SYNTHESIS OF 5-SUBSTITUTED 1,3,4-THIADIAZOL-2-YL-SULFANYLACETIC ACID DERIVATIVES

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ABSTRACT

The study is devoted to the design and synthesis of new 2,5-disubstituted 1,3,4-thiadiazoles 3a-k as a promising multi-targeted pharmacological scaffold. Heterocyclization of acylated thiosemicarbazides 1a-i with carbon disulfide lead to the intermediate 5-R-carboxylamino-1,3,4-thiadiazol-2-thiols 2a-i. Further S-alkylation of compounds 2a-i with chloroacetic acid amides and ethyl ester allowed to obtain the target 5-R-carboxylamino-1,3,4-thiadiazol-2-yl-sulfanylacetic acid derivatives 3a-k. The developed method could be used for producing of molecular diversity of disubstituted 5-amino-1,3,4-thiadiazol-2-thiols via variation of substituents on both functional groups. Synthesized compounds are discussed as prospective anticonvulsants and antiproliferative agents.

Keywords: 5-amino-1,3,4-thiadiazole-2-thiols, S-alkylation, chloroacetic acid derivatives

INTRODUCTION

Synthesis of small nitrogen containing heterocycles are of a special interest nowadays because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. Thiadiazoles has attracted wide-spread attention of medicinal chemists due to their chemical potential and high pharmacological efficacy and low side effects.

At the moment 1,3,4-thiadiazoles are the most studied class among the other thiadiazole isomers and their 2,5-disubstituted derivatives have been widely discussed in terms of the interesting biological activities (1-6). In particular, such class as 5-amino-1,3,4-thiadiazole-2-thiol derivatives are known as antimicrobial (7), anticonvulsant (8-10), anti-depressant (11), anti-anxiety (12), anti-diabetic (13) agents. The therapeutic importance of 1,3,4-thiadiazole ring prompted us to design new molecules in which substituents could be arranged in a pharmacophore pattern to display higher pharmacological activities. That is why the purpose of the work was to obtain new series of derivatives via combination of 1,3,4-thiadiazole, well-known heterocyclic pharmacophore, with hydrophobic (hetero)aromatic rings and hydrogen bonding groups such as amide groups. In new compounds the introduction of the secondary pharmacophores such as halogens (Cl, Br, CF₃), sulfonamide group, as well as another heterocycle (oxazole,

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furan, thiophene) may also contribute to the biological activity via synergistic effects.

MATERIAL AND METHODS

Melting points were determined on a Kofler bench. Elemental analysis has been done using Carlo Erba elemental analyzer. ^1H NMR spectra were recorded on Bruker DRX-500 spectrometer at 500 MHz using DMSO- d_6 as solvent and TMS as an internal standard. Infrared spectra were recorded for all compounds using a Nicolet (Thermo Fisher) Model 380 FTIR with an attenuated total reflectance (ATR) sampling device Smart Performer with a ZnSe crystal. The purity of synthesized compounds was confirmed by TLC using the plates Sorbfil and toluene–acetone–ethanol–ammonia (45:45:7:3) as the eluent.

General procedure for the synthesis of 5-R-carbonylamino-1,3,4-thiadiazol-2-thioles (2a-i).

60 ml of mother liquor (in which the reaction had been carried out already five times) and 0.1 mole of the corresponding acylated thiosemicarbazide **1a-i** were placed in apparatus equipped with stirrer, dropper, reflux condenser and an escape for gas. 6.0 ml (0.1 mole) of carbon disulfide was dropped in from a dropping container at 40°C during 4 hours. Then reaction mixture was heated at vigorous reflux for 1 hour (until vigorous gas development subsided). The process was monitored by TLC until exhaustion of the initial compounds. Reaction mixture is cooled down and solid product is filtered off with suction. All products **2a-i** were used in the further synthetic step without additional purification.

General procedure for the synthesis of 5-R-carbonylamino-1,3,4-thiadiazol-2-yl-sulfanylacetic acid derivatives (3a-k).

0.01 Mole of 5-R-carbonylamino-1,3,4-thiadiazol-2-thiole (**2a-i**), 0.01 mole of the corresponding chloroacetic acid amide (or ethyl ester), 0.84 g (0.015 mole) of potassium hydroxide in 50 ml of ethanol boil under the reflux for 1 hour. The process was monitored by TLC until exhaustion of the initial compounds. Reaction mixture is cooled down and the solid product is filtered off with suction. The product was purified by recrystallization from ethanol.

