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RESEARCH ARTICLE

Search for Biologically Active Substances with Antimicrobial and Antifungal Action in the series of 2.5-disubstituted 1, 3, 4-tiadiazoles

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ABSTRACT:

A range of derivatives of sulfonyl-substituted nitrogen-containing heterocyclic systems has been extended by synthesis of 2N (R)-5R[1]-1,3,4-thiadiazol-2-yl-arylsulfonamides and N-(diethylsulfamoyl)-N-(5-ethyl-1,3,4-thiadiazol-2-yl)benzamides. It was established that acylation of 5-ethylsulfanyl-1,3,4-thiadiazole-2-amine by heteryl-substituted acid chlorides allowed for obtaining not reported in the literature heterocyclic compounds, which structure contained two cycles of 1,3,4-thiadiazole. The structure and purity of the obtained compounds was confirmed by ^{1}H NMR-spectroscopy, elemental analysis, and thin-layer chromatography. Pharmacological studies on antimicrobial and antifungal activity have shown that all the compounds tested have sensitivity to both Gram-positive, and Gram-negative bacteria. In addition, the obtained substances have exhibited antifungal activity against Candida albicans. The studies have identified compound 4-butoxy-N-{5-[({[5- (ethylsulfanyl)-1,3,4-thiadiazol-2-yl] carbomoyl} methyl) sulfanyl] -1,3,4-thiadiazol-2-yl} benzamide with high antimicrobial activity further studies of which are promising.

KEYWORDS: synthesis, 2.5-disubstituted 1, 3, 4-tiadiazoles, antibacterial and antifungal activity.

INTRODUCTION:

Modern antibacterial and antifungal drugs do not always provide satisfactory chemotherapeutic results, which is due to the fact that microorganisms develop resistance to them. That is why the search for biologically active substances in this field is an actual task for pharmaceutical chemistry. Analysis of scientific literature suggests that there is a growing interest in investigation of the mechanism of the N-S bond formation in biological objects, which is owing to the confirmed important role of aromatic sulfonic acid derivatives in inhibition of enzymes. Therefore, a certain interest in the search for new active substances with antimicrobial and antifungal activity was attributed to compounds, which composition includes a sulfonamide moiety [1-5,18,19].

In addition, literature has some data about the high potential of studies on antimicrobial activity of substances that contain several cycles with one or more heteroatoms within a single molecule [6,7,9-17]. Based on the high potential of such modification, we have planned functionalization of 2-amino-5-(alkyl)-1,3,4-thiadiazoles in two ways: by introducing a sulfonamide moiety into the synthesized molecules, and by introducing the second 1,3,4-thiadiazole cycle into the molecule. Both modifications have been planned for a specific purpose – to see how these combinations will affect antimicrobial and antifungal properties of the molecule in general. Introduction of 2-amino-5- (alkyl) -1,3,4-thiadiazoles of the sulfonamide moiety into the second position of the molecule was carried out in a dry pyridine medium with interaction with substituted aryl sulphonyl chlorides. Their interaction with amines can be carried out in various solvents (benzol, acetone, dioxane, etc.) in the presence of a hydrogen chloride acceptor released during the reaction. Tertiary amines are widely used as hydrogen chloride acceptors. Therefore, in order to obtain target compounds, we have

suggested interaction of 2-amino-5-R-1,3,4-thiadiazole with di- and three-substituted aryl sulphonyl chlorides in the pyridine medium, which can at the same time serve as a hydrogen chloride acceptor.

Synthesis of new substances, which molecule contains two 1,3,4-thiadiazole cycles and aryl, alkyl, carbamoyl, and sulfonyl moieties at positions 2 and 5, was carried out by interaction with acid chlorides of heteryl-substituted acids.

Synthesis of substances, representatives of different representative series of 2,5-disubstituted-1,3,4-thiadiazoles, will provide an opportunity to identify patterns of the "structure-activity" relationship and to use the obtained results for predicting activity of new compounds.

MATERIALS AND METHODS:

Reagents manufactured by Sigma-Aldrich, USA, were used in the work. The necessary reagents were obtained and purified using standard techniques. Melting temperatures were determined using a Kofler plate. Elemental analysis of the nitrogen content was performed by the Dumas' method. Identity of substances and control of reactions was carried out by TLC on Sorbfil UV-254 plates. The chromatogram was developed in UV rays of the "Chromatographic irradiator UFS 254/365" device (mode of 254 nm). R*f* was determined in the toluene-acetone- ethanol-ammonia system (45:45:7:3). ^{1}H NMR-spectra were recorded by Varian Mercury 200 MHz instrument, the solvent was DMSO–d_6, tetramethyl silane (TMS) was used as internal standard. Chemical shifts are provided with the δ scale (ppm).

