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Synthesis, characterization, and *in vitro* anticancer evaluation of 2,4-disulfonylsubstituted 5-aminothiazoles

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A B S T R A C T

Novel 2,4-disulfonylsubstituted 5-aminothiazoles were synthesized and their anticancer activity was assessed at a high dose (10 μM) against NCI 60 cancer cell lines. Compounds **24** and **25** showed the antiproliferative activity with mean growth inhibition about 66.0%. Replacing 4-hydroxypiperidine **24** with the more hydrophilic N-methyl piperazine **25** increased the number of sensitive cell lines while replacing these hydrophilic groups with lipophilic ones abolished the anticancer activity. The COMPARE analysis showed that the tested compounds had a moderate positive correlation with alkylating agents (CCNU and methyl CCNU) and with a purine nucleotide biosynthesis inhibitor analog (L-cysteine). The results indicate that the above mechanisms of antitumor action of standard compounds are not the main ones for the tested compounds due to the lack of a high correlation. The results of this study allow us to consider compounds **24** and **25** as a basis for their further functionalization to obtain more active compounds.

1. Introduction

Cancer, resulting from the uncontrolled proliferation of undifferentiated cells, is a severe disease worldwide. Among cancer treatment methods, chemotherapy is the primary method in which cancer cells are destroyed using a variety of natural and synthetic compounds. Despite significant progress in the development of new chemotherapeutic agents, cancer treatment remains a complex problem due to the toxicity, resistance, and lack of selectivity of currently available anticancer drugs.

Thiazole is a 5-membered heterocycle containing sulfur and nitrogen atoms, which has multiple reaction sites and serves as a backbone in several compounds widely used in drug development. Its derivatives have a broad spectrum of biological activity interacting with various molecular targets, presented in more than 18 drugs approved by the FDA for clinical use.[1] Among them are compounds that control cell proliferation and apoptosis and have antitumor activity, such as alpelisib, dasatinib, dabrafenib, ixabepilone, patellamide A and epothilone.[2] The synthesis of thiazole derivatives interacting with various molecular targets and structure-function relationships to support rational design in the construction of thiazole-based anticancer agents is the focus of recent literature reviews on developing novel compounds with anticancer potential.[3-5] It was previously shown that sulfonyl-containing derivatives of some azoles demonstrated high antiproliferative and cytotoxic activity against various cancer cell lines,[6-9] which served as the basis for the design, synthesis, and evaluation of the anticancer activity of thiazole sulfonyl derivatives presented in this work.

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2. Results and Discussion

2.1 The one dose assay

Most of the synthesized compounds did not show anticancer activity against cell lines of the total panel. Compounds **1-23** inhibited the growth of most cell lines tested by less than 20%. However, compounds **24** and **25** demonstrated antiproliferative activity against some cell lines of most subpanels, except for the CNS and Prostate subpanels for both compounds and Ovarian for **24** (**Table 1**). These compounds showed cytotoxicity only against the Breast cancer MDA-MB-468 cell line.

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

Compound	Cancer cell subpanel						
	Leukemia	**Lung**	**Colon**	**Melanoma**	**Ovarian**	**Renal**	**Breast**
24	CCRF-CEM (76) HL-60(TB) (65) K-562 (71) MOLT-4 (62) SR (84)	NCI-H460 (54) NCI-H522 (80)	HCT-15 (77) SW-620 (55)-	LOX IMVI (50) MDA-MB-435 (83) UACC-62 (58)		RXF 393 (66)	MCF7 (57) BT-549 (51) MDA-MB-468 (121)
25	CCRF-CEM (80) HL-60(TB) (82) K-562 (84) MOLT-4 (70) SR (84)	NCI-H460 (60) NCI-H522 (85)	HCT-116 (53) HCT-15 (75) SW-620 (64)-	LOX IMVI (70) MDA-MB-435 (92) SK-MEL-2 (51) UACC-62 (52)	OVCAR-3 (54) OVCAR-8 (52) NCI/ADR-RES (56)	786-0 (53) RXF 393 (70) SN12C (54)	MCF7 (57) BT-549 (57) T-47D (62) MDA-MB-468 (115)

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

Compounds **24** and **25** showed the same non-selective antiproliferative activity against cell lines of the NCI 60 total panel with mean growth inhibition values of 65.9±3.1 and 66.0±2.8%, respectively. However, compound **25**, unlike **24**, inhibited the growth of 3 cell lines of Ovarian cancer and exceeded the latter in terms of the number of sensitive lines (**24** and **16**, respectively). The number of cell lines of each subpanel sensitive to compound **25**, expressed as a percentage, is as follows: (the number of lines is given in brackets): Leukaemia - 83 (5), breast - 67 (4), Ovarian - 57 (4), Melanoma - 50 (4), Colon - 50 (3), Renal - 43 (3) and Lung - 29 (2) and to compound **24**: Leukaemia - 83 (5), breast - 50 (3), Melanoma - 38 (3), Colon - 33 (2), Lung - 29 (2) and Renal- 14 (1).

The structures of these compounds differed only in the substituents in the fifth position of the oxazole; that is, according to PubChem (https://pubchem.ncbi.nlm.nih.gov/), the replacement of 4-hydroxypiperidine (XLogP3-AA = -0.3) with the more hydrophilic N-methyl piperazine (XLogP3-AA = -0.4) led to an increase in the number of sensitive cell lines, whereas replacement of these hydrophilic groups with lipophilic isopropyl amine (XLogP3-AA = 0.1), furan-2-ylmethylamine, diethylamine (XLogP3 = 0.6), or pipepredine (XLogP3 = 0.8), giving compounds **20-23**, accordingly, eliminated anticancer activity. The activity of the derivatives also depended on the functionalization of the second position because even in the presence of hydrophilic substituents in the fifth position, the absence of the toluyl radical in the second position (compounds **17-19**) did not give active compounds. Both compounds showed cytotoxicity only against the Breast cancer MDA-MB-468 cell line. Thus, compound **25** showed more significant activity than **24** against the full NCS 60 cancer panel regarding the number of sensitive cell lines at the same activity. These compounds were analyzed by correlation analysis with standard drugs with established molecular mechanisms of action to suggest their possible targets.