The IUPAC names of the synthesized compounds **3a-k** together with the interpretation of their

IR and ^1H NMR spectra, elemental analysis data, the melting points and the individual yields are presented below; the chemical structures are presented in Fig. 2.

3-(2-Chlorophenyl)-N-[5-({2-[(4-fluorophenyl)amino]-2-oxoethyl}sulfanyl)-1,3,4-thiadiazol-2-yl]-5-methyl-1,2-oxazole-4-carboxamide (3a). The yield is 76%. M.p. 182–184°C. $R_f=0.31$. $\text{C}_{21}\text{H}_{15}\text{ClFN}_5\text{O}_3\text{S}_2$. Found, %: N 13.98, S 12.76. Calculated, N 13.90, S 12.73%. IR (neat), ν , cm^{-1} : 3228 (N-H), 3076 (C-H ar), 2928 (C-H alk), 1672 (I amide), 1535, 1507, 1406, 1315, 1212, 1058, 834. ^1H NMR, δ , ppm: 2.71 (s, 3H, CH_3), 4.21 (s, 2H, CH_2), 7.16 (t, $J=8.82$ Hz, 2H, H_{ar}), 7.48–7.63 (m, 6H, H_{ar}), 10.39 (s, 1H, NH), 12.93 (s, 1H, NH).

3-(2-Chlorophenyl)-N-[5-({2-[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl}sulfanyl)-1,3,4-thiadiazol-2-yl]-5-methyl-1,2-oxazole-4-carboxamide (3b). The yield is 80%. M.p. 250–252°C. $R_f=0.16$. $\text{C}_{19}\text{H}_{16}\text{ClN}_7\text{O}_3\text{S}_3$. Found, %: N 18.83, S 18.45. Calculated, N 18.78, S 18.43%. IR (neat), ν , cm^{-1} : 3165 (N-H), 3030 (CH ar), 2907 (C-H alk), 1688 (I amide), 1564, 1324, 1061, 874, 758. ^1H NMR, δ , ppm: 1.15 (t, $J=7.38$ Hz, 3H, CH_2CH_3), 2.70 (s, 3H, CH_3), 3.84 (q, $J=7.38$ Hz, 2H, CH_2CH_3), 4.24 (s, 2H, CH_2), 7.17 (t, $J=8.80$ Hz, 2H, H_{ar}), 7.53–7.61 (m, 2H, H_{ar}), 10.39 (s, 1H, NH), 12.81 (s, 1H, NH).

2,5-Dichloro-N-[5-({2-[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl}sulfanyl)-1,3,4-thiadiazol-2-yl]benzamide (3c). The yield is 75%. M.p. 288–290°C. $R_f=0.30$. $\text{C}_{15}\text{H}_{12}\text{Cl}_2\text{N}_6\text{O}_2\text{S}_3$. Found, %: N 17.75, S 20.19. Calculated, N 17.68, S 20.23%. IR (neat), ν , cm^{-1} : 3167 (N-H), 3028 (C-H ar), 2925 (C-H_{alk}), 1682 (I amide), 1592, 1548, 1345, 1306, 1234, 1107, 966, 821. ^1H NMR, δ , ppm: 1.16 (t, $J=7.37$ Hz, 3H, CH_2CH_3), 3.84 (q, $J=7.36$ Hz, 2H, CH_2CH_3), 4.25 (s, 2H, CH_2), 7.62 (d, $J=8.08$ Hz, 1H, H_{ar}), 7.77 (dd, $J=8.08$, 1.81 Hz, 1H, H_{ar}), 8.10 (d, $J=1.80$ Hz, 1H, H_{ar}), 10.21 (s, 1H, NH), 13.02 (s, 1H, NH).