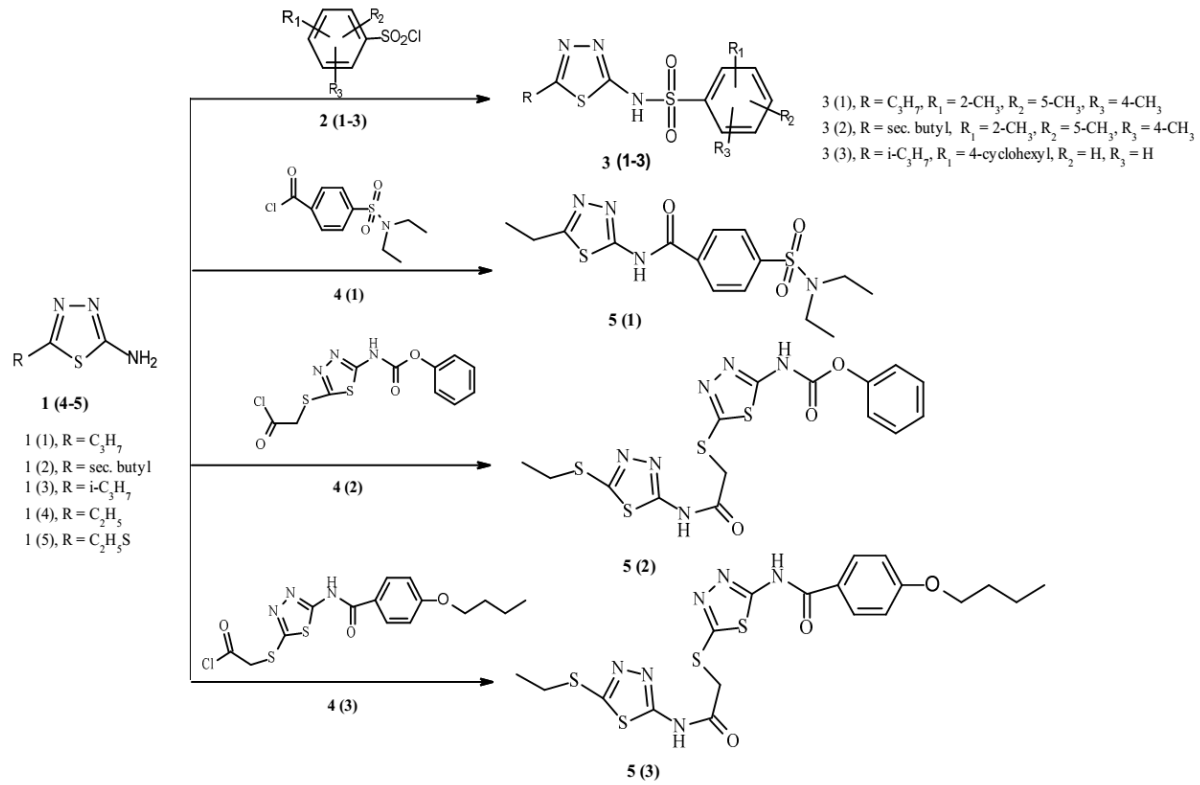
Microbial suspension of microorganisms was prepared using the Densi-La-Meter device (manufactured by PLIVA-Lachema, Czech Republic, wavelength of 540 nm). Synchronization of cultures was carried out using low temperature (4°C). The microbial load was 107 microbial cells per 1 ml of medium and was established using the McFarland standard. An 18-24 hour culture of microorganisms was used. For studies, Mueller-Hinton agar was used (HIMedia Laboratories Pvt. Ltd. India, expiration date of the medium is XII 2018, manufactured in India). For Candida albicans, Sabouraud-dextrose agar was used (manufactured in India, HIMedia Laboratories Pvt. Ltd. India, expiration date of the medium is XII 2018). Drug diffusion into agar was carried out by the "well" method. Activity of antibacterial drugs was determined on two layers of solid medium poured in Petri dishes. "Starving" non-inoculated media (agar-agar, water, salts) were used in the lower layer. The lower layer represents a substrate with 10 mL of "starving agar", on which 3-6 thin-walled stainless steel cylinders 10mm in diameter and 10mm in height were mounted in a strictly horizontal manner. Around the cylinders, the upper layer was poured, consisting of agarized nutrient medium melted and cooled to 40°C, into which the respective standard of the overnight culture of the test microbe was transferred. Previously, the upper layer was mixed thoroughly until a homogeneous mass was formed. The volume of the upper layer medium ranged from 14 to 16mL. Dishes were dried at room temperature for 30-40 minutes and placed into the thermostatic oven for 18-24hours, and then 5-6 disks were applied to the surface of the inoculated medium with sterile forceps. Dishes with disks were incubated at room temperature for another 30–40 minutes, then at 37°C for 18–24 hours.

