

As part of the international scientific program of the US National Institutes of Health, testing of the antitumor activity of thiazole-4-sulfonamides **12–15** was carried

out. Screening studies were carried out *in vitro* on 60 cancer cell lines that cover current types of human cancers (lines of lung, kidney, CNS, ovarian, prostate, breast, epithelial cancer, as well as leukemia and melanoma) when exposed to a substance at a concentration of 1×10^{-5} M, as a result of which the growth percentage (GP) of cancer cell lines was determined in comparison with the control (control, 100%) [24–27].

It was found that the level of antitumor activity of 5-phenyl-1,3-thiazole-4-sulfonamides **12–15** determines the structure of the amine fragment. Compounds **13**, **14d**, and **15a–15d**, which contain bulky sulfonamide groups in their structure, showed the lowest activity, inhibiting the growth of cancer cells by less than 20% (GP > 80%). The activity of piperazine derivatives **14g–14k** is somewhat higher, except for 1-(4-methoxyphenyl)piperazine **14i** (Table 1). At the same time, only some cell lines were moderately sensitive to the action of compounds **14g**, **14h** and **14j**, **14k** (GP < 80%). The best indicator in this group of thiazolyl-4-sulfonamides was found for the 1-(3-chlorophenyl)piperazine derivative **14h**, which

Scheme 3.



reduced the growth of colon cancer cell line HT29 to 68.13%.

Amino-unsubstituted thiazolyl-4-sulfonamide **12** and 2,6-dimethylmorpholinyl derivative **14f** had a moderate inhibitory effect (GP < 80%) on the growth of SNB-75 (CNS) and UO-31 (kidney cancer, **14f**) cell lines.

Among the tested thiazolyl-4-sulfonamides, 4-methyl-1-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperidine **14c** showed the highest activity (Table 1). Thus, a noticeable decrease in the growth of most leukemia cancer cells (GP 25.52–66.75%) and CNS (GP 30.71–57.90%) was found. In relation to subpanels of kidney cancer and breast cancer, compound **14c** was more selective. At the same time, the rate of inhibition of the renal line RFX 393 exceeded 90% (GP 9.28%). Also, the renal line 786-0

(GP 30.81%) and HS 578T (GP 40.25%) of breast cancer have a high sensitivity to thiazole **14c**.

In conclusion, a method was proposed for the synthesis of 5-phenyl-1,3-thiazole-4-sulfonyl chloride and 5-phenyl-1,3-thiazole-4-sulfonamides, new promising antitumor agents, the high level of activity of which was experimentally confirmed on 60 tumor cell lines. The method is based on a synthetic sequence involving cyclization of ethyl 2-[[1-(benzylsulfonyl)-2-oxo-2-phenylethyl]amino]-2-oxoacetate obtained from available reagents under the action of Lawesson's reagent.

EXPERIMENTAL

All reagents and solvents used in synthetic procedures were purchased from Aldrich and used without further purification.

Table 1. Antitumor activity of thiazole-4-sulfonamides **12** and **14** ($c\ 1 \times 10^{-5}$ M)

Compound (NSC code)	Average GP, %	GP range, %	GP values for the most sensitive cell lines, %
12 (829993)	100.55	77.85–109.32	77.85 (SNB-75/CNS)
14c (829989)	81.99	9.28–116.16	66.75 (MOLT-4/leukemia) 25.52 (RPMI-8226/leukemia) 55.69 (SR/leukemia) 30.71 (SF-295/CNS) 44.27 (SF-539/CNS) 55.64 (SNB-75/CNS) 57.90 (U251/CNS) 30.81 (786-0/kidney cancer) 9.28 (RXF 393/kidney cancer) 40.25 (HS 578T/breast cancer)
14e (829988)	101.08	73.26–119.77	73.26 (SNB-75/CNS) 79.28 (UO-31/kidney cancer)
14g (829991)	99.73	77.67–123.06	77.67 (SNB-75/CNS)
14h (829997)	91.97	68.13–116.71	73.24 (K-562/leukemia) 77.05 (MOLT-4/leukemia) 78.04 (PRMI-8226/leukemia) 77.63 (EKVX/lung cancer) 73.77 (HCT-116/colon cancer) 75.94 (HCT-15/colon cancer) 68.13 (HT29/colon cancer) 73.90 (T-47D/breast cancer)
14j (829992)	96.09	70.00–116.18	70.00 (SNB-75/CNS) 73.43 (A498/kidney cancer)
14k (829990)	99.83	77.48–118.12	77.48 (SNB-75/CNS)

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 and 126 MHz). The internal standard was TMS. The signals of ^{13}C atoms (methyl, methylene, methine, and quaternary carbon atoms) were assigned using the APT method, taking into account the known range of chemical shifts of carbon atoms included in the functional groups. IR spectra (KBr) were recorded on a Bruker VERTEX 70 instrument. Mass spectra were recorded on an Agilent 1200 LCMCD SL instrument [chemical ionization (APCI), electrospray ionization (ESI)]. Melting points were determined on a Fisher-Johns apparatus. Elemental analyzes were performed at the Analytical Laboratory of the Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine. The content of carbon and hydrogen was determined by the Pregl gravimetric method, nitrogen—by the gravimetric

Dumas micromethod, sulfur—by the Schöniger titrimetric method, and chlorine—by the mercurimetric method.