2.2 COMPARE correlations

The results of a COMPARE analysis of the similarity of the GI_{50} and TGI vectors of compounds **24** and **25** approximated from their average graphs with those of known standard antitumor agents calculated from a five-dose analysis are presented in **Table 2**. The COMPARE analysis showed that the mean graphs of test compounds had a moderate positive correlation with compounds with alkylating agents at the GI_{50} vector (CCNU and methyl CCNU); the purine nucleotide biosynthesis inhibitor analog L-cysteine at the TGI vector, respectively, when compared to the corresponding vectors of the standard compounds that were calculated from the data of the five-dose analysis. However, when comparing average graphs obtained from the single dose assay alone, these compounds showed a moderate correlation (r: 0.51-0.57) with the anthracycline antibiotic N, N-dibenzyl daunomycin for both vectors. The mechanism of action of N, N-dibenzyl daunomycin includes intercalation of the drug molecule into nucleic acid and inhibition of topoisomerase II activity, which leads to the arrest of DNA replication and transcription.[13] The results indicate that the above mechanisms of antitumor activity of standard compounds are unlikely for the tested compounds due to the lack of high correlation. In addition, the lack of selectivity of

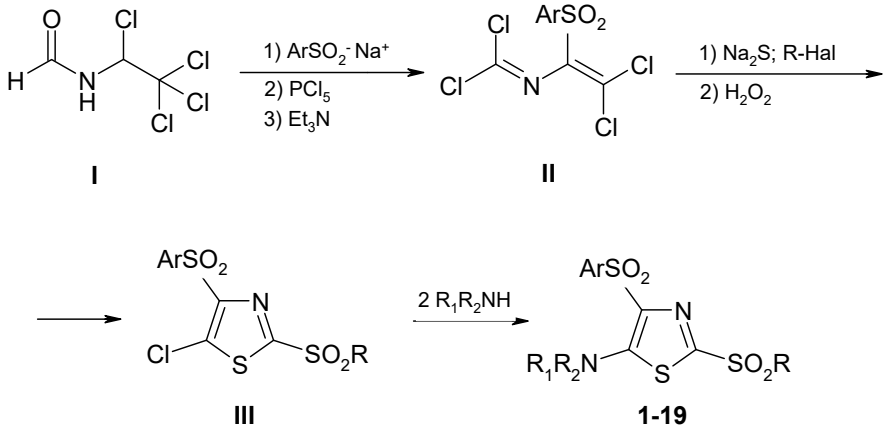
both compounds concerning sensitive cell lines indicates their influence on the general molecular mechanisms that ensure the life cycle of these lines.

Table 2. Standard agent COMPARE correlations for compounds **24** and **25**.

Compound	Correlating drug	Correlation coefficient	Reported Mechanism(s)
		GI_{50}	
24	CCNU	0.68	CCNU and methyl-CCNU alkylate and crosslink DNA, as well as carbamoylate DNA and proteins, resulting in the inhibition of DNA and RNA synthesis and disruption of RNA processing[10,11]
25	methyl-CCNU	0.63	
		TGI	
24	L-cysteine	0.71	L-glutamine antagonist, selectively acting on the enzymes of purine nucleotide biosynthesis[12]
25	analogue	0.65	

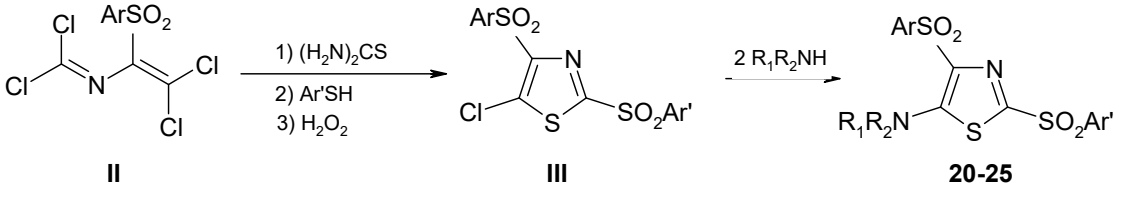
2.3 Chemistry

The synthesis of 5-amino-2,4-sulfonylsubstituted 1,3-thiazoles **1-19** is described in **Scheme 1**. Chosen (1,2,2,2-tetrachloroethyl)formamide **I**[14] as the starting substance. Compound **I** reacted with the appropriate sodium aryl sulfonate, and then compounds were processed by two equivalents of phosphorus pentachloride. Then, under the action of triethylamine, hydrogen chloride was released with the formation of [(2,2-dichloro-1-arylsulfonyl)vinyl]carbonimidic dichloride **II**. Compounds **II** were reacting with excess sodium sulfide followed by alkyl halide with the formation of 5-chloro-2-(alkylthio)-4-(arylsulfonyl)-1,3-thiazoles, which were converted into the appropriate 5-chloro-2-(alkylsulfonyl)-4-(arylsulfonyl)-1,3-thiazoles **III**[15] by oxidation with hydrogen peroxide in acetic acid. For the nucleophilic substitution of the chlorine atom, thiazoles **III** were processed by two equivalents of the appropriate amine with the formation of compounds **1-19**.



