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Solvent-Free Synthesis, ADME Prediction, and Evaluation of Antibacterial Activity of Novel Sulfonamide Derivatives

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Abstract—A series of novel sulfonamides containing a 2-amino-1,3-thiazole fragment have been synthesized using a simple and efficient method under solvent-free conditions. The obtained *N*-(4-sulfamoyl-1,3-thiazol-2-yl)-4-nitrobenzamides were evaluated for their antibacterial activity against *S. aureus* and *E. coli*, and *in silico* ADME prediction was performed to find biological behavior.

Keywords: sulfonamides, 1,3-thiazol-2-amine, *N*-(4-sulfamoyl-1,3-thiazol-2-yl)-4-nitrobenzamides, antibacterial activity, ADME prediction.

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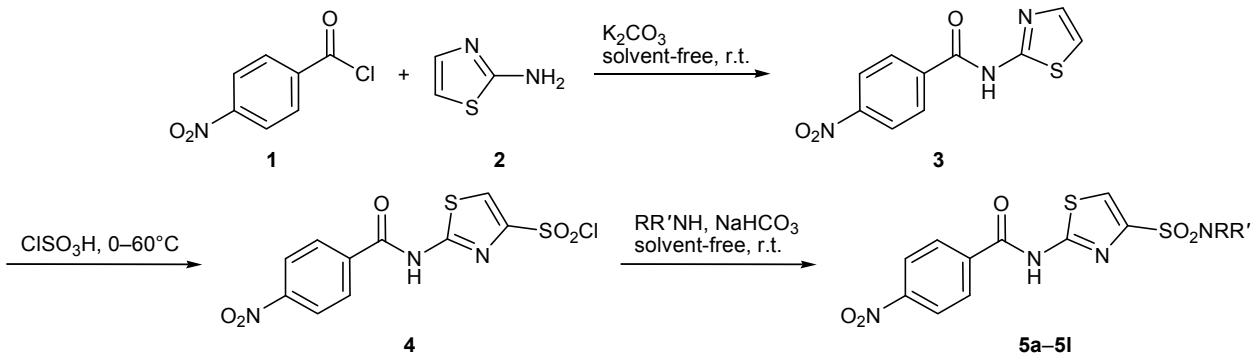
Sulfonamides are a class of medicinal compounds that show a wide range of biological activities, including antibacterial [1], anti-inflammatory [2], antifungal [3], antiprotozoal [4], HIV protease inhibitory [5], anti-Alzheimer [6], and anticancer [7]. Another important scaffold is a thiazole ring which is present in natural compounds such as vitamin B1 (thiamine) [8]. Aminothiazole derivatives are important for medicinal chemistry and are used in the development of drugs for the treatment of allergies [9], hypertension [10], inflammation [11], schizophrenia [12], and bacterial [13] and HIV infections [14]. In addition, 2-aminothiazoles are known as estrogen receptor ligands [15] and fungicides [14]. The importance of aminothiazole and sulfonamide moieties in drug discovery stimulates advanced studies aimed at creating new molecules containing both these scaffolds. For example, sulfonamides with a thiazole ring were synthesized and found to inhibit human carbonic anhydrases [16, 17]. DiMauro et al. [18] recently reported new azetidine sulfonamide and aminothiazole sulfone derivatives as efficient glycine receptor potentiators. Furthermore, many compounds with a sulfonamide–thiazolone core showed different biological activities as lactoperoxidase inhibitors [19], HCV inhibitors [20], and antibacterial and cytotoxic agents [21]. In continuation of our interest in sulfonamide synthesis [1, 22–25], herein we report a simple, efficient, and inexpensive method for the synthesis of thiazole-4-sulfonamides containing a 4-nitrobenzamide fragment. Also, their *in vitro* antibacterial activities against gram-negative (*E. coli*) and gram-positive (*S. aureus*) bacteria were assayed, and *in silico* ADME prediction was performed using online servers.