Ethyl 2-[(1-hydroxy-2-oxo-2-phenylethyl)amino]-2-oxoacetate (6). To a solution of 67.0 g (0.5 mol) of freshly distilled phenylglyoxal in 250 mL of THF was added 58.5 g (0.5 mol) of ethyl 2-amino-2-oxoacetate. The resulting solution was boiled for 6 h and then kept at 20–25°C for 12 h. The solvent was removed in vacuum and 500 mL of water was added to the residue. The resulting solid was filtered off, washed with water and dried in a desiccator over P_2O_5 . Compound **6** was purified by recrystallization from ethanol. Yield 94.26 g (75%), beige crystals, mp 99–101°C (EtOH). IR spectrum, ν , cm^{-1} : 703, 751, 1283 m (C–O), 1400 s (C–O), 1579 s (C=O), 1687 m (C=O), 3364 br (NH), 3422 br (OH). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 1.26 t (3H, OCH_2CH_3 , $^3J_{\text{HH}}$ 7.5 Hz), 4.24 q (2H, OCH_2CH_3 , $^3J_{\text{HH}}$ 7.5 Hz), 6.30 d (1H, C^1H , $^3J_{\text{HH}}$ 6.0 Hz), 6.83 br. s

(1H, OH), 7.54 t (2H, C^{3'}H, C^{5'}H, ³J_{HH} 8.0 Hz), 7.66 t (1H, C^{4'}H, ³J_{HH} 8.0 Hz), 7.97 d (2H, C^{2'}H, C^{6'}H, ³J_{HH} 8.0 Hz), 9.45 d (1H, NH, ³J_{HH} 6.0 Hz). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 13.8 (CH₃), 62.3 (OCH₂), 73.0 (C(H)OH), 128.7 (2C), 128.8 (2C), 133.7, 133.8, 157.1 (COCO₂Et), 160.4 (COCO₂Et), 194.0 (COPh). Mass spectrum, *m/z* (*I*_{rel.}, %): 252.1 (100) [*M* + H]⁺. Found, %: C 57.43; H 5.20; N 5.54. C₁₂H₁₃NO₅. Calculated, %: C 57.37; H 5.22; N 5.58.

Ethyl 2-[(1-chloro-2-oxo-2-phenylethyl)amino]2-oxoacetate (7). To a solution of 100.4 g (0.4 mol) of compound **6** in 250 mL of anhydrous THF was added 32.6 mL (0.45 mol) of thionyl chloride. The solution was stirred at 20–25°C for 24 h. The solvent was removed in vacuum and 200 mL of anhydrous hexane was added to the residue. The solid was filtered off, washed with hexane and dried in vacuum. Yield 86.3 g (80%), colorless crystals, mp 48–50°C (hexane). IR spectrum, ν, cm⁻¹: 611, 688, 805, 1181 s (C–O), 1289 br. s (C–O), 1506, 1687 s (C=O), 1710 s (C=O), 1743 s (C=O), 2995, 3343 (NH). ¹H NMR spectrum (CDCl₃), δ, ppm: 1.43 t (3H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 4.43 q (2H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 7.07 d (6.47 d (1H, CHCl, ³J_{HH} 9.0 Hz), 7.56 t (2H, C^{3'}H, C^{5'}H, ³J_{HH} 8.0 Hz), 7.70 t (1H, C^{4'}H, ³J_{HH} 8.0 Hz), 8.10 d (2H, C^{2'}H, C^{6'}H, ³J_{HH} 8.0 Hz), 8.68 br. d (1H, NH, ³J_{HH} 9.0 Hz). ¹³C NMR spectrum (CDCl₃), δ_C, ppm: 13.5 (CH₃), 59.1 (OCH₂), 63.4 (CHCl), 128.7 (2C), 129.1 (2C), 131.1, 134.6, 155.4 (COCO₂Et), 158.5 (COCO₂Et), 186.7 (COPh). Mass spectrum, *m/z* (*I*_{rel.}, %): 270.5 (100) [*M* + H]⁺. Found, %: C 53.50; H 4.45; Cl 13.26; N 5.16. C₁₂H₁₂ClNO₄. Calculated, %: C 53.44; H 4.49; Cl 13.15; N 5.19.

Ethyl 2-[[1-(benzylsulfanyl)-2-oxo-2-phenylethyl]-amino]-2-oxoacetate (8). To a solution of 80.7 g (0.3 mol) of compound **7** in 200 mL of anhydrous acetonitrile was added 37.2 g (0.3 mol) of benzyl mercaptan and 42 mL (0.3 mol) of triethylamine. The solution was heated to boiling and left for 12 h at 20–25°C, then 500 mL of water was added. The formed precipitate was filtered off and washed with water. Compound **8** was purified by recrystallization from ethanol. Yield 83.6 g (78%), pale yellow crystals, mp 109–111°C (EtOH). IR spectrum, ν, cm⁻¹: 704, 766, 977, 1194 m (C–O), 1285 s (C–O), 1679 s (C=O), 1704 s (C=O), 1735 s (C=O), 3348 m (NH). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 1.29 t (3H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 3.81 d (1H, SCH_AH_B, ²J_{HH} 14.0 Hz), 3.94 d (1H, SCH_AH_B, ²J_{HH} 14.0 Hz), 4.26 q (2H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 6.47 d (1H, C¹H, ³J_{HH}

8.0 Hz), 7.28–7.31 m (5H, SCH₂Ph), 7.47 t (2H, C^{3'}H, C^{5'}H, ³J_{HH} 8.0 Hz), 7.65 t (1H, C^{4'}H, ³J_{HH} 8.0 Hz), 7.86 d (2H, C^{2'}H, C^{6'}H, ³J_{HH} 8.0 Hz), 9.32 d (1H, NH, ³J_{HH} 8.0 Hz). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 13.8 (CH₃), 33.9 (SCH₂Ph), 56.1 (SC(H)NH), 62.3 (OCH₂), 127.2, 128.5 (2C), 128.7 (2C), 128.7 (2C), 129.1 (2C), 133.4, 133.9, 137.1, 157.1 (COCO₂Et), 160.1 (COCO₂Et), 190.9 (COPh). Mass spectrum, *m/z* (*I*_{rel.}, %): 358.1 (100) [*M* + H]⁺. Found, %: C 63.92; H 5.34; N 3.89; S 9.01. C₁₉H₁₉NO₄S. Calculated, %: C 63.85; H 5.36; N 3.92; S 8.97.