N-[5-({2-[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl}sulfanyl)-1,3,4-thiadiazol-2-yl]-2-methyl-3-nitrobenzamide (3d). The yield is 79%. M.p. 250°C (with decomposition). $R_f=0.46$. $\text{C}_{16}\text{H}_{15}\text{N}_7\text{O}_4\text{S}_3$. Found, %: N 21.14, S 20.76. Calculated, N 21.06, S 20.66%. IR (neat), ν , cm^{-1} : 3252 (N-H), 3086 (C-H ar), 2914 (C-H alk), 1683 (I amide), 1555, 1526, 1311, 1184, 727. ^1H NMR, δ , ppm: 1.15 (t, $J=7.38$ Hz, 3H,

CH₂CH₃), 2.43 (s, 3H, CH₃), 3.84 (q, *J*=7.38 Hz, 2H, CH₂CH₃), 4.25 (s, 2H, CH₂), 7.60 (t, *J*=7.78 Hz, 1H, H_{ar}), 7.90 (d, *J*=7.78 Hz, 1H, H_{ar}), 8.05 (d, *J*=7.78 Hz, 1H, H_{ar}), 10.75 (s, 1H, NH), 13.05 (s, 1H, NH).

N-[5-[(2-[(2,5-dimethylphenyl)amino]-2-oxoethyl)sulfanyl]-1,3,4-thiadiazol-2-yl]-2-methyl-3-nitrobenzamide (**3e**). The yield is 76%. M.p. 190-192°C. C₂₀H₁₉N₅O₄S₂. R_f=0.40. Found, %: N 15.39, S 14.04. Calculated, N 15.31, S 14.02%. IR (neat), ν, cm⁻¹: 3365 (N-H), 3070 (C-H ar), 2923 (C-H alk), 1686 (I amide), 1559, 1530, 1323, 1180, 762. ¹H NMR, δ, ppm: 2.17 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 4.25 (s, 2H, CH₂), 6.92 (d, *J*=7.27 Hz, 1H, H_{ar}), 7.10 (d, *J*=7.27 Hz, 1H, H_{ar}), 7.26 (s, 1H, H_{ar}), 7.59 (t, *J*=7.79 Hz, 1H, H_{ar}), 7.90 (d, *J*=7.79 Hz, 1H, H_{ar}), 8.06 (d, *J*=7.79 Hz, 1H, H_{ar}), 9.66 (s, 1H, NH), 13.34 (br. s, 1H, NH).

Ethyl {5-[(5-bromo-2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfanylacetate (**3f**). The yield is 74%. M.p. 158-160°C. R_f=0.44. C₁₃H₁₁BrClN₃O₃S₂. Found, %: N 9.70, S 14.74. Calculated, N 9.62, S 14.68%. IR (neat), ν, cm⁻¹: 3153 (N-H), 3060 (C-H ar), 2928 (C-H alk), 2782, 1731 (C=O ester), 1686 (I amide), 1561, 1332, 1300, 1174, 1030, 815. ¹H NMR, δ, ppm: 1.21 (t, *J*=7.01 Hz, 3H, CH₂CH₃), 4.16 (q, *J*=6.92 Hz, 2H, CH₂CH₃), 4.21 (s, 2H, CH₂), 7.57 (d, *J*=8.40 Hz, 1H, H_{ar}), 7.78 (dd, *J*=8.40, 2.18 Hz, 1H, H_{ar}), 7.98 (d, *J*=2.18 Hz, 1H, H_{ar}), 13.32 (br. s, 1H, NH).

Ethyl 4-[2-({5-[4-(dimethylsulfamoyl)benzamido]-1,3,4-thiadiazol-2-yl}sulfanyl)acetamido]benzoate (**3g**). The yield is 77%. M.p. 260-262°C. R_f=0.25. C₂₂H₂₃N₅O₆S₃. Found, %: N 12.80, S 17.56. Calculated, N 12.74, S 17.50%. IR (neat), ν, cm⁻¹: 3385 (N-H), 3036 (C-H ar), 2974 (C-H alk), 2919, 1702 (C=O ester), 1691 (I amide), 1526, 1332, 1310, 1294, 1275, 1163, 1105, 700. ¹H NMR, δ, ppm: 1.32 (t, *J*=7.05 Hz, 3H, CH₂CH₃), 2.60 - 2.74 (m, 6H, 2*CH₃), 4.26 - 4.35 (m, 4H, 2*CH₂), 7.74 (d, *J*=8.82 Hz, 2H, H_{ar}), 7.89-7.97 (m, 4H, H_{ar}), 8.32 (d, *J*=8.30 Hz, 2H, H_{ar}), 10.72 (s, 1H, NH), 13.41 (br. s, 1H, NH).