The synthesis of target thiazolesulfonamides was accomplished in three steps as shown in Scheme 1. First, 4-nitro-*N*-(1,3-thiazol-2-yl)benzamide (**3**) was prepared by the reaction of 2-aminothiazole with 4-nitrobenzoyl chloride in the presence of potassium carbonate at room temperature under solvent-free conditions. Compound **3** was then treated with chlorosulfonic acid to obtain the corresponding sulfonyl chloride **4**. The latter was sufficiently pure and was used without further purification in reactions with various primary aromatic amines and dipropylamine in the presence of sodium hydrogen carbonate to afford sulfonamides **5a–5l** (Table 1). The reactions were

Scheme 1.



R = H, R′ = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 2-MeOC$_6$H$_4$ (**c**), 4-MeC$_6$H$_4$ (**d**), 2,4-Me$_2$C$_6$H$_3$ (**e**), 2-MeC$_6$H$_4$ (**f**), 4-ClC$_6$H$_4$ (**g**), 3-ClC$_6$H$_4$ (**h**), 4-BrC$_6$H$_4$ (**i**), 4-EtC$_6$H$_4$ (**j**), naphthalen-2-yl (**k**); R = R′ = Pr (**l**).

carried out under solvent-free conditions at room temperature, and the yields were 74–87% in 15–35 min. The products were isolated with high purity just by adding water to the reaction mixture, followed by filtration. Thiazolesulfonamides **5a**–**5l** were characterized by ^{1}H NMR and ^{13}C NMR spectra.

All compounds **5a**–**5l** were screened for their *in vitro* antibacterial activity against *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922) as gram-positive and gram-negative bacteria, respectively. The minimum inhibitory concentrations (MIC) were determined by using the agar diffusion method [26, 27]. DMSO was used as a solvent, and ampicillin, as the reference drug. The obtained data are collected in Table 2.

The results were analyzed using SPSS 16.0 for Windows (Table 3). One-sample Shapiro–Wilk test [28] was used to assess the normality of data distribution. The non-parametric Kruskal-Wallis test [29] was used to compare the antibacterial activity of different compounds against *S. areus* and *E. coli*. When the differences between groups were statistically significant, Dunn's post hoc test was used for multiple group comparisons. The level of significance was set at $P \leq 0.05$. As seen from Table 3, the Kruskal–Wallis test showed significant differences between all compounds against *S. aureus* ($P = 0.04$) and *E. coli* ($P = 0.002$).

The results of statistical analysis (Table 3) showed that *N*-(4-methylphenyl)-substituted sulfonamide **5d** was the most effective among the examined series against gram negative bacteria (*S. aureus*). This suggests that compounds with electron-donating groups in the *para* position are more active than those with electron-withdrawing groups (**5g**–**5i**). Introduction of a methyl group at the 2-position (**5f**) leads to decrease in the activity. However, based on the post hoc analysis, there is no significant differences between the compounds except for **5h** ($p = 0.032$). *N*-Phenyl sulfonamide **5a** was the most potent compound against *E. coli*. Introduction of any group into the aniline moiety significantly decreased the antibacterial activity, suggesting that substitution at the aniline ring is not desirable. Statistically, significant differences were observed between **5a** and **5d** ($p = 0.047$), **5a** and **5j** ($p = 0.001$), and **5a** and **5l** ($p = 0.010$).

Pharmacokinetic parameters (absorption, distribution, metabolism, and excretion) of the synthesized compounds were estimated by submitting the structures to the PreADMET online software tool (http://

Table 1. Synthesis of thiazolesulfonamides **5a**–**5l**[a]

Comp. no.	Reaction time, min	Yield,[b] %
5a	15	81
5b	20	80
5c	25	82
5d	20	87
5e	25	75
5f	20	80
5g	20	80
5h	35	81
5i	35	87
5j	30	74
5k	25	76
5l	20	76

[a] All the reactions were performed using 1 mmol of $NaHCO_3$ under solvent-free conditions.

[b] Isolated yield.

Table 2. Antimicrobial activities of thiazolesulfonamides **5a**–**5l** against *S. aureus* and *E. coli* expressed as inhibition zone diameters[a] (mm)

Compound no.	c = 5 μg/mL		c = 2.5 μg/mL		c = 1.25 μg/mL		c = 0.6 μg/mL		c = 0.3 μg/mL	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*
5a	20	18	16	17	13	17	11	16	–	15
5b	18	17	16	14	13	13	–	12	–	11
5c	14	16	–	15	–	15	–	12	–	11
5d	19	12	18	11	17	9	16	7	15	4
5e	18	16	16	12	13	11	11	10	–	–
5f	18	14	14	11	10	10	9	8	–	5
5g	13	16	12	15	10	15	9	14	–	10
5h	11	15	–	14	–	7	–	–	–	–
5i	15	14	11	11	8	10	–	9	–	–
5j	17	12	12	12	–	11	–	11	–	10
5k	15	11	–	11	–	10	–	9	–	–
5l	16	14	13	13	–	12	–	12	–	11

[a] Dash stands for no activity.