5-Phenyl-1,3-thiazole-4-sulfonyl chloride (11). A mixture of 89.2 g (0.25 mol) of oxoacetate **8** and 101 g (0.25 mol) of Lawesson's reagent in 200 mL of anhydrous dioxane was refluxed for 8 h. Then the mixture was kept at 20–25°C for 12 h. The solvent was removed in vacuum. To the residue was added 100 mL of 5% NaOH aqueous solution. The reaction product was extracted from the resulting oil with chloroform (2×100 mL), the extract was dried with CaCl₂. The solvent was removed in vacuum and the residue was dissolved in 100 mL of ethanol. To a solution containing ethyl 4-(benzylsulfanyl)-5-phenyl-1,3-thiazole-2-carboxylate **9** was added 100 mL of 10% NaOH aqueous solution, boiled for 1 h and left at 20–25°C for 2 h. Next, hydrochloric acid (conc.) was added to the solution to pH 2 and boiled for 1 h. After cooling, the solvent was removed in vacuum and 200 mL of water was added to the residue. The product was extracted with chloroform (2×100 mL), the extract was dried with CaCl₂. The solvent was removed in vacuum, the residue was dissolved in 80 mL of acetic acid (95%), and gaseous Cl₂ was bubbled through the solution containing benzyl-5-phenyl-1,3-thiazol-4-ylsulfide **10** for 30 min, maintaining the temperature of the reaction mixture within 0–5°C. Next, the solution was kept at 0–5°C for 2 h and then poured into ice (500 g). The formed precipitate was filtered off and dried in a vacuum desiccator over P₂O₅. Compound **11** was purified by recrystallization from toluene. Yield 42.2 g (65%), colorless crystals, mp 114–116°C (toluene). IR spectrum, ν, cm⁻¹: 555, 571, 756, 1193 s (SO₂), 1382 s (SO₂), 1424, 3096. ¹H NMR spectrum (CDCl₃), δ, ppm: 7.51–7.55 m (3H, H-Ar), 7.58 d (2H, C^{2'}H, C^{6'}H, ³J_{HH} 8.0 Hz), 8.89 s (1H, C²H). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 7.37–7.39 m (3H, 5-Ph), 7.73–7.76 m (2H, 5-Ph), 9.11 s (1H, C²H). ¹³C NMR spectrum (CDCl₃), δ_C, ppm: 126.3, 128.2 (2C), 29.8 (2C), 130.2, 146.0 (C⁴), 152.0 (C²). Mass spectrum, *m/z* (*I*_{rel.}, %): 260.6 (100) [*M* + H]⁺. Found, %: C 41.68; H 2.32;

N 5.35; S 24.72. $C_9H_6ClNO_2S_2$. Calculated, %: C 41.62; H 2.33; N 5.39; S 24.69.

5-Phenyl-1,3-thiazole-4-sulfonamide (12). A solution of 2.59 g (0.01 mol) of sulfonyl chloride **11** in 30 mL of anhydrous dioxane was added dropwise with stirring and cooling (0°C) to a 25% aqueous ammonia solution (70 mL). The resulting suspension was stirred for 30 min at 20–25°C. The solid was filtered off and washed with water. Compound **12** was purified by recrystallization from ethanol. Yield 2.04 g (85%), colorless crystals, mp 166–168°C (EtOH). IR spectrum, ν , cm^{-1} : 515, 603, 655, 696, 759, 1147 s (SO_2), 1183, 1275, 1344 s (SO_2), 1425, 1556, 3150 m (NH_2), 3342 m (NH_2). 1H NMR spectrum (DMSO- d_6), δ , ppm: 7.45–7.46 m (3H, 5-Ph), 7.58–7.60 m (2H, 5-Ph), 7.65 s (2H, NH_2), 9.20 s (1H, C^2H). ^{13}C NMR spectrum (DMSO- d_6), δ_C , ppm: 128.2 (2C), 129.0, 129.2, 130.2 (2C), 139.5, 150.1 (C^4), 153.5 (C^2). Mass spectrum, m/z (I_{rel} , %): 240.0 (100) [$M + H$] $^+$. Found, %: C 45.03; H 3.34; N 11.65; S 26.72. $C_9H_8N_2O_2S_2$. Calculated, %: C 44.98; H 3.36; N 11.66; S 26.69.

General procedure for the synthesis of 5-phenyl-1,3-thiazole-4-sulfonamide derivatives 13–15. To a solution of 2.59 g (0.01 mol) of sulfonyl chloride **11** in 30 mL of anhydrous dioxane was added 0.01 mol of the corresponding aniline or dialkylamine and 1.4 mL (0.01 mol) of triethylamine. The mixture was boiled for 2 h and left at 20–25°C for 12 h. The solvent was removed in a vacuum, and 50 mL of water was added to the residue. The solid was filtered off, washed with water and purified by crystallization from ethanol.