RESULTS AND DISCUSSIONS:

2-amino-5-alkyl-1,3,4-thiadiazoles ***1 (1 -5),*** which were resynthesized by reaction of substituted thiosemicarbazides with aliphatic acids in the presence of concentrated sulfuric acid at a temperature of 70°C for 3 hours were used as initial product for the synthesis of 2,5-disubstituted 1,3,4-thiadiazoles ***3 (1-3)*** and ***5 (1-3).*** N-(5-R-1,3,4-thiadiazol-2-yl)-2,4,5-R'-benzene-1-sulfonamides **3 (1-3)** were obtained by reaction of 2-amino-5-R-1,3,4-thiadiazoles ***1 (1-3)*** with di- and three-substituted arylsulfonyl chlorides in dry pyridine [8]. The substitution of disubstituted arylsulfonyl chlorides for three-substituted ones does not significantly affect the yields of the desired reaction product. They are low and are in the range of 54-57%. The yield of the final product with a cyclohexyl substituent is one of the lowest, probably due to steric complications.

4- (Diethylsulfamoyl)-N-(5-ethyl-1,3,4-thiadiazol-2-yl)benzamide ***5(1),*** phenyl N-{5-[({[5- (ethylsulfanyl)-1,3,4-thiadiazol-2-yl]carbomoyl}methyl)sulfanyl]-1,3,4-thiadiazol-2-yl}carbamate ***5(2)*** and 4-butoxy-N-{5-[({[5- (ethylsulfanyl)-1,3,4-thiadiazole-2-yl]carbomoyl}methyl)sulfanyl]-1,3,4-thiadiazol-2-yl}benzamide ***5(3)*** were obtained by acylation of 2-amino-5-(ethyl,thioethyl)-1,3,4-thiadiazoles ***1(4-5)*** by acid chlorides ***4 (1-3)*** in dry pyridine (Scheme 1). Chlorides were obtained from commercial sources.

Scheme 1



Synthesized substances ***3(1-3)*** and ***5(1)*** are white crystalline substances, freely soluble in ethanol when heated, chloroform and acetone, poorly soluble in water.

Compounds ***5(2)*** and ***5(3)*** are white crystals, soluble in ethanol and not soluble in water.

The structure and purity of the obtained substances were confirmed by elemental analysis, ^{1}H NMR spectroscopy, thin layer chromatography.

Antimicrobial and antifungal activity of new compounds were determined by the generally accepted method of double serial dilutions in a culture fluid with a microbial load of 1 million microbial cells in 1 mL of Sabouraud-dextrose broth [9, 10, 15].

The study of antimicrobial and antifungal activity was performed using individual test germ cultures, representatives of both gram-positive and gram-negative microflora. According to the WHO recommendations, the assessment of the activity of samples in relation to gram-positive microorganisms was carried out with the reference strain - Staphylococcus aureus ATCC 25922.

The activity of substances with respect to Gram-negative microorganisms were tested using Escherichia coli strains ATCC 25922 (enteropathogenic strain), as well as Proteus vulgaris ATCC 4636, Pseudomonas aeruginosa ATCC 27853, which corresponds to the strain KDSV 27853 (catalog No. 190127). For the same purpose, the strain Bacillus subtilis ATCC 6633, which corresponds to the strain GNIISCLS 7241 (catalog No. 010011), was used.

Determination of antifungal activity was performed using a strain of yeast-like fungus Candida albicans ATCC 885/653.