Table 3. Statistical analysis of the antibacterial activity of compounds **5a**–**5l** according to one-sample Shapiro–Wilk, non-parametric Kruskal–Wallis, and Dunn's post hoc tests

Comp. no.	*S. aureus*						*E. coli*					
	mean	SD	medium	range	K.–W.	sig.	mean	SD	medium	range	K.–W.	sig.
5a	12.00	7.52	13	0–20	20.38	0.04	16.60	1.14	17	15–18	29.21	0.002
5b	9.40	8.76	13	0–18			13.40	2.30	13	11–17		
5c	2.80	6.26	0	0–14			13.80	2.17	15	11–16		
5d	17.00	1.58	17	15–19			8.60	3.21	9	4–12		
5e	11.60	7.02	13	0–18			9.80	5.93	11	0–16		
5f	10.20	6.72	10	0–18			9.60	3.36	10	5–14		
5g	8.80	5.17	10	0–13			14.00	2.35	15	10–16		
5h	2.20	4.92	0	0–11			7.20	7.26	7	0–15		
5i	6.80	6.69	8	0–15			8.80	5.26	10	0–14		
5j	5.80	8.14	0	0–17			11.20	0.84	11	10–12		
5k	3.00	6.71	0	0–15			8.20	4.66	10	0–11		
5l	5.80	8.01	0	0–16			12.40	1.14	12	11–14		

preadmet.bmdrc.org/). The results are given in Table 4. In oral administration, human intestinal absorption (HIA%) is a good parameter to characterize the absorption of a drug across membranes of the gastrointestinal tract. In this regard, the use of Caco-2 monolayers helps us to evaluate drug absorption through the small intestine. In PreADMET, well absorbed compounds show HIA between 70 and 100%. The HIA and Caco-2 cell permeability data showed the best absorption of **5j** and **5l** from human epithelium. Ligands with a c_{brain}/c_{blood} ratio of more than 2 show high absorption to CNS, but most of the candidates were found to have middle blood–brain barrier (BBB) permeability. Compound **5d** showed the best BBB absorption. The amount of a drug bound to proteins in plasma is characterized by the plasma protein binding (PPB) parameter. The efficiency of a drug in our body is related to the unbound drug in plasma. Molecules with lower PPB would be less active but the duration of their action would be prolonged. According to the

Table 4. Predicted ADME properties of compounds **5a–5l** obtained from PreADMET server

Ligand	BBB	Caco-2	HIA	PPB
5a	0.0184773	0.383095	87.778296	41.943193
5b	0.0911656	0.45288	82.920426	95.487992
5c	0.13715	0.438641	95.017061	100
5d	0.44766	0.417879	87.190986	99.234401
5e	0.171927	0.453796	88.523966	96.498753
5f	0.134903	0.417979	87.190710	97.674910
5g	0.146753	0.39517	91.638655	100
5h	0.146137	0.412586	91.638648	100
5i	0.153904	0.39596	94.155271	100
5j	0.134816	9.33853	92.378163	99.449429
5k	0.13715	0.438641	95.017061	100
5l	0.147585	12.7834	84.393615	86.393261

Table 5. Physicochemical properties of compounds **5a–5l** for assessment of the drug-likeness

Ligand	m_i logP [a]	TPSA,[b] Å^2	MW[c]	N_{ON}[d]	N_{OHNH}[e]	N_{rotb}[f]	Violation
5a	2.9	133.98	404.43	9	2	6	0
5b	2.95	143.22	434.45	10	2	7	0
5c	2.9	143.22	434.45	10	2	7	0
5d	3.34	133.98	418.46	9	2	6	0
5e	3.72	133.98	432.48	9	2	6	0
5f	3.29	133.98	418.46	9	2	6	0
5g	3.57	133.98	438.87	9	2	6	0
5h	3.55	133.98	438.87	9	2	6	0
5i	3.7	133.98	483.32	9	2	6	0
5j	3.52	125.19	432.48	9	1	7	0
5k	4.08	133.98	454.49	9	2	6	0
5l	3.2	125.19	412.49	9	1	9	0