Ethyl 4-[2-({5-[2-(4-chlorophenoxy)acetamido]-1,3,4-thiadiazol-2-yl}sulfanyl)acetamido]benzoate (**3h**). The yield is 78%. M.p. 188-190°C. R_f=0.36. C₂₁H₁₉ClN₄O₅S₂. Found, %: N 11.12, S 12.69. Calculated, N 11.05, S 12.65%. IR (neat), ν, cm⁻¹: 3378 (N-H), 3085 (C-H ar), 2930 (C-H alk), 1705 (C=O ester), 1692 (I amide), 1556, 1331, 1300, 1261, 1140, 1123, 814. ¹H NMR, δ, ppm: 1.31 (t, *J*=7.04 Hz, 3H, CH₂CH₃),

4.21 (s, 2H, CH₂), 4.25 - 4.34 (m, 4H, 2*CH₂), 7.75 (d, *J*=8.78 Hz, 2H, H_{ar}), 7.79 (d, *J*=7.50 Hz, 2H, H_{ar}), 7.90-7.97 (m, 2H, H_{ar}), 8.28 (d, *J*=8.30 Hz, 2H, H_{ar}), 10.34 (s, 1H, NH), 13.40 (br. s, 1H, NH).

N-{5-[(2-[(2-chloro-5-(trifluoromethyl)phenyl)amino]-2-oxoethyl)sulfanyl]-1,3,4-thiadiazol-2-yl}-2-phenylacetamide (**3i**). The yield is 76%. M.p. 220-222°C. R_f=0.75. C₁₉H₁₄ClF₃N₄O₂S₂. Found, %: N 11.54, S 13.22. Calculated, N 11.51, S 13.17. IR (neat), ν, cm⁻¹: 3248 (N-H), 3036 (C-H ar), 2928 (C-H alk), 1673 (I amide), 1694 (I amide), 1673, 1557, 1530, 1331, 1135, 1120, 1081, 823. ¹H NMR, δ, ppm: 4.35 (s, 2H, CH₂), 4.47 (s, 2H, CH₂), 7.35-7.50 (m, 5H, H_{ar}), 7.58 (d, *J*=7.80 Hz, 1H, H_{ar}), 7.78 (d, *J*=7.80 Hz, 1H, H_{ar}), 8.23 (s, 1H, H_{ar}), 10.19 (s, 1H, NH), 13.12 (s, 1H, NH).

5-Bromo-*N*-{5-[(2-[(2-chloro-5-(trifluoromethyl)phenyl)amino]-2-oxoethyl)sulfanyl]-1,3,4-thiadiazol-2-yl}furan-2-carboxamide (**3j**). The yield is 77%. M.p. 248-250°C. R_f=0.31. C₁₆H₉BrClF₃N₄O₃S₂. Found, %: N 10.41, S 11.90. Calculated, N 10.34, S 11.84. IR (neat), ν, cm⁻¹: 3252 (N-H), 3035 (C-H ar), 2928 (C-H alk), 1699 (I amide), 1670 (I amide), 1524, 1334, 1306, 1124, 765. ¹H NMR, δ, ppm: 4.35 (s, 2H, CH₂), 7.57 (d, *J*=7.80 Hz, 1H, H_{ar}), 7.72 (d, *J*=1.00 Hz, 1H, H_{ar}), 7.78 (d, *J*=7.80 Hz, 1H, H_{ar}), 8.06 (d, *J*=1.00 Hz, 1H, H_{ar}), 8.23 (s, 1H, H_{ar}), 10.17 (s, 1H, NH), 13.13 (br. s., 1H, NH).

N-{5-[(2-[(2-chloro-5-(trifluoromethyl)phenyl)amino]-2-oxoethyl)sulfanyl]-1,3,4-thiadiazol-2-yl}thiophene-2-carboxamide (**3k**). The yield is 79%. M.p. 220-222°C. R_f=0.35. C₁₆H₁₀ClF₃N₄O₂S₃. Found, %: N 11.75, S 20.13. Calculated, N 11.70, S 20.09%. IR (neat), ν, cm⁻¹: 3265 (N-H), 3204 (N-H), 3042 (C-H ar), 2922 (C-H alk), 1671 (I amide), 1648 (I amide), 1530, 1332, 1304, 1263, 1173, 1113, 853, 719. ¹H NMR, δ, ppm: 4.36 (s, 2H, CH₂), 7.29 (t, *J*=4.15 Hz, 1H, H_{ar}), 7.58 (d, *J*=8.30 Hz, 1H, H_{ar}), 7.78 (d, *J*=8.30 Hz, 1H, H_{ar}), 8.03 (d, *J*=3.63 Hz, 1H, H_{ar}), 8.23 (s, 1H, H_{ar}), 8.30 (d, *J*=3.63 Hz, 1H, H_{ar}), 10.20 (s, 1H, NH), 13.25 (br. s., 1H, NH).