Scheme 1. Synthesis of 2,4-disulfonylsubstituted 5-aminothiazoles **1-19**

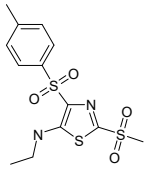
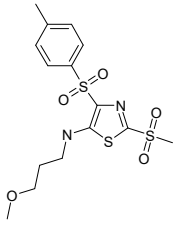
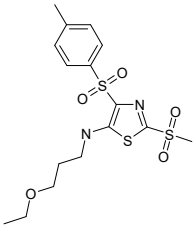
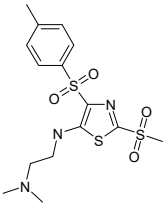
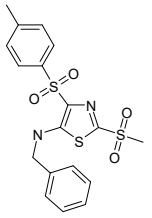
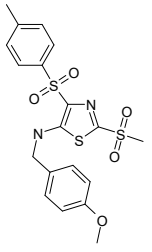
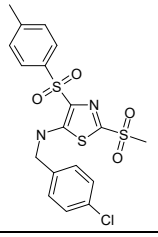
The synthesis of 5-amino-2,4-(arylsulfonyl)-1,3-thiazoles **20-25** is presented in **Scheme 2**. The three-stage reaction sequence includes accession of [(2,2-dichloro-1-arylsulfonyl)vinyl]carbonimidic dichloride **II** with thiourea, the addition of arylmercaptan, and oxidation with hydrogen peroxide in acetic acid. 5-Amino-2,4-(arylsulfonyl)-1,3-thiazoles **20-25** were received by heating 5-chloro-2,4-(arylsulfonyl)-1,3-thiazoles **III** with two equivalents of the appropriate amine in acetonitrile. Data of synthesized new derivatives 1,3-thiazole are reliably confirmed by NMR (^{1}H NMR and ^{13}C NMR), chromato-mass, and elemental analyses.

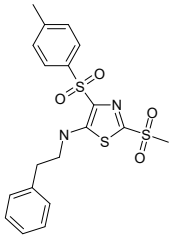
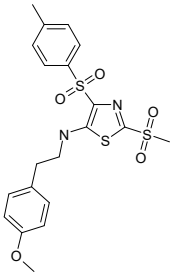
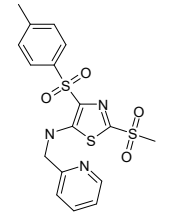
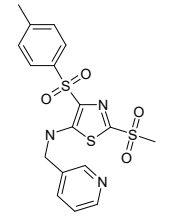
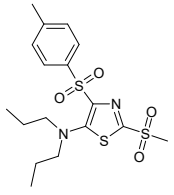
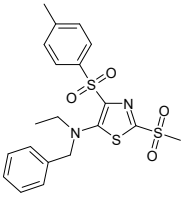
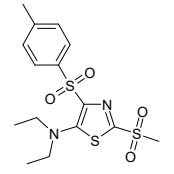
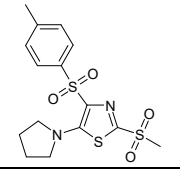


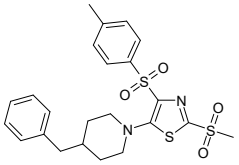
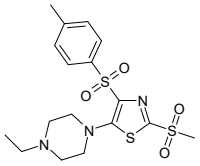
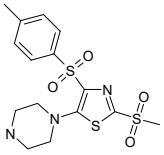
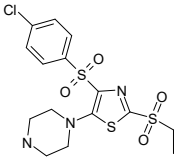
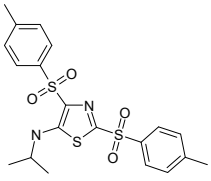
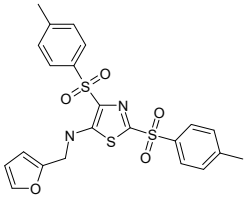
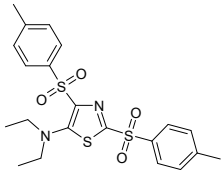
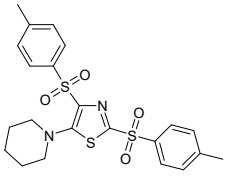
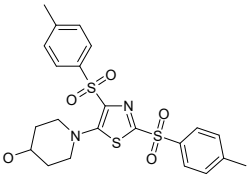
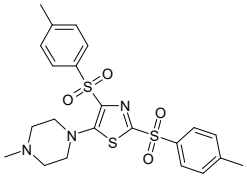
Scheme 2. Synthesis of 2,4-disulfonylsubstituted 5-aminothiazoles **20-25**

Synthesized compounds **1-25** were submitted for *in vitro* antitumor screening at the National Cancer Institute (NCI), USA, against a full panel of NCI 60 cell lines, and the NSC codes, shown in **Table 3**, were received.

Table 3. Chemical structures of synthesized compounds

Number	NSC	Structure	Name
1	776621		Ethyl[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine
2	776622		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl](3-methoxypropyl)amine
3	776623		(3-Ethoxypropyl)[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine
4	776624		N'-[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]-N,N-dimethylethane-1,2-diamine
5	776625		Benzyl[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine
6	776626		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl](4-methoxybenzyl)amine
7	776627		(4-Chlorobenzyl)[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine

8	776630		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]phenethylamine
9	776631		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl][2-(4-methoxyphenyl)ethyl]amine
10	776629		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]pyridine-2-ylmethylamine
11	776628		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]pyridine-3-ylmethylamine
12	776619		[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]dipropylamine
13	776620		Benzylethyl-[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine
14	776633		Diethyl[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine
15	776602		2-Methanesulfonyl-5-pyrrolidine-1-yl-4-(toluene-4-sulfonyl)thiazole