[a] Octanol–water partition coefficient.
[b] Polar surface area.
[c] Molecular weight.
[d] Number of hydrogen-bond acceptors (O and N atoms).
[e] Number of hydrogen-bond donors (OH and NH groups).
[f] Number of rotatable bonds.

preADMET analysis, most of the tested compounds have PPB values higher than 90%, except for **5a** (PPB 42%) which must be more effective than other candidates.

In silico physicochemical parameters were estimated using the Molinspiration server (http://www.molinspiration.com); the results are collected in Table 5. Several factors such as molecular weight (MW), number of rotatable bonds (N_{rotb}), logarithm of partition coefficient (m_i logP), number of hydrogen bond acceptors (N_{ON}), number of hydrogen bonds donors (N_{OHNH}), topological polar surface area (TPSA), and Lipinski's rule of five were calculated. The topological polar surface area (PSA) [30] value is a critical factor to predict oral administration of a drug; it is calculated from the surface areas over all polar atoms, primarily oxygen and nitrogen atoms and hydrogens attached thereto. If a molecule have a TPSA value less than 140 Å^2, it must have suitable intestinal permeability, and TPSA less than 60 Å^2 shows well

blood–brain barrier penetration. As follows from Table 4, all the examined compounds should be well absorbed in human intestine. According to data obtained from preADMET and Molinspiration server, none of the candidates has good BBB penetration. Lipophilicity [31] of a molecule is an important physicochemical factor to estimate passive diffusion of a compound through intestinal membrane; it is quantified as $\log P_{o/w}$. All compounds **5a**–**5l** have $\log P_{o/w} < 5$ and are expected to have suitable lipophilicity for intestinal absorption. The ability of hydrogen bonding is another parameter for drug permeability. For ideal absorption, the number of hydrogen bond donors and acceptors must be less than 5 and 10, respectively. Good oral bioavailability is also affected by the number of rotatable bonds, which must be less than 10. In this scenario, the physicochemical parameters of all synthetic ligands obey Lipinski's rule of five [31], and no violation of this rule was observed; thus, the compounds meet all criteria for good permeability.

In summary, we have proposed an efficient synthesis of sulfonamides a 1,3-thiazole moiety at room temperature under solvent-free conditions, which can be regarded as a mild and eco-friendly process. Furthermore, it has other benefits such as short reaction times, high yield, and simple experimental procedure. Antibacterial activity of the synthesized compounds against gram negative and positive strains has been studied. According to the obtained data, compound **5d** is the best candidate against *S. aureus*. ADME analysis using preADMET server has revealed good HIA and Caco-2 parameters, indicating good absorption into intestinal tract. Prediction of physicochemical properties by Molinspiration server has demonstrated that **5d** is a good candidate for further investigation in future. Good antibacterial activity of **5i** and **5l** against *E. coli* and their suitable ADME and physicochemical parameters makes them promising for further testing *in vitro* and *in vivo*.

EXPERIMENTAL

All chemicals were purchased from Merck and Aldrich. The melting points were measured in open capillary tubes. The IR spectra were recorded as KBr pellets on a Perkin Elmer FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-400 instrument with TMS as internal standard. The progress of reactions was monitored by TLC on Polygram silica gel (Merck).

4-Nitro-*N*-(1,3-thiazol-2-yl)benzamide (3). A mixture of 2-aminothiazole (0.2 g, 1 mmol), 4-nitrobenzoyl chloride (0.37 g, 1 mmol), and potassium carbonate (1.5 mmol) was ground in a mortar at room temperature under solvent-free conditions. The progress of the reaction was monitored by TLC using *n*-hexane–ethyl acetate (1 : 1, v/v) as solvent. When the reaction was complete, 25 ml of water was added, and the mixture was stirred for 5 min. The product was filtered off and washed with water; it was used in the next step without further purification. Yield (90%), yellow solid, mp 123–125°C, R_f 0.4 (hexane–EtOAc, 1 : 1). IR spectrum, ν, cm^{-1}: 3142 (N–H), 1670 (C=O), 1298.24, 1324.40 (SO_2),1348.72 (NO_2).