The study of antibacterial activity was performed using "standard" culture media. Taking into account the physical properties of substances, namely, the insolubility in water, testing was carried out by the method of diffusion into agar (by the method of disks).

Analysis of results was carried out by measuring zones of growth inhibition, which includes the diameter of the disks themselves. Evaluation of the activity of new antibacterial substances, as well as the study of antibiotic-resistant strains were carried out using the following criteria:

- The absence of zones of growth inhibition of microorganisms around the well, as well as a zone of growth inhibition up to 10 mm indicated that the microorganism is not sensitive to the test substance introduced into the well or to its concentration;

- Zones of growth inhibition with a diameter of 10–15 mm indicated a low sensitivity of the culture to the studied concentration of the antibacterial substance;
- Zones of growth inhibition with a diameter of 15-25 mm were regarded as an indicator of the sensitivity of the microorganism to the test substance;
- Zones of growth inhibition with diameter which exceeded 25 mm, indicate a high sensitivity of microorganisms to the test substance.

As a result of studies of six test compounds it was found that they all have sensitivity to both gram-positive and gram-negative bacteria. Also, all compounds have showed antifungal activity against Candida albicans ATCC 885/653. Zones of growth inhibition for all studied substances with a diameter of 15-25 mm were regarded as an indicator of high sensitivity of microorganisms. In the case of 4-butoxy-N-{5-[({[5-(ethylsulfanyl)-1,3,4-thiadiazol-2-yl]carbomoyl}methyl)sulfanyl]-1,3,4-thiadiazol-2-yl}benzamide ***5(3)*** it was a single case when the diameter of the growth inhibition zone with respect to the Bacillus subtilis ATCC strain was 25 mm, so high sensitivity to this substance was detected and it could be recommended for further more detailed study (Table 1).

Discussing the dependence "structure - antimicrobial activity", it can be noted that the introduction of the benzenesulfonamide moiety into the molecule has almost no effect on the level of biological activity of the tested compounds, their activity does not exceed the activity of the starting materials. Introduction of the second 1,3,4-thiadiazole cycle to the synthesized molecules increases the antimicrobial properties of the molecule. This group includes the most promising substance 4-butoxy-N-{5-[({[5-(ethylsulfanyl)-1,3,4-thiadiazol-2-yl]carbomoyl} methyl)sulfanyl]-1,3,4-thiadiazol-2-yl} benzamide ***5 (3)).*** Probably, the main contribution to the high antimicrobial and antifungal properties of the substance is made by the presence of two 1,3,4-thiadiazole cycles in the molecule.

In addition, it's worth paying attention to the fact that the compounds of this group combine antibacterial and antifungal activity. Consequently, these substances may be effective as potential broad spectrum antimicrobial agents. Therefore, further in-depth studies of this class of compounds should be considered promising and relevant.

N- [5-propyl-1,3,4-thiadiazol-2-yl] -2,4,5-trimethyl-benzene-1-sulfonamide 3 (1)

0.01 mol (1.43 g) of 5-propyl-1,3,4-thiadiazol-2-amine was dissolved in anhydrous pyridine at heating, 0.015 mol (3.28 g) of 2,4,5-trimethylbenzene-1-sulfonyl chloride was added and heated at 85° C for 30 minutes. After cooling, the reaction mixture was poured into water, acidified with hydrochloric acid to pH = 3-3.5. The precipitate was filtered, washed with water and dried. Crystallized from ethanol.

54% yield, T. melt. = 146-148 ºC (ethanol). R*f* = 0.53. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 0.95 (dd, 3H, CH_3), 1.73 (s, 2H, CH_2), 2.95 (dd, 2H, CH_2), 2.64 (s , 3H, CH_3), 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.27 s, 1H, 7.60 s 1H (H-Ar), 14.10 (s, 1H, NH). 12.90% N, 19.64% S calculated for $C_{14}H_{19}N_3O_2S_2$ Found,%: N 12.92, S 19.66.

N- [5-(butan-2-yl) -1,3,4-thiadiazol-2-yl]-2,4,5-trimethyl-benzen-1-sulfonamide (3.2)

0.01 mol (1.57 g) of 5-(butan-2-yl)-1,3,4-thiadiazol-2-amine was dissolved in anhydrous pyridine at heating, 0.015 mol (3.28 g) of 2,4,5-trimethylbenzene-1-sulfonyl chloride was added and heated at a temperature of 85° C for 30 minutes. After cooling, the reaction mixture was poured into water, acidified with hydrochloric acid to pH = 3-3.5. The precipitate was filtered, washed with water and dried. Crystallized from ethanol.