N-[4-(4-Morpholinylsulfonyl)phenyl]-5-phenyl-1,3-thiazole-4-sulfonamide (13). Yield 3.35 g (72%), colorless crystals, mp 181–183°C (EtOH). IR spectrum, ν , cm^{-1} : 533, 585, 603, 741, 831, 935, 1109 m (C–O–C), 1142 s (SO_2), 1165 s (SO_2), 1345 s (SO_2), 1596, 3236 s (NH). 1H NMR spectrum (DMSO- d_6), δ , ppm: 2.80 t (4H, NCH_2 , $^3J_{HH}$ 4.0 Hz), 3.61 t (4H, OCH_2 , $^3J_{HH}$ 4.0 Hz), 7.24 d (2H, C^2H , C^6H , $^3J_{HH}$ 8.0 Hz), 7.50 br. s (5H, 5-Ph), 7.60 d (2H, C^3H , C^5H , $^3J_{HH}$ 8.0 Hz), 9.19 s (1H, C^2H), 11.29 s (1H, NH). ^{13}C NMR spectrum (DMSO- d_6), δ_C , ppm: 45.9 (2C, NCH_2), 65.2 (2C, OCH_2), 118.5 (2C), 128.4 (3C), 128.5, 129.1 (2C), 129.7, 130.1 (3C), 142.5, 143.6, 154.8 (C^2). Mass spectrum, m/z (I_{rel} , %): 466.3 (100) [$M + H$] $^+$. Found, %: C 49.07; H 4.09; N 9.05; S 20.71. $C_{19}H_{19}N_3O_5S_3$. Calculated, %: C 49.02; H 4.11; N 9.03; S 20.66.

1-[(5-Phenyl-1,3-thiazol-4-yl)sulfonyl]piperidine (14a). Yield 2.41 g (78%), colorless crystals, mp 117–

119°C (EtOH). IR spectrum, ν , cm^{-1} : 586, 719, 826, 938, 1051, 1143 s (SO_2), 1158, 1189, 1348, 1361 s (SO_2), 2930, 3049. 1H NMR spectrum (DMSO- d_6), δ , ppm: 1.45–1.52 m (6H, C^3H_2 – C^5H_2), 3.17–3.19 m (4H, C^2H_2 , C^6H_2), 7.46–7.48 m (3H, 5'-Ph), 7.53–7.54 m (2H, 5'-Ph), 9.25 s (1H, C^2H). ^{13}C NMR spectrum (DMSO- d_6), δ_C , ppm: 23.1 (C^4H_2), 25.0 (2C, C^3H_2 , C^5H_2), 46.8 (2C, NCH_2), 128.2, 128.6 (2C), 129.4, 130.2 (2C), 142.7, 146.3 (C^4), 154.5 (C^2). Mass spectrum, m/z (I_{rel} , %): 309.2 (100) [$M + H$] $^+$. Found, %: C 54.58; H 5.20; N 9.11; S 20.75. $C_{14}H_{16}N_2O_2S_2$. Calculated, %: C 54.52; H 5.23; N 9.08; S 20.79.

3-Methyl-1-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperidine (14b). Yield 2.74 g (85%), colorless crystals, mp 105–107°C (EtOH). IR spectrum, ν , cm^{-1} : 594, 745, 1145 s (SO_2), 1350 s (SO_2), 1425, 2934. 1H NMR spectrum (DMSO- d_6), δ , ppm: 0.84 d (3H, CH_3 , $^3J_{HH}$ 8.0 Hz), 0.93–0.99 m (1H, $C^4H_AH_B$), 1.38–1.47 m (1H, $C^4H_AH_B$), 1.54–1.58 m (1H, C^3H), 1.65–1.69 m (2H, C^5H_2), 2.41–2.50 m (1H, $C^6H_AH_B$), 2.67–2.76 m (1H, $C^6H_AH_B$), 3.50–3.56 m (2H, C^2H_2), 7.47–7.48 m (3H, 5'-Ph), 7.53–7.55 m (2H, 5'-Ph), 9.25 s (1H, C^2H). ^{13}C NMR spectrum (DMSO- d_6), δ_C , ppm: 21.0 (CH_3), 24.4 (C^5H_2), 30.4 (C^4H_2), 31.6 (C^3H), 46.4 (NC^6H_2), 53.0 (NC^2H_2), 128.2 (2C), 128.6, 129.4, 130.2 (2C), 141.4, 142.7 (C^4), 154.5 (C^2). Mass spectrum, m/z (I_{rel} , %): 323.1 (100) [$M + H$] $^+$. Found, %: C 55.93; H 5.59; N 8.67; S 19.92. $C_{15}H_{18}N_2O_2S_2$. Calculated, %: C 55.87; H 5.63; N 8.69; S 19.89.