16	776603		4-Benzyl-1-[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]piperidine
17	776604		1-Ethyl-4-[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]piperazine
18	784876		1-[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]piperazine
19	762310		1-[4-(4-Chlorobenzenesulfonyl)-2-ethanesulfonylthiazol-5-yl]piperazine
20	836266		[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]isopropylamine
21	762270		[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]furan-2-ylmethylamine
22	762269		[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]diethylamine
23	762268		1-[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]-piperidine
24	836264		1-[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]-piperidine-4-ol
25	836265		1-[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]-4-methyl-piperazine

3. Conclusions

Novel 2,4-disulfonylsubstituted 5-aminothiazoles have been synthesized in good yields and evaluated for their anticancer activity. Only compounds **24** and **25** showed activity against certain cancer cell lines of the NCI 60 panel in the one dose assay. These compounds had no cytostatic activity and inhibited cell growth non-selectively by an average of 66% in 16 and 24 cell lines, respectively. The COMPARE analysis showed that the mean graphs of test compounds had a moderate positive correlation with compounds with alkylating agents at the GI50 vector (CCNU and methyl CCNU) and the purine nucleotide biosynthesis inhibitor analog L-cysteine at the TGI vector, respectively, when compared to the corresponding vectors of standard compounds calculated from the five dose analysis. When comparing the results of the correlation analysis of the average graphs obtained in the one dose assay, both compounds showed a moderate correlation with the topoisomerase II inhibitor N, N-dibenzyl daunomycin. Due to the lack of high correlation, it is unlikely that the mechanisms of the standard compounds described above play a primary role in the antitumor activity of these compounds. The results of this study give grounds to consider compounds **24** and **25** as the basis for their further functionalization to obtain derivatives of 2,4-disulfonylsubstituted 5-aminothiazoles with more excellent antitumor activity.

Acknowledgements

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Conflict of Interests

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

4. Experimental

4.1. Materials and Methods

All chemicals and solvents for the synthetic work were acquired from commercial sources and used without further purification. The reaction progress was monitored by the TLC method. Melting points were determined on a Fisher-Johns apparatus. IR spectra were recorded on a Vertex-70 spectrometer from KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 spectrometer (400 and 126 MHz, respectively) in DMSO-d$_6$, taking its residual protons signal as a standard. Chromato–mass spectra were recorded using an Agilent 1100 Series liquid chromatography–mass spectrometry system equipped with a diode array and an Agilent LC\MSD SL mass-selective detector. Parameters of chromatography–mass spectral analysis: column Zorbax SB-C18, 1.8 μm, 4.6×15 mm; solvents: DMSO. Combustion elemental analysis was performed by hand in the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry analytical laboratory. The carbon and hydrogen contents were determined using the Pregl gravimetric method, nitrogen – using Duma's gasometrical micromethod, sulfur – by the Scheininger titrimetric method, and chlorine – by the mercurometric method.

4.2. General procedure

The general method of synthesis of 5-amino-2,4-sulfonyl-1,3-thiazoles **1–25**.

A mixture of 0.01 mol of one of the 5-chloro-2,4-sulfonyl-1,3-thiazole **III** and 0.02 mol of corresponding amine in 30 ml of acetonitrile boiling for 2 h. The solution was cooled to room temperature; the precipitate was filtered and washed with water. Alternatively, the solvent was removed *in vacuo*, and the residue was washed with 2-propanol. The precipitate was filtered and washed with water.

4.3 Physical and Spectral Data

*Ethyl-[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine **1***

Yield 48%. White crystal, mp 156°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.21 (3H, t, *J*=6.9 Hz), 2.38 (3H, s), 3.26-3.33 (5H, m), 7.44 (2H, d, *J*=7.8 Hz), 7.85 (2H, d, *J*=7.8 Hz), 7.93 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ: 13.5, 21.5, 43.2, 45.5, 125.8, 127.1, 130.6, 138.9, 144.5, 144.9, 162.2. MS (ES), *m/z* (I_{rel}, %): 361.0 $[M+H]^+$**,** 359.0 $[M–H]^-$**.** Anal. calcd for $C_{13}H_{16}N_2O_4S_3$, %: C, 43.32; H, 4.47; N, 7.77; S, 26.68. Found, %: C, 43.12; H, 4.49; N, 7.68; S, 26.70.

*[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl](3-methoxypropyl)amine **2***

Yield 63%. Yellow crystal, mp 143-144°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.88 (2H, p, *J*=5.9 Hz), 2.38 (3H, s), 3.26 (3H, s), 3.34 (3H, s), 3.42 (2H, t, *J*=5.6 Hz), 7.44 (2H, d, *J*=8.0 Hz), 7.84 (2H, d, *J*=8.0 Hz), 8.01 (1H, t, *J*=5.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 27.5, 42.7, 48.3, 58.0, 69.7, 125.3, 126.5, 130.0, 138.3, 144.1, 144.4, 162.0. MS

(ES), *m/z* (I_{rel}, %): 405.0 $[M+H]^+$**.** Anal. calcd for $C_{15}H_{20}N_2O_5S_3$, %: C, 44.54; H, 4.98; N, 6.92; S, 23.78. Found, %: C, 44.28; H, 4.99; N, 6.56; S, 23.69.

(3-Ethoxypropyl)[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine ***3***

Yield 68%. White crystal, mp 133-134°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.12 (3H, t, *J*=7.0 Hz), 1.78 – 1.95 (2H, m), 2.39 (3H, s), 3.23 – 3.37 (5H, m), 3.37 – 3.52 (4H, m), 7.45 (2H, d, *J*=8.0 Hz), 7.83 (2H, d, *J*=8.1 Hz), 7.96 (1H, t, *J*=5.4 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 15.4, 21.5, 28.3, 43.2, 49.0, 66.0, 68.1, 125.7, 127.0, 130.5, 138.8, 144.6, 144.9, 162.5. MS (ES), *m/z* (I_{rel}, %): 353.6 $[M-SO_2]^-$. Anal. calcd for $C_{16}H_{22}N_2O_5S_3$, %: C, 45.91; H, 5.30; N, 6.69; S, 22.98. Found, %: C, 45.79; H, 5.42; N, 6.56; S, 22.90.