2-(4-Nitrobenzamido)thiazole-4-sulfonyl chloride (4). Chlorosulfonic acid (9 mmol) was added to 1 mmol of amidothiazole **3,** and the mixture was stirred for 1 h at room temperature and then for 24 h at 60°C. The product was isolated by simple filtration and washed with water several times. Compound **4** was obtained with high purity and was used in the next step without any purification. Yield (85%), cream solid, mp 110–112, R_f 0.66 (hexane–EtOAc, 3:2). IR spectrum, ν, cm^{-1}: 3122 (N–H), 1734 (C=O), 1292, 1350 (SO_2).

Thiazolesulfonamides 5a–5l (*general procedure*). A mixture of sulfonyl chloride **4** (1 mmol), the corresponding amine (1 mmol), and sodium hydrogen carbonate (1 mmol) was ground in a mortar at room temperature under solvent-free conditions. After completion of the reaction (TLC, hexane–EtOAc), 25 mL of water was added, the mixture was stirred for 30 min, and the precipitate was filtered off.

4-Nitro-*N*-(4-phenylsulfamoyl-1,3-thiazol-2-yl)-benzamide (5a). Yield 81%, cream solid, mp 123–125°C, R_f 0.36 (hereinafter, hexane–EtOAc, 3:2). IR spectrum, ν, cm^{-1}: 3081 (N–H, amide), 3288 (N–H, sulfonamide), 1679 (C=O), 1146, 1536 (SO_2). ^{1}H NMR spectrum, δ, ppm: 7.12 d.d (1H, J = 7.2, 7.6 Hz), 7.20 d (2H, J =7.6 Hz), 8.01 s (1H), 8.29 d (2H, J = 8.8 Hz), 8.38 d (2H, J = 8.8 Hz), 10.56 s (1H, NH), 12.40 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 115.7, 120.7, 124.1, 125.1, 128.9, 129.8, 130.4, 137.4, 137.7, 143.8, 150.3, 163.2, 165.2. 2. Found, %: C 49.61; H 3.26; N 14.21. $C_{10}H_{12}N_4O_4S_2$. Calculated, %: C 49.48; H 3.11; N 14.42.

***N*-[4-(4-Methoxyphenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide 5b.** Yield 80%, cream solid, mp 268–270°C, R_f 0.26. IR spectrum, ν, cm^{-1}: 3113 (N–H, amide), 3279 (N–H, sulfonamide), 1679 (C=O),

1293, 1145 (SO_2). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, OCH_3), 6.89 d (2H, J = 4.6 Hz), 7.09 d (2H, J = 4.4 Hz), 7.89 s (1H), 8.30 d (2H, J = 4.4 Hz), 8.39 d (2H, J = 8.8 Hz), 10.20 s (1H, NH), 13.53 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.6, 114.9, 124.1, 124.1, 129.0, 130.1, 130.4, 137.4, 143.5, 150.3, 157.4, 136.0, 165.1. Found, %: C 48.92; H 3.24; N 13.5. $C_{17}H_{14}N_4O_5S_2$. Calculated, %: C 48.80; H 3.37; N 13.39.

***N*-[4-(2-Methoxyphenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5c).** Yield 82%, cream solid, mp 265–167°C, R_f 0.33. IR spectrum, ν, cm^{-1}: 3081 (N–H, amide), 3285 (N–H, sulfonamide), 1681 (C=O), 1108, 1537 (SO_2). ^{1}H NMR spectrum, δ, ppm: 3.60 s (2H, J = 2.96 Hz), 6.93–7.00 m (2H), 7.19–7.29 m, 7.31 s (1H), 7.30 d.d (2H, J = 6.4, 7.0 Hz), 9.83 s (1H, NH), 13.25 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 55.9, 112.4, 121.1, 124.1, 125.2, 126.4, 127.8, 130.3, 130.5, 137.4, 142.9, 150.3, 153.3, 162.9. Found, %: C 48.98; H 3.20; N 13.53. $C_{17}H_{14}N_4O_5S_2$. Calculated, %: C 48.80; H 3.37; N 13.39.