4-Methyl-1-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperidine (14c). Yield 2.58 g (80%), colorless crystals, mp 92–94°C (EtOH). IR spectrum, ν , cm^{-1} : 583, 726, 919, 1144 s (SO_2), 1185, 1347 m (SO_2), 1359, 1420, 2925. 1H NMR spectrum (DMSO- d_6), δ , ppm: 0.88 d (3H, CH_3 , $^3J_{HH}$ 8.0 Hz), 1.02–1.13 m (2H, $C^3H_AH_B$, $C^5H_AH_B$), 1.38–1.47 m (1H, C^4H), 1.62–1.67 m (2H, $C^3H_AH_B$, $C^5H_AH_B$), 2.73–2.80 m (2H, $C^2H_AH_B$, $C^6H_AH_B$), 3.59–3.64 m (2H, $C^2H_AH_B$, $C^6H_AH_B$), 7.46–7.48 m (3H, 5'-Ph), 7.53–7.55 m (2H, 5'-Ph), 9.25 s (1H, C^2H). ^{13}C NMR spectrum (DMSO- d_6), δ_C , ppm: 21.4 (CH_3), 29.6 (C^4H), 33.1 (2C, C^3H_2 , C^5H_2), 46.2 (2C, NCH_2), 128.2 (2C), 128.6, 129.4, 130.2 (2C), 142.7, 146.2 (C^4), 154.5 (C^2). Mass spectrum, m/z (I_{rel} , %): 323.0 (100) [$M + H$] $^+$. Found, %: C 55.92; H 5.60; N 8.66; S 19.93. $C_{15}H_{18}N_2O_2S_2$. Calculated, %: C 55.87; H 5.63; N 8.69; S 19.89.

2-[(5-Phenyl-1,3-thiazol-4-yl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (14d). Yield 2.50 g (70%), colorless crystals, mp 129–131°C (EtOH). IR spectrum,

ν , cm^{-1} : 591, 701, 728, 758, 827, 960, 1024, 1073, 1147 s (SO_2), 1332 s (SO_2), 1413, 1449, 2836, 3076. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 2.85 t (2H, C^4H_2 , $^3J_{\text{HH}}$ 6.0 Hz), 3.54 t (2H, C^3H_2 , $^3J_{\text{HH}}$ 6.0 Hz), 4.45 s (2H, C^1H_2), 7.14–7.17 m (4H, $\text{C}^5\text{H}-\text{C}^8\text{H}$), 7.48–7.50 m (3H, 5'-Ph), 7.56–7.59 m (2H, 5'-Ph), 9.21 s (1H, C^2H). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ_{C} , ppm: 28.4 (C^4H_2), 44.0 (NC^3H_2), 47.3 (NC^1H_2), 126.2, 128.3, 128.5 (2C), 128.7, 129.6, 130.2 (2C), 131.8, 133.3, 143.0, 146.2 (C^4), 154.7 (C^2). Mass spectrum, m/z (I_{rel} , %): 357.0 (100) [$M + \text{H}$] $^+$. Found, %: C 60.71; H 4.50; N 7.81; S 18.04. $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$. Calculated, %: C 60.65; H 4.52; N 7.86; S 17.99.

4-[(5-Phenyl-1,3-thiazol-4-yl)sulfonyl]morpholine (14e). Yield 2.36 g (76%), colorless crystals, mp 125–127°C (EtOH). IR spectrum, ν , cm^{-1} : 585, 726, 951, 1110 s (C–O–C), 1151 s (SO_2), 1258, 1353 s (SO_2), 1421, 1445, 2972, 3063. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.18–3.21 m (4H, C^3H_2 , C^5H_2), 3.60–3.63 m (4H, C^2H_2 , C^6H_2), 7.45–7.56 m (5H, 5'-Ph), 9.28 s (1H, C^2H). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ_{C} , ppm: 46.2 (2C, NCH_2), 65.7 (2C, OCH_2), 128.3 (2C), 128.4, 129.5, 130.2 (2C), 143.5, 145.5 (C^4), 154.8 (C^2). Mass spectrum, m/z (I_{rel} , %): 311.0 (100) [$M + \text{H}$] $^+$. Found, %: C 50.37; H 4.51; N 9.00; S 20.71. $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3\text{S}_2$. Calculated, %: C 50.30; H 4.55; N 9.03; S 20.66.

2,6-Dimethyl-4-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]morpholine (14f). Yield 2.84 g (84%), colorless crystals, mp 125–127°C (EtOH). IR spectrum, ν , cm^{-1} : 594, 1013, 1082 m (C–O–C), 1154 s (SO_2), 1351 s (SO_2), 1421, 2870, 2971, 3081. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 1.07 d (6H, CH_3 , $^3J_{\text{HH}}$ 8.0 Hz), 2.49–2.54 m (2H, $\text{C}^3\text{H}_A\text{H}_B$, $\text{C}^5\text{H}_A\text{H}_B$), 3.48–3.51 m (2H, $\text{C}^3\text{H}_A\text{H}_B$, $\text{C}^5\text{H}_A\text{H}_B$), 3.55–3.57 m (2H, C^2H , C^6H), 7.47–7.49 m (3H, 5'-Ph), 7.55–7.57 m (2H, 5'-Ph), 9.28 s (1H, C^2H). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ_{C} , ppm: 18.4 (CH_3), 50.8 (2C, NCH_2), 70.9 (2C, OCH), 128.3 (2C), 128.4, 129.6, 130.2 (2C), 143.3, 145.8 (C^4), 154.8 (C^2). Mass spectrum, m/z (I_{rel} , %): 157.0 (40), 339.0 (100) [$M + \text{H}$] $^+$. Found, %: C 53.29; H 5.33; N 8.25; S 18.99. $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{S}_2$. Calculated, %: C 53.23; H 5.36; N 8.28; S 18.95.