N'-[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]-N,N-dimethylethane-1,2-diamine ***4***

Yield 58%. White crystal, mp 147-148°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.22 (6H, s), 2.39 (3H, s), 2.53 (2H, d, *J*=4.3 Hz), 3.25 – 3.40 (5H, m), 7.45 (2H, d, *J*=8.0 Hz), 7.81 (3H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.6, 43.2, 45.5, 47.9, 57.0, 127.1, 130.6, 138.8, 145.0, 145.3, 146.3, 157.5. MS (ES), *m/z* (I_{rel}, %): 311, 387.8. Anal. calcd for $C_{15}H_{21}N_3O_4S_3$, %: C, 44.65; H, 5.25; N, 10.41; S, 23.84. Found, %: C, 45.02; H, 5.30; N, 10.26; S, 23.79.

Benzyl[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine ***5***

Yield 88%. White crystal, mp 185°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.38 (3H, s), 3.31 (3H, s), 4.55 (2H, d, *J*=5.4 Hz), 7.27 – 7.41 (5H, m), 7.46 (2H, d, *J*=7.7 Hz), 7.91 (2H, d, *J*=7.5 Hz), 8.67 (1H, t). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 42.5, 52.1, 126.1, 126.7, 127.5, 127.8, 128.7, 130.1, 135.7, 138.2, 144.6, 144.7, 161.4. MS (ES), *m/z* (I_{rel}, %): 423.0 $[M+H]^+$, 421.0 $[M-H]^-$. Anal. calcd for $C_{18}H_{18}N_2O_4S_3$, %: C, 51.17; H, 4.29; N, 6.63; S, 22.76. Found, %: C, 51.23; H, 4.32; N, 6.56; S, 22.80.

[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl](4-methoxybenzyl)amine ***6***.

Yield 92%. White crystal, mp 170°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.39 (3H, s), 3.30 (3H, s), 3.73 (3H, s), 4.45 (2H, s), 6.93 (2H, d, *J*=8.0 Hz), 7.32 (2H, d, *J*=8.0 Hz), 7.46 (2H, d, *J*=7.7 Hz), 7.88 (2H, d, *J*=7.7 Hz), 8.60 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 42.5, 51.4, 55.0, 114.1, 126.0, 126.6, 127.2, 129.1, 130.1, 138.2, 144.5, 144.7, 158.9, 161.2. MS (ES), *m/z* (I_{rel}, %): 451.0 $[M-H]^-$. Anal. calcd for $C_{19}H_{20}N_2O_5S_3$, %: C, 50.43; H, 4.45; N, 6.19; S, 21.25. Found, %: C, 50.29; H, 4.38; N, 6.03; S, 21.30.

(4-Chlorobenzyl)[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine ***7***

Yield 90%. Yellow crystal, mp 184°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.39 (3H, s), 3.31 (3H, s), 4.53 (2H, d, *J*=4.9 Hz), 7.33 – 7.56 (6H, m), 7.89 (2H, d, *J*=7.1 Hz), 8.68 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 42.5, 51.4, 126.2, 126.6, 128.7, 129.4, 130.1, 132.4, 134.8, 138.2, 144.6, 144.8, 161.2. MS (ES), *m/z* (I_{rel}, %): 457.0 $[M]^+$, 455.0 $[M-2H]^-$. Anal. calcd for $C_{18}H_{17}ClN_2O_4S_3$, %: C, 47.31; H, 3.75; Cl, 7.76; N, 6.13; S, 21.05. Found, %: C, 47.25; H, 3.82; Cl, 7.80; N, 5.98; S, 21.10.

[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]phenethylamine ***8***

Yield 86%. White crystal, mp 185°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.39 (3H, s), 2.95 (2H, t, *J*=6.7 Hz), 3.30 (3H, s), 3.48 – 3.56 (2H, m), 7.17 – 7.36 (5H, m), 7.43 (2H, d, *J*=7.8 Hz), 7.76 (2H, d, *J*=8.1 Hz), 7.88 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 40.0, 42.6, 53.6, 121.7, 123.0, 126.7, 130.1, 137.2, 138.2, 144.5, 144.8, 149.2, 155.0, 161.9. MS (ES), *m/z* (I_{rel}, %): 437.0 $[M+H]^+$, 435.0 $[M-2H]^-$. Anal. calcd for $C_{19}H_{20}N_2O_4S_3$, %: C, 52.27; H, 4.62; N, 6.42; S, 22.03. Found, %: C, 52.30; H, 4.73; N, 6.38; S, 22.08.

[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl][2-(4-methoxyphenyl)ethyl]amine ***9***

Yield 88%. White crystal, mp 176°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.39 (3H, s), 2.88 (2H, t, *J*=6.6 Hz), 3.30 (3H, s), 3.48 (2H, t, *J*=6.0 Hz), 3.71 (3H, s), 6.83 (2H, d, *J*=8.3 Hz), 7.15 (2H, d, *J*=8.3 Hz), 7.43 (2H, d, *J*=8.0 Hz), 7.77 (2H, d, *J*=8.1 Hz), 7.84 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 32.8, 42.7, 51.8, 55.0, 113.8, 125.3, 126.5, 129.9, 130.0, 130.0, 138.3, 144.0, 144.4, 157.9, 162.0. MS (ES), *m/z* (I_{rel}, %): 467.0 $[M+H]^+$, 465.0 $[M-2H]^-$. Anal. calcd for $C_{20}H_{22}N_2O_5S_3$, %: C, 51.48; H, 4.75; N, 6.00; S, 20.62. Found, %: C, 51.32; H, 4.78; N, 5.96; S, 20.58.