56% yield, T. melt. = 138-140 ° C (ethanol). R*f* = 0.68. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.35 (dd, 6H, 2 × C<u>H</u>$_3$), 2.29 (s, 3H, C<u>H</u>$_3$), 2.34 (s, 3H, C<u>H</u>$_3$), 2.64 (s, 3H, C<u>H</u>$_3$), 2.95 (dd, 2H, C<u>H</u>$_2$), 1.82 (t, 1H, C<u>H</u>), 7.27 s, 1H, 7.60 s 1H (H-Ar), 14. 10 (s, 1H, N<u>H</u>). 12.34% N, 18.83% S calculated for $C_{15}H_{21}N_3O_2S_2$. Found,%: N 12.35, S 18.85.

Table 1: Antifungal and antimicrobial activity of the studied compounds.

Substances	The diameters of the zones of growth inhibition in mm, the number of repetitions of the experiment n = 2					
	Staphylococcus aureus ATCC 25923	Escherichia coli ATCC 25922	Proteus vulgaris ATCC 4636	Pseudomonas aeruginosa ATCC 27853	Basillus subtilis ATCC 6633	Candida albicans ATCC 653/885
3(1)	24, 23	22, 23	18, 18	17, 19	24, 24	19, 18
3(2)	23, 23	22, 23	19, 18	19, 18	23, 23	17, 17
3(3)	24, 24	21, 20	17, 17	20, 18	23, 25	18, 18
5(1)	22, 22	20, 21	17, 17	18, 18	23, 23	18, 18
5(2)	23, 23	23, 21	18, 18	19, 18	24, 24	17, 18
5(3)	23, 22	22, 20	17, 18	19, 19	25, 24	19, 18

N- [5-(propan-2-yl)-1,3,4-thiadiazol-2-yl]-4-cyclohexyl-benzen-1-sulfonamide 3 (3)

0.01 mol (1.43 g) of 5- (propan-2-yl) -1,3,4-thiadiazol-2-amine was dissolved in anhydrous pyridine at heating. 0.015 mol (3.9 g) of 4-cyclohexyl-benzen-1-sulfonyl chloride was added and heated at a temperature of 85°C for 30 minutes. After cooling, the reaction mixture was poured into water, acidified with hydrochloric acid to pH = 3-3.5. The precipitate was filtered, washed with water and dried. Crystallized from ethanol.

54% yield, T. melt. = 142-144 ° C (ethanol). R*f* = 0.68. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.35 (dd, 6H, 2 × C<u>H</u>$_3$), 1.85 (t, 1H, C<u>H</u>), 1.25-2.05 m, 10 H, 5.03 m, 1H (H-cyclohexyl), 7.57 dd, 2H, 7.73 dd. 2H (H-Ar), 14.10 (s, 1H, N<u>H</u>). Calculated 11.46 % N, 17,50 % S for $C_{17}H_{23}N_3O_2S_2$. Found, %: N 11.47, S 17.51.

N-[5-ethyl-1,3,4-thiadiazol-2-yl]-4-(diethylsulfamoyl)-benzamide 5 (1)

0.01 mol (1.3 g) of 5-ethyl-1,3,4-thiadiazol-2-amine was dissolved in anhydrous pyridine at heating, 0.015 mol (4.13 g) of 4- (diethylsulfamoyl) benzoyl chloride was added and heated at a temperature of 85° C for 30 minutes. After cooling, the reaction mixture was poured into water, acidified with hydrochloric acid to pH = 3-3.5. The precipitate was filtered, washed with water and dried. Crystallized from ethanol.

70% yield, T. melt. = 218-220 ° C (ethanol). R*f* = 0.53. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.0 (s, 3H, C<u>H</u>$_3$), 1.2 (s, 6H, 2 × C<u>H</u>$_3$), 2.1-2.2 (m, 2H, C<u>H</u>$_2$- CH$_2$), 2.3-2.4 (m, 2H, CH$_2$-C<u>H</u>$_2$), 3.15-3.4 (m, 2H, C<u>H</u>$_2$), 7.1-7.4 (dd, 4H, H-Ar), 13.8 (s, 1H, N<u>H</u>). 15.16% N, 17.36% S calculated for $C_{15}H_{20}N_4O_3S_2$ Found,%: N 15.15, S 17.35.