1-Phenyl-4-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperazine (14g). Yield 3.12 g (81%), colorless crystals, mp 145–147°C (EtOH). IR spectrum, ν , cm^{-1} : 549, 585, 755, 947, 1150 s (SO_2), 1241, 1349 s (SO_2), 1504, 1598, 2823, 3082. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.17–3.20 m (2H, C^3H , C^5H), 3.34–3.36 m (4H, C^2H_2 ,

C^6H_2), 6.82 t (1H, C^4H , $^3J_{\text{HH}}$ 6.0 Hz), 6.94 d (2H, C^2H , C^6H , $^3J_{\text{HH}}$ 8.0 Hz), 7.22 t (2H, C^3H , C^5H , $^3J_{\text{HH}}$ 8.0 Hz), 7.48–7.49 m (3H, 5'-Ph), 7.56–7.59 m (2H, 5'-Ph), 9.28 s (1H, C^2H). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ_{C} , ppm: 46.0 (2C, SO_2NCH_2), 48.3 (2C, PhNCH_2), 116.2 (2C), 119.6, 128.3 (2C), 128.4, 129.0 (2C), 129.5, 130.2 (2C), 143.4, 145.7 (C^4), 150.5, 154.8 (C^2). Mass spectrum, m/z (I_{rel} , %): 386.2 (100) [$M + \text{H}$] $^+$. Found, %: C 59.28; H 4.93; N 10.85; S 16.69. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}_2$. Calculated, %: C 59.20; H 4.97; N 10.90; S 16.64.

1-(3-Chlorophenyl)-4-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperazine (14h). Yield 3.28 g (78%), colorless crystals, mp 154–156°C (EtOH). IR spectrum, ν , cm^{-1} : 586, 731, 952, 1150 s (SO_2), 1240, 1355 s (SO_2), 1490, 1593, 2839, 3087. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.23–3.26 m (4H, C^3H_2 , C^5H_2), 3.32–3.34 m (4H, C^2H_2 , C^6H_2), 6.82 d (1H, C^4H , $^3J_{\text{HH}}$ 8.0 Hz), 6.90 d (1H, C^4H , $^3J_{\text{HH}}$ 8.0 Hz), 6.96 s (1H, C^2H), 7.22 t (1H, C^5H , $^3J_{\text{HH}}$ 8.0 Hz), 7.48–7.49 m (3H, 5'-Ph), 7.56–7.58 m (2H, 5'-Ph), 9.27 s (1H, C^2H). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ_{C} , ppm: 45.9 (2C, SO_2NCH_2), 47.7 (2C, ArNCH_2), 114.3, 115.3, 118.8, 128.3 (2C), 128.4, 129.6, 130.2 (2C), 130.5, 133.8, 143.4, 145.6 (C^4), 151.7, 154.8 (C^2). Mass spectrum, m/z (I_{rel} , %): 421.0 (100) [$M + \text{H}$] $^+$. Found, %: C 54.41; H 4.35; N 9.94; S 15.32. $\text{C}_{19}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}_2$. Calculated, %: C 54.34; H 4.32; N 10.01; S 15.27.

1-(4-Methoxyphenyl)-4-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperazine (14i). Yield 3.16 g (76%), colorless crystals, mp 151–153°C (EtOH). IR spectrum, ν , cm^{-1} : 585, 733, 823, 948, 1150 s (SO_2), 1248 s (C–O), 1355 s (SO_2), 1514, 2833, 3082. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.05–3.06 m (4H, C^3H_2 , C^5H_2), 3.33–3.34 m (4H, C^2H_2 , C^6H_2), 3.68 s (3H, OCH_3), 6.82 d (2H, C^3H , C^5H , $^3J_{\text{HH}}$ 8.0 Hz), 6.90 d (2H, C^2H , C^6H , $^3J_{\text{HH}}$ 8.0 Hz), 7.47–7.49 m (3H, 5'-Ph), 7.56–7.58 m (2H, 5'-Ph), 9.28 s (1H, C^2H). ^{13}C NMR spectrum ($\text{DMSO}-d_6$), δ_{C} , ppm: 46.2 (2C, SO_2NCH_2), 49.7 (2C, ArNCH_2), 55.2 (OCH_3), 114.3 (2C), 118.3 (2C), 128.3 (2C), 128.4, 129.5, 130.2 (2C), 143.0, 1144.9, 145.6 (C^4), 153.6, 154.8 (C^2). Mass spectrum, m/z (I_{rel} , %): 416.2 (100) [$M + \text{H}$] $^+$. Found, %: C 57.90; H 5.04; N 10.08; S 15.48. $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3\text{S}_2$. Calculated, %: C 57.81; H 5.09; N 10.11; S 15.43.

1-(4-Fluorophenyl)-4-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]piperazine (14j). Yield 3.35 g (83%), colorless crystals, mp 121–123°C (EtOH). IR spectrum, ν , cm^{-1} : 585, 699, 730, 830, 945, 1150 m (SO_2), 1189, 1233, 1352 s (SO_2), 1508, 2820, 3082. ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.12–3.14 m (4H, C^3H_2 , C^5H_2), 3.32–3.34 m (4H,

C²H₂, C⁶H₂), 6.94–6.98 m (2H, C^{2''}H, C^{6''}H), 7.04–7.08 m (2H, C^{3''}H, C^{5''}H), 7.48–7.49 m (3H, 5'-Ph), 7.56–7.59 m (2H, 5'-Ph), 9.28 s (1H, C²H). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 46.1 (2C, SO₂NCH₂), 49.1 (2C, ArNCH₂), 115.4 d (2C, C^{3''}, C^{5''}, ²J_{CF} 23.0 Hz), 118.1 d (2C, C^{2''}, C^{6''}, ³J_{CF} 7.5 Hz), 128.3 (2C), 128.4, 129.5, 130.2 (2C), 143.4 d (C^{1''}, ⁴J_{CF} 3.5 Hz), 145.6, 147.5 (C^{4'}), 154.8 (C^{2'}), 156.5 d (C^{4''}, ¹J_{CF} 237.0 Hz). Mass spectrum, *m/z* (*I*_{rel.}, %): 404.3 (100) [*M* + H]⁺. Found, %: C 56.62; H 4.47; N 10.39; S 15.93. C₁₉H₁₈FN₃O₂S₂. Calculated, %: C 56.56; H 4.50; N 10.41; S 15.89.