[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]pyridin-2-ylmethylamine ***10***

Yield 78%. Yellow crystal, mp 179-180°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.39 (3H, s), 3.33 (3H, s), 4.65 (2H, d, *J*=4.8 Hz), 7.30 – 7.38 (1H, m), 7.42 (1H, d, *J*=7.8 Hz), 7.46 (2H, d, *J*=8.0 Hz), 7.83 (1H, t, *J*=8.3 Hz), 7.89 (2H, d, *J*=8.1 Hz), 8.58 (1H, d, *J*=4.0 Hz), 8.61 – 8.68 (1H, m). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 42.6, 53.6, 121.7, 123.0, 126.0,

126.7, 130.1, 137.2, 138.2, 144.5, 144.8, 149.2, 155.0, 161.9. MS (ES), *m/z* (I_{rel}, %): 250.6, 342.0 [M-Ms]$^-$, 358.8 [M-SO_2]$^-$. Anal. calcd for $C_{17}H_{17}N_3O_4S_3$, %: C, 48.21; H, 4.05; N, 9.92; S, 22.71. Found, %: C, 48.32; H, 4.11; N, 9.76; S, 22.69.

[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]pyridin-3-ylmethylamine ***11***

Yield 82%. White crystal, mp 193°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.38 (3H, s), 3.32 (3H, s), 4.58 (2H, d, *J*=5.8 Hz), 7.40 (1H, dd, *J*=7.5, 5.0 Hz), 7.46 (2H, d, *J*=8.0 Hz), 7.81 (1H, d, *J*=7.7 Hz), 7.89 (2H, d, *J*=7.9 Hz), 8.51 (1H, d, *J*=4.5 Hz), 8.62 (1H, s), 8.69 (1H, t, *J*=5.8 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 42.5, 49.8, 123.8, 126.3, 126.6, 130.1, 131.6, 135.4, 138.1, 144.6, 144.9, 149.0, 149.0, 161.2. MS (ES), *m/z* (I_{rel}, %): 424.0 [M+H]$^+$, 422.0 [M-H]$^-$. Anal. calcd for $C_{17}H_{17}N_3O_4S_3$, %: C, 48.21; H, 4.05; N, 9.92; S, 22.71. Found, %: C, 48.36; H, 4.09; N, 9.82; S, 22.74.

[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]dipropylamine ***12***

Yield 76%. White crystal, mp 96°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.79 (6H, t, *J*=7.3 Hz), 1.55 (4H, h, *J*=7.1 Hz), 2.40 (3H, s), 3.28 (3H, s), 3.41 (4H, t, *J*=7.3 Hz), 7.45 (2H, d, *J*=7.9 Hz), 7.77 (2H, d, *J*=8.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 10.8, 20.0, 21.0, 42.2, 58.6, 127.3, 129.7, 132.3, 138.2, 144.3, 147.7, 162.7. MS (ES), *m/z* (I_{rel}, %): 417.0 [M+H]$^+$. Anal. calcd for $C_{17}H_{24}N_2O_4S_3$, %: C, 49.02; H, 5.81; N, 6.72; S, 23.09. Found, %: C, 48.96; H, 5.89; N, 6.54; S, 22.94.

Benzylethyl[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine ***13***

Yield 85%. Yellow crystal, mp 123°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.14 (3H, t, *J*=7.0 Hz), 2.40 (3H, s), 3.29 (3H, s), 3.53 (2H, q, *J*=6.9 Hz), 4.61 (2H, s), 7.22 – 7.38 (5H, m), 7.45 (2H, d, *J*=8.0 Hz), 7.80 (2H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 11.8, 21.1, 42.0, 52.9, 59.2, 127.5, 127.73, 127.74, 128.6, 129.8, 134.5, 135.6, 137.7, 144.5, 150.0, 162.8. MS (ES), *m/z* (I_{rel}, %): 451.0 [M+H]$^+$. Anal. calcd for $C_{20}H_{22}N_2O_4S_3$, %: C, 53.31; H, 4.92; N, 6.22; S, 21.35. Found, %: C, 53.25; H, 4.87; N, 6.05; S, 21.30.

Diethyl[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]amine ***14***

Yield 76%. White crystal, mp 125-126°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.10 (6H, t, *J*=6.9 Hz), 2.40 (3H, s), 3.28 (3H, s), 3.48 (4H, q, *J*=6.7 Hz), 7.44 (2H, d, *J*=7.8 Hz), 7.78 (2H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 11.8, 21.1, 42.2, 51.2, 127.4, 129.7, 133.1, 138.1, 144.3, 147.9, 162.2. MS (ES), *m/z* (I_{rel}, %): 389.0 [M+H]$^+$. Anal. calcd for $C_{15}H_{20}N_2O_4S_3$, %: C, 46.37; H, 5.19; N, 7.21; S, 24.76. Found, %: C, 46.41; H, 5.21; N, 7.18; S, 24.69.

2-Methanesulfonyl-5-pyrrolidin-1-yl-4-(toluene-4-sulfonyl)thiazole ***15***

Yield 85%. White crystal, mp 212°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.93 – 2.06 (4H, m), 2.40 (3H, s), 3.26 (3H, s), 3.46 – 3.58 (4H, m), 7.44 (2H, d, *J*=8.1 Hz), 7.78 (2H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.0, 26.0, 42.5, 56.0, 127.2, 127.6, 129.8, 139.3, 143.2, 143.9, 159.5. MS (ES), *m/z* (I_{rel}, %): 387.0 [M+H]$^+$. Anal. calcd for $C_{15}H_{18}N_2O_4S_3$, %: C, 46.61; H, 4.69; N, 7.25; S, 24.89. Found, %: C, 46.53; H, 4.75; N, 7.19; S, 24.83.