Phenyl N-{5-[({[5-(ethylsulfanyl)-1,3,4-thiadiazol-2-yl]carbamoyl}methyl)sulfanyl]-1,3,4-thiadiazol-2-yl} ***carbamate 5 (2)***

0.01 mol (1.6 g) of 5-ethylsulfanyl-1,3,4-thiadiazol-2-amine was dissolved in anhydrous pyridine at heating, 0.015 mol (4.9 g) of phenyl N-{5-[(2-chloro-2-oxo-ethyl)sulfanyl]-1,3,4-thiadiazol-2-yl}carbamate was added and heated at 85° C for 30 minutes. After cooling, the reaction mixture was poured into water, acidified with hydrochloric acid to pH = 3-3.5. The precipitate was filtered, washed with water and dried. Crystallized from ethanol.

72% yield, T. melt. = 252-254 ° C (ethanol). R*f* = 0.69. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.39 (s, 3H, C<u>H</u>$_3$), 3.22 (s, 2H, C<u>H</u>$_2$), 3.94 (s, 2H, C<u>H</u>$_2$), 7.23-7,49 m, 5H (H-Ar), 12.26 (s, 1H, N<u>H</u>), 12.62 (s, 1H, N<u>H</u>). 18.49% N, 28.24% S calculated for $C_{15}H_{14}N_6O_3S_4$. Found,%: N 18.47, S 28.19.

N- {5 - [({[5- (ethylsulfanyl) -1,3,4-thiadiazol-2-yl] carbamoyl} methyl) sulfanyl] -1,3,4-thiadiazol-2-yl} -4-butoxy -benzamide 5 (3)

0.1 mol (1.6 g) of 5-ethylsulfanyl-1,3,4-thiadiazol-2-amine was dissolved in anhydrous pyridine at heating, 0.15 mol (5.7 g) of 2-{[5-(4-butoxy-benzamido)-1,3,4-thiadiazol-2-yl]sulfanyl}acetyl chloride was added and heated at a temperature of 85°C for 30 minutes. After cooling, the reaction mixture was poured into water, acidified with hydrochloric acid to pH = 3-3.5. The precipitate was filtered, washed with water and dried. Crystallized from ethanol.

70% yield, T. melt. = 260-264 ° C (ethanol). R*f* = 0.69. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 0.94 (s, 3H, C<u>H</u>$_3$), 1.22 (m, 9H, OC$_4$<u>H</u>$_9$), 1.64 (s, 2H, C<u>H</u>$_2$), 2.61 (s, 2H, C<u>H</u>$_2$), 7.0 dd, 2H, 7.89 dd, 2H (H-Ar), 12.62 (s, 1H, N<u>H</u>), 12.73 (s, 1H, N<u>H</u>). 16.46% N, 25.11% S calculated for $C_{19}H_{22}N_6O_3S_4$. Found,%: N 16.46, S 25.10.

CONCLUSIONS:

1. It was extended the range of derivatives of sulfanyl-substituted nitrogen-containing heterocyclic systems by synthesis of N-(5-R-1,3,4-thiadiazol-2-yl)-2,4,5-R'-benzene-1-sulfonamides and N-(diethylsulfamoyl)-N-(5-ethyl-1,3,4-thiadiazol-2-yl) benzamides through chemical modification of the amino group in 5-R-1,3,4-thiadiazol-2-amines.
2. It was established that acylation of 5-ethylsulfanyl-1,3,4-thiadiazol-2-amine by heteryl-substituted acids allowed for obtaining not reported in literature heterocyclic compounds, which structure contained two cycles of 1,3,4-thiadiazole.
3. The structure and purity of the obtained compounds was confirmed by ^{1}H NMR-spectroscopy, elemental analysis and thin layer chromatography.
4. Pharmacological studies on antimicrobial and antifungal activity have shown that all the compounds tested have sensitivity to both Gram-positive, and Gram-negative bacteria. In addition, the obtained substances have exhibited antifungal activity against Candida albicans.
5. Studies allowed to identify 4-butoxy-N-{5-[({[5-(ethylsulfanyl)-1,3,4-thiadiazol-2-yl]carbomoyl}methyl)sulfanyl]-1,3,4-thiadiazol-2-yl}benzamide compound with high antimicrobial activity, further studies of which are promising.

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