Ethyl 4-[(5-phenyl-1,3-thiazol-4-yl)sulfonyl]-1-piperazinecarboxylate (14k). Yield 2.90 g (76%), colorless crystals, mp 109–111°C (EtOH). IR spectrum, ν, cm⁻¹: 588, 723, 950, 1150 s (SO₂), 1253 s (C–O), 1353 s (SO₂), 1422, 1440, 1696 s (C=O), 2869, 3093. ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 1.17 t (3H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 3.19–3.22 m (4H, C³H₂, C⁵H₂), 3.42–3.45 m (4H, C²H₂, C⁶H₂), 4.02 q (2H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 7.47–7.49 m (3H, 5'-Ph), 7.55–7.56 m (2H, 5'-Ph), 9.26 s (1H, C²H). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 14.6 (CH₃), 46.0 (2C, SO₂NCH₂), 49.1 (OCH₂), 61.1 (2C, CO-NCH₂), 128.3 (2C), 129.6, 129.7, 130.2 (3C), 154.4, 154.9 (C^{2'}), 165.2 (CO). Mass spectrum, *m/z* (*I*_{rel.}, %): 382.3 (100) [*M* + H]⁺. Found, %: C 50.44; H 4.98; N 11.03; S 16.83. C₁₆H₁₉N₃O₄S₂. Calculated, %: C 50.38; H 5.02; N 11.02; S 16.81.

***N*-(1,1-Dioxotetrahydrothiophen-3-yl)-*N*-(4-methylbenzyl)-5-phenyl-1,3-thiazole-4-sulfonamide (15a).** Yield 3.56 g (77%), colorless crystals, mp 160–162°C (EtOH). IR spectrum, ν, cm⁻¹: 598, 753, 1113 s (SO₂), 1139 s (SO₂), 1315 s (SO₂), 1346 s (SO₂), 1426, 3011. ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 1.99–2.04 m (1H, O₂SC^{2'}H_AH_B), 2.13–2.16 m (1H, O₂SC^{2'}H_AH_B), 2.27 s (3H, CH₃), 3.02–3.16 m (4H, O₂SC^{5'}H₂C^{4'}H₂), 4.42 d (1H, NCH_AH_B, ²J_{HH} 18.0 Hz), 4.56 d (1H, NCH_AH_B, ²J_{HH} 18.0 Hz), 4.74–4.76 m (1H, O₂SC^{2'}H₂C^{3'}H), 7.13 d (2H, C^{2''}H, C^{6''}H, ³J_{HH} 8.0 Hz), 7.21 d (2H, C^{3''}H, C^{5''}H, ³J_{HH} 8.0 Hz), 7.46–7.49 m (3H, 5-Ph), 7.53–7.55 m (2H, 5-Ph), 9.26 s (1H, C²H). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 20.7 (CH₃), 27.5 (C⁴H₂), 47.7 (C⁵H₂), 50.4 (C²H₂), 51.4 (C³H), 54.1 (NCH₂), 127.0 (2C), 128.3 (3C), 129.0 (3C), 129.6, 130.2 (3C), 135.2, 136.5, 155.1 (C²). Mass spectrum, *m/z* (*I*_{rel.}, %): 463.5 (100) [*M* + H]⁺. Found, %: C 54.58; H 4.74; N 6.04; S 20.83. C₂₁H₂₂N₂O₄S₃. Calculated, %: C 54.52; H 4.79; N 6.06; S 20.79.

***N*-(1,1-Dioxotetrahydrothiophen-3-yl)-*N*-(4-methoxybenzyl)-5-phenyl-1,3-thiazole-4-sulfonamide**

(15b). Yield 3.54 g (74%), colorless crystals, mp 147–149°C (EtOH). IR spectrum, ν, cm⁻¹: 598, 753, 944, 1035, 1112 m (SO₂), 1138 s (SO₂), 1314 s (SO₂), 1345 s (SO₂), 1515, 2959, 3008. ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 2.00–2.05 m (1H, O₂SC^{2'}H_AH_B), 2.12–2.16 m (1H, O₂SC^{2'}H_AH_B), 3.03–3.17 m (4H, O₂SC^{5'}H₂C^{4'}H₂), 3.73 s (3H, OCH₃), 4.39 d (1H, NCH_AH_B, ²J_{HH} 16.0 Hz), 4.53 d (1H, NCH_AH_B, ²J_{HH} 16.0 Hz), 4.73–4.77 m (1H, O₂SC^{2'}H₂C^{3'}H), 6.89 d (2H, C^{2''}H, C^{6''}H, ³J_{HH} 8.0 Hz), 7.25 d (2H, C^{3''}H, C^{5''}H, ³J_{HH} 8.0 Hz), 7.46–7.48 m (3H, 5-Ph), 7.53–7.56 m (2H, 5-Ph), 9.29 s (1H, C²H). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 27.5 (C⁴H₂), 47.5 (C⁵H₂), 50.5 (C²H₂), 51.4 (C³H), 54.1 (NCH₂), 55.1 (OCH₃), 113.9 (2C), 128.3 (2C), 128.4 (2C), 129.6, 129.9, 130.2 (2C), 143.0, 144.9, 146.5, 155.1 (C²), 158.5 (C^{4'}-OCH₃). Mass spectrum, *m/z* (*I*_{rel.}, %): 479.4 (100) [*M* + H]⁺. Found, %: C 52.79; H 4.60; N 5.89; S 20.11. C₂₁H₂₂N₂O₅S₃. Calculated, %: C 52.70; H 4.63; N 5.85; S 20.10.