4-Benzyl-1-[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]piperidine ***16***

Yield 95%. White crystal, mp 142°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.29 – 1.48 (3H, m), 1.58 – 1.75 (2H, m), 2.40 (3H, s), 2.53 – 2.64 (2H, m), 2.98 (2H, t, *J*=11.7 Hz), 3.29 (3H, s), 3.64 (2H, d, *J*=11.2 Hz), 7.16 – 7.25 (3H, m), 7.26 – 7.34 (2H, m), 7.43 (2H, d, *J*=7.9 Hz), 7.80 (2H, d, *J*=8.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.1, 30.7, 35.9, 41.7, 42.2, 55.5, 125.9, 127.5, 128.2, 129.0, 129.8, 134.2, 137.7, 139.8, 144.5, 149.9, 163.8. MS (ES), *m/z* (I_{rel}, %): 490.0 [M]$^-$. Anal. calcd for $C_{23}H_{26}N_2O_4S_3$, %: C, 56.30; H, 5.34; N, 5.71; S, 19.60. Found, %: C, 56.41; H, 5.32; N, 5.62; S, 19.76.

1-Ethyl-4-[2-methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]piperazine ***17***

Yield 73%. White crystal, mp 127°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.40 (3H, s), 2.44 – 2.53 (3H, m), 2.58 – 2.71 (4H, m), 3.32 (3H, s), 3.33 – 3.41 (4H, m), 3.54 (2H, t, *J*=5.7 Hz), 7.45 (2H, d, *J*=7.9 Hz), 7.82 (2H, d, *J*=8.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.1, 42.2, 52.0, 54.8, 58.4, 59.7, 127.6, 129.8, 135.0, 137.5, 144.6, 150.9, 163.6. MS (ES), *m/z* (I_{rel}, %): 157.0, 378.8. Anal. calcd for $C_{17}H_{23}N_3O_4S_3$, %: C, 47.53; H, 5.40; N, 9.78; S, 22.39. Found, %: C, 47.62; H, 5.38; N, 9.65; S, 22.40.

1-[2-Methanesulfonyl-4-(toluene-4-sulfonyl)thiazol-5-yl]piperazine ***18***

Yield 59%. White crystal, mp 229-230°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.41 (3H, s), 3.25 – 3.31 (4H, m), 3.34 (3H, s), 3.47 – 3.75 (4H, m), 7.46 (2H, d, *J*=8.3 Hz), 7.86 (2H, d, *J*=8.2 Hz), 9.50 (2H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.1, 42.1, 42.2, 51.6, 118.9, 127.7, 129.9, 136.7, 137.2, 144.9, 162.5. MS (ES), *m/z* (I_{rel}, %): 285.2, 391.2. Anal. calcd for $C_{15}H_{19}N_3O_4S_3$, %: C, 44.87; H, 4.77; N, 10.47; S, 23.96. Found, %: C, 45.02; H, 4.79; N, 10.30; S, 24.00.

1-[4-(4-Chlorobenzenesulfonyl)-2-ethanesulfonylthiazol-5-yl]piperazine ***19***

Yield 56%. White crystal, mp 136°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.99 (3H, t, *J*=7.3 Hz), 2.75 – 2.93 (4H, m), 3.18 – 3.43 (7H, m), 7.72 (2H, d, *J*=8.4 Hz), 7.92 (2H, d, *J*=8.5 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 7.4, 45.2, 49.3, 56.7, 130.0, 130.1, 133.6, 139.5, 139.8, 139.9, 165.0. MS (ES), *m/z* (I_{rel}, %): 206.4, 248.2, 293.0, 357.6. Anal. calcd for $C_{15}H_{18}ClN_3O_4S_3$, %: C, 41.33; H, 4.16; Cl, 8.13; N, 9.64; S, 22.06. Found, %: C, 41.35; H, 4.21; Cl, 8.16; N, 9.57; S, 22.09.

[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]isopropylamine ***20***

Yield 72%. White crystal, mp 186°C. δ_H(400 MHz, DMSO-d_6): 1.27 (6H, d, *J*=6.0 Hz), 2.34 (3H, s), 2.36 (3H, s), 3.38 – 3.45 (1H, m), 7.38 (2H, d, *J*=7.7 Hz), 7.40 – 7.52 (3H, m), 7.78 (4H, d, *J*=7.1 Hz). ^{13}C NMR (101 MHz, DMSO) δ 21.5, 21.6, 21.6, 54.3, 126.4, 127.1, 128.1, 130.5, 130.9, 136.3, 138.6, 144.8, 144.9, 146.0, 161.4. MS (ES), *m/z* (I_{rel}, %): 465.0 $[M+H]^+$. Anal. calcd for $C_{20}H_{22}N_2O_4S_3$, %: C, 53.31; H, 4.92; N, 6.22; S, 21.35. Found, %: C, 53.24; H, 4.85; N, 6.03; S, 21.29.

[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]furan-2-ylmethylamine ***21***

Yield 78%. White crystal, mp 169-170°C. δ_H(400 MHz, DMSO-d_6): 2.37 (3H, s), 2.38 (3H, s), 4.53 (2H, s), 6.37 – 6.59 (2H, m), 7.40 (2H, d, *J*=8.0 Hz), 7.44 (2H, d, *J*=8.1 Hz), 7.66 (1H, s), 7.71 – 7.84 (4H, m), 8.42 (1H, s). ^{13}C NMR (126 MHz, DMSO) δ: 21.0, 21.1, 45.2, 110.0, 110.6, 126.6, 127.0, 127.6, 130.0, 130.4, 135.6, 138.0, 143.5, 144.5, 144.9, 145.6, 148.3, 161.3. MS (ES), *m/z* (I_{rel}, %): 172.2, 248.6, 376.0. Anal. calcd for $C_{22}H_{20}N_2O_5S_3$, %: C, 54.08; H, 4.13; N, 5.73; S, 19.69. Found, %: C, 54.13; H, 4.18; N, 5.61; S, 19.57.