***N*-[4-(4-Methylphenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5d).** Yield 87%, cream solid, mp 277–279°C, R_f 0.66. IR spectrum, ν, cm^{-1}: 3113 (N–H, amide), 3253 (N–H, sulfonamide), 1681 (C=O), 1146, 1344 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H), 7.08 d (2H, J = 8 Hz), 7.12 d (2H, J = 8 Hz), 7.91 s (1H), 8.30 d (2H, J = 8.4 Hz), 8.39 d (2H, J = 8.4 Hz), 10.40 s (1H, NH), 13.55 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.8, 121.3, 124.1, 129.1, 130.2, 130.5, 134.4, 134.9, 135.1, 137.4, 143.8, 150.3, 150.3, 163.1, 165.1. Found, %: C 50.62; H 3.62; N 13.79. $C_{17}H_{14}N_4O_5S_2$. Calculated, %: C 50.74; H 3.51; N 13.92.

***N*-[4-(2,4-Dimethylphenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5e).** Yield 75%, cream solid, mp 235–237°C, R_f 0.3. IR spectrum, ν, cm^{-1}: 3068 (N–H, amide), 3279 (N–H, sulfonamide), 1679 (C=O), 1144, 1285 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, CH_3), 3.24 s (3H, CH_3), 6.93 d (2H, J = 8.4 Hz), 7.04 s (1H), 7.82 s (1H), 8.33 d (2H, J = 8.8 Hz), 8.40 d (2H, J = 8.8 Hz), 9.81 s (1H, NH), 13.53 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.2, 20.9, 124.1, 127.3, 127.5, 130.5, 131.9, 132.1, 135.2, 136.8, 137.4, 143.1, 150.3, 163.1, 165.1. Found, %: C 51.75; H 3.69; N 13.58. $C_{18}H_{16}N_4O_4S_2$. Calculated, %: C 51.91; H 3.87; N 13.45.

***N*-[4-(2-Methylphenylsulfamoyl)-1,3-thiazol-2-yl)-4-nitrobenzamide (5f).** Yield 80%, cream solid, mp 239–242°C, R_f 0.3. IR spectrum, ν, cm^{-1}: 3282 (N–H), 3061, 1679 (C=O), 1144, 1345 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2. 21 s (3H), 7.09 d (1H, J = 3.6 Hz), 7.16–7.23 m (3H), 7.52 s (1H), 8.31–8.41 m (4H), 9.95 s (1H, NH), 13.57 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.2, 124.1, 124.1, 127.,1 127.1, 127.4, 130.2, 130.5, 131.3, 134.8, 135.1, 137.3, 143.1, 150.3, 163.1, 165.1. Found, %: C 50.52; H 3.45; N 13.78. $C_{17}H_{14}N_4O_4S_2$. Calculated, %: C 50.74; H 3.51; N 13.92.

***N*-[4-(4-Chlorophenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5g).** Yield 80%, cream solid, mp 157–159°C, R_f 0.53. IR spectrum, ν, cm^{-1}: 3114 (N–H, amide), 3278 (N–H, sulfonamide), 1679 (C=O), 1147, 1343 (SO_2). ^{1}H NMR spectrum, δ, ppm: 7.21 d (2H, J = 8.4 Hz), 7.39 d (2H, J = 8.4 Hz), 8.05 s (1H), 8.30 d (2H, J = 8.4 Hz), 8.39 d (2H, J = 8.4 Hz), 10.73 s (1H, NH), 13.57 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 122.3, 124.1, 128.6, 129.2, 129.8, 130.5, 136.8, 137.4, 144.1, 150.4, 163.4, 165.2. Found, %: C 45.62; H 2.53; N 13.14. $C_{16}H_{11}ClN_4O_4S_2$. Calculated, %: C 45.45; H 2.62; N 13.25.