***N*-(1,1-Dioxotetrahydrothiophen-3-yl)-*N*-(4-ethoxybenzyl)-5-phenyl-1,3-thiazole-4-sulfonamide**

(15c). Yield 3.60 g (73%), colorless crystals, mp 171–173°C (EtOH). IR spectrum, ν, cm⁻¹: 598, 753, 845, 1043, 1113 s (SO₂), 1140 s (SO₂), 1177, 1253 s (C–O), 1290, 1318 s (SO₂), 1349 s (SO₂), 1515, 1613, 2975, 3081. ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 1.31 t (3H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 1.99–2.05 m (1H, O₂SC^{2'}H_AH_B), 2.12–2.16 m (1H, O₂SC^{2'}H_AH_B), 3.02–3.17 m (4H, O₂SC^{5'}H₂C^{4'}H₂), 3.99 q (2H, OCH₂CH₃, ³J_{HH} 7.5 Hz), 4.39 d (1H, NCH_AH_B, ²J_{HH} 18.0 Hz), 4.52 d (1H, NCH_AH_B, ²J_{HH} 18.0 Hz), 4.72–4.77 m (1H, O₂SC^{2'}H₂C^{3'}H), 6.87 d (2H, C^{2''}H, C^{6''}H, ³J_{HH} 8.0 Hz), 7.23 d (2H, C^{3''}H, C^{5''}H, ³J_{HH} 8.0 Hz), 7.46–7.48 m (3H, 5-Ph), 7.53–7.54 m (2H, 5-Ph), 9.29 s (1H, C²H). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 14.7 (CH₃), 27.5 (C⁴H₂), 47.5 (C⁵H₂), 50.5 (C²H₂), 51.5 (C³H), 54.1 (NCH₂), 63.0 (OCH₂), 114.3 (2C), 128.3 (2C), 128.4 (2C), 129.6, 129.7, 130.2 (2C), 143.0, 146.5, 149.3, 155.0 (C²), 157.8 (C^{4'}-OEt). Mass spectrum, *m/z* (*I*_{rel.}, %): 493.5 (100) [*M* + H]⁺. Found, %: C 53.66; H 4.87; N 5.65; S 19.58. C₂₂H₂₄N₂O₅S₃. Calculated, %: C 53.64; H 4.91; N 5.69; S 19.53.

***N*-(1,1-Dioxotetrahydrothiophen-3-yl)-*N*-(4-fluorobenzyl)-5-phenyl-1,3-thiazole-4-sulfonamide**

(15d). Yield 3.31 g (71%), colorless crystals, mp 115–117°C (EtOH). IR spectrum, ν, cm⁻¹: 598, 751, 844, 1034, 1114 s (SO₂), 1138 s (SO₂), 1230, 1313 s (SO₂), 1347 s (SO₂), 1430, 1510, 1605, 2957, 3010. ¹H NMR spectrum

(DMSO- d_6), δ , ppm: 1.93–2.04 m (1H, O₂SC²H_AH_B), 2.13–2.20 m (1H, O₂SC²H_AH_B), 3.04–3.21 m (4H, O₂SC⁵H₂C⁴H₂), 4.47 d (1H, NCH_AH_B, ²J_{HH} 18.0 Hz), 4.60 d (1H, NCH_AH_B, ²J_{HH} 18.0 Hz), 4.73–4.82 m (1H, O₂SC²H₂C³H), 7.14–7.18 m (2H, C²H, C⁶H), 7.35–7.38 m (2H, C³H, C⁵H), 7.47–7.48 m (3H, 5-Ph), 7.53–7.54 m (2H, 5-Ph), 9.29 s (1H, C²H). ¹³C NMR spectrum (DMSO- d_6), δ_C , ppm: 27.5 (C⁴H₂), 47.2 (C⁵H₂), 50.4 (C²H₂), 51.3 (C³H), 54.1 (NCH₂), 115.2 d (2C, C³′, C⁵′, ²J_{CF} 21.4 Hz), 128.2, 128.3 (2C), 129.0 d (2C, C²′, C⁶′, ³J_{CF} 8.8 Hz), 129.7, 130.2 (2C), 134.4, 143.2, 146.3, 155.1 (C²), 160.3 d (C⁴′, ¹J_{CF} 238.0 Hz). Mass spectrum, m/z (I_{rel} , %): 467.2 (100) [$M + H$]⁺. Found, %: C 51.54; H 4.07; N 5.97; S 20.68. C₂₀H₁₉FN₂O₄S₃. Calculated, %: C 51.48; H 4.10; N 6.00; S 20.62.

Study of antitumor activity. The methodology of *in vitro* antitumor screening, as well as the rules for data interpretation, are described in detail on the NCI Development Therapeutics Program website [28].

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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