[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]diethylamine ***22***

Yield 82%. Yellow crystal, mp 94°C. δ_H(400 MHz, DMSO-d_6): 1.12 (6H, t, *J*=7.0 Hz), 2.40 (3H, s), 2.43 (3H, s), 3.51 (4H, q, *J*=7.0 Hz), 7.37 (4H, d, *J*=8.0 Hz), 7.59 (2H, d, *J*=8.4 Hz), 7.63 (2H, d, *J*=8.3 Hz). ^{13}C NMR (126 MHz, DMSO) δ: 11.7, 21.08, 21.12, 51.3, 127.53, 123.57, 129.5, 130.1, 132.7, 135.4, 138.0, 144.2, 145.3, 146.4, 161.9. MS (ES), *m/z* (I_{rel}, %): 465.0 $[M+H]^+$. Anal. calcd for $C_{21}H_{24}N_2O_4S_3$, %: C, 54.29; H, 5.21; N, 6.03; S, 20.70. Found, %: C, 54.46; H, 5.18; N, 5.92; S, 20.61.

1-[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]piperidine ***23***

Yield 90%. White crystal, mp 151°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.51 – 1.59 (2H, m), 1.60 – 1.73 (4H, m), 2.40 (3H, s), 2.42 (3H, s), 3.34 – 3.39 (4H, m), 7.37 (4H, d, *J*=8.0 Hz), 7.60 (2H, d, *J*=8.1 Hz), 7.65 (2H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.07, 21.11, 22.4, 24.6, 56.3, 127.5, 127.6, 129.6, 130.2, 133.8, 135.3, 137.7, 144.4, 145.4, 148.5, 163.8. MS (ES), *m/z* (I_{rel}, %): 328.2, 358.6, 370.8. Anal. calcd for $C_{22}H_{24}N_2O_4S_3$, %: C, 55.44; H, 5.08; N, 5.88; S, 20.18. Found, %: C, 55.36; H, 5.11; N, 5.63; S, 20.21.

1-[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]piperidin-4-ol ***24***

Yield 87%. White crystal, mp 155°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.52 – 1.65 (2H, m), 1.76 – 1.96 (2H, m), 2.39 (3H, s), 2.41 (3H, s), 3.18 – 3.29 (2H, m), 3.49 – 3.61 (2H, m), 3.65 – 3.82 (1H, m), 4.84 (1H, d), 7.33 – 7.42 (4H, m), 7.61 (2H, d, *J*=8.2 Hz), 7.65 (2H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.1, 21.1, 33.1, 53.1, 63.7, 127.5, 127.6, 129.6, 130.2, 133.9, 135.2, 137.7, 144.4, 145.4, 148.6, 163.5. MS (ES), *m/z* (I_{rel}, %): 248.4, 293.0, 352.6. Anal. calcd for $C_{22}H_{24}N_2O_5S_3$, %: C, 53.64; H, 4.91; N, 5.69; S, 19.53. Found, %: C, 53.54; H, 4.86; N, 5.46; S, 19.58.

1-[2,4-Bis-(toluene-4-sulfonyl)thiazol-5-yl]-4-methylpiperazine ***25***

Yield 88%. White crystal, mp 157°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.21 (3H, s), 2.40 (3H, s), 2.41 (3H, s), 2.43 – 2.49 (4H, m), 3.36 – 3.42 (4H, m), 7.38 (4H, m), 7.63 (2H, d, *J*=8.2 Hz), 7.67 (2H, d, *J*=8.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 21.1, 21.1, 45.3, 53.4, 54.8, 127.6, 127.7, 129.6, 130.2, 134.6, 135.1, 137.5, 144.5, 145.5, 149.6, 163.4. MS (ES), *m/z* (I_{rel}, %): 492.0 $[M+H]^+$. Anal. calcd for $C_{22}H_{25}N_3O_4S_3$, %: C, 53.75; H, 5.13; N, 8.55; S, 19.56. Found, %: C, 53.69; H, 5.06; N, 8.37; S, 19.64.

4.4 In Vitro anticancer screening of the tested compounds

4.4.1 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 anticancer screening was initiated by cell inoculating of each 60 panel lines into a series of standard 96-well microtiter plates at 5000–40000 cells/well in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine

(day 0), and then preincubated in the absence of drug at 37 °C and 5% CO_2 for 24 h. Test compounds were added to the plates at one concentration of 10^{-5} M (day 1), followed by incubation for 48 h at the same conditions. Then, the media were removed, and the cells were fixed *in situ*, washed, and dried (day 3). The sulforhodamine B assay was used for cell density determination based on cellular protein content measurement. After an incubation period, cell monolayers were fixed with 10% (wt/vol) trichloroacetic acid and stained for 30 min, after which the excess dye was removed by washing repeatedly with 1% (vol/vol) acetic acid. The bound stain was resolubilized in a 10 mM Tris base solution and measured spectrophotometrically on automated microplate readers for OD determination at 510 nm.

4.4.2 NCI 60 cell panel COMPARE correlations.

Compounds having similar activity profiles often have similar mechanisms of action and resistance. In order to evaluate the likeness of new compounds with the drugs already present in NCI databases, we need to perform a similarity assessment. 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 concerning compounds from the standard agent database with a known mechanism of action. The following scale of interpretation of pair correlation coefficients was used:[16] 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.

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