***N*-[4-(3-Chlorophenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5h).** Yield 81%, cream solid, mp 158–160°C, R_f 0.4. IR spectrum, ν, cm^{-1}: 3114 (N–H, amide), 3287 (N–H, sulfonamide), 1677 (C=O), 1147, 1345 (SO_2). ^{1}H NMR spectrum, δ, ppm: 7.18 d (2H, J = 7.7 Hz), 7.22 s (1H), 7.18 d.d (J = 7.9, 8 Hz), 10.87 s (1H, NH), 13.60 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 118.6, 119.7, 124.1, 124.7, 128.6, 130.4, 131.5, 134.1, 137.3, 139.3, 144.2, 150.3, 163.4, 165.1. Found, %: C 45.66; H 2.59; N 13.19. $C_{16}H_{11}ClN_4O_4S_2$. Calculated, %: C 45.45; H 2.62; N 13.25.

***N*-[4-(4-Bromophenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5i).** Yield 87%, cream solid, mp 237–240°C, R_f 0.6. IR spectrum, ν, cm^{-1}: 3114 (N–H, amide), 3283 (N–H, sulfonamide), 1679 (C=O), 1147, 1344 (SO_2). ^{1}H NMR spectrum, δ, ppm: 7.16 d (2H, J = 8.4 Hz), 7.52 d (2H, J = 8.4 Hz), 8.07 s (1H), 8.30 d (2H, J = 8.4 Hz), 8.39 d (2H, J = 8.0 Hz), 10.76 s (1H, NH), 13.60 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 117.2, 122.5, 124.1, 128.5, 130.4, 132.6, 137.1, 137.3, 144.1, 150.3, 163.3, 165.1. Found, %: C 41.26; H 2.24; N 12.12. $C_{16}H_{11}BrN_4O_4S_2$. Calculated, %: C 41.12; H 2.37; N 11.99.

***N*-[4-(Ethylphenylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5j).** Yield 74%, cream solid, mp 235–237°C, R_f 0.3. IR spectrum, ν, cm^{-1}: 3132 (N–H), 1683 (C=O), 1165, 1349 (SO_2). ^{1}H NMR spectrum, δ_C, ppm: 1.04 s (3H), 3.69 q (2H, J = 6.7 Hz),

7.23 d (2H, J = 6.8 Hz), 13.65 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.3, 29.5, 124.1, 127.1, 128.7, 129.0, 129.7, 130.5, 137.3, 138.5, 143.8, 150.3, 163.2, 165.1. Found, %: C 52.16; H 3.69; N 13.57. $C_{18}H_{16}N_4O_4S_2$. Calculated, %: C 51.91; H 3.87; N 13.45.

***N*-[4-(Naphthalen-2-ylsulfamoyl)-1,3-thiazol-2-yl]-4-nitrobenzamide (5k).** Yield 76%, cream solid, mp 225–230°C, R_f 0.3. IR spectrum, ν, cm^{-1}: 3285 (N–H), 1678 (C=O), 1142, 1346 (SO_2). ^{1}H NMR spectrum, δ, ppm: 7.33 d (1H, J = 7.2 Hz), 7.85 s (J = 10 Hz), 7.87 s (2H, J = 8 Hz), 7.94 t (1H, J = 5.2, 3.6 Hz), 8.127 t (1H, J = 3.6 Hz), 8.31 d (2H, J = 8.8 Hz), 8.39 d (2H, J = 8.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 123.5, 124.0, 124.1, 126.1, 126.7, 126.8, 127.7, 128.8, 130.0, 130.83, 130.5, 132.3, 134.4, 150.3. Found, %: C 54.86; H 3.15; N 12.62. $C_{20}H_{14}N_4O_4S_2$. Calculated, %: C 54.79; H 3.22; N 12.78.

***N*-[4-(Dipropylsulfamoyl)-1,3-thiazol-2-yl)-4-nitrobenzamide (5l).** Yield 76%, cream solid, mp 236–240°C, R_f 0.3. IR spectrum, ν, cm^{-1}: 3076 (N–H, amide), 1675 (C=O), 1149, 1303 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.93 t (6H, J = 8.4 Hz), 1.56 s (4H), 3.08 t (4H, J = 8.7 Hz), 8.16 s (1H), 8.33 d (2H, J = 8.8 Hz), 8.42 d (2H, J = 8.8 Hz), 13.63 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 11.4, 22.3, 124.1, 128.3, 130.4, 142.8, 150.3, 162.6, 165.1. Found, %: C 48.62; H 4.97; N 14.05. $C_{16}H_{20}N_4O_4S_2$. Calculated, %: C 48.47; H 5.08; N 14.13.

CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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