RESULTS AND DISCUSSION

A series of 5-R-carbonylamino-1,3,4-thiadiazol-2-thioles (**2a-i**) has been obtained by reaction of thiosemicarbazides **1a-i** with carbon disulfide in aqueous solution that contains 1570% of an ammonium salt of the corresponding bis-2,5-dimercapto-1,3,4-thiadiazole (mother liquor of previous reac-

tions) (Fig. 1). Reaction was carried out under reflux for 5 hours, and, as a result, the semi-products **2a-i** were obtained in high yields (80-85%).

It is known that alkylation of mercapto group of 1,3,4-thiadiazoles with various reagents is carried out in DMF/K₂CO₃ (14), EtOH/KOH (15,16), EtOH/

S-alkylation. The methylene group chemical shifts range from 4.21 ppm to 4.35 ppm. Signals of (hetero)aromatic and aliphatic substituents (R₁ and R₂) are in accordance with the structures of the obtained compounds.

In IR spectra of the products **3a-k** weak N-H

Fig. 1. General scheme of synthesis of 5-R-carbonylamino-1,3,4-thiadiazol-2-thioles **2a-i**.

CH₃COONa, THF/NaOH (1), DMF/KOH (17), DMF/NaH (18), EtOH/Et₃N (19). In our case the reaction of 5-R-amino-2-mercapto-1,3,4-thiadiazoles (**2a-i**) with ethyl ester and different amides of chloroacetic acid was successfully performed in ethanol solution in the presence of potassium hydroxide (Fig. 2).

The synthesized compounds **3a-k** are white crystalline substances that are soluble in ethanol, DMF and insoluble in water. The structure assignment of these compounds was established by elemental analysis, ¹H NMR and IR spectroscopy data.

In ¹H NMR spectra of the target compounds peaks between 10.17 ppm to 10.75 ppm correspond to the protons of amide group on C-2 position of thiadiazole ring. The singlet of amide group introduced at the last step appeared from 12.81 ppm to 13.43 ppm. Signal of proton of mercapto group around 13.2 ppm is not shown in the products **3ak**, that proves

band in the 3385-3135 cm⁻¹, alkyl CH stretching band in the 2928-2921 cm⁻¹, aromatic C-H stretching band in the 3060-3035 cm⁻¹ are observed. The strong band recorded at 1698-1648 cm⁻¹ belongs to the carbonyl in the amide moiety of the side chain (amide I). The spectra of the compounds **3f**, **3g**, **3h** contain the strong band in the 1731-1702 cm⁻¹ which proves the CO double bond of their ester groups. In spectra of the compounds **3i-k** the strong N-H bands are presented that might be due to the Hbond formation between chlorine atom and NH group.

To predict spectrum of biological activities for new compounds the computer program PASS was used (20). The biological activities with probability values are enlisted in Table 1. It could be seen that most of the predicted inhibitory properties are associated with antiproliferative activity (21,22). For example, signal transducers and activators of transcrip-

Fig. 2. General scheme of synthesis of 5-R-carbonylamino-1,3,4-thiadiazol-2-yl-sulfanylacetic acid derivatives **3a-k**.

Table 1. Data of PASS prediction for compounds **3a-k**.

Compound	Activity predicted						
	Transcription factor STAT3 inhibitor	Transcription factor STAT inhibitor	Cytidine deaminase inhibitor	Mcl-1 antagonist	Transcription factor inhibitor	Calpain inhibitor	Cl-transporting ATPase inhibitor
3a	0.862	0.889	-	-	0.632	-	-
3b	0.603	0.598	-	-	-	-	-
3c	0.791	0.754	0.511	0.745	0.547	-	0.586
3d	0.785	0.740	0.581	0.788	0.574	0.555	-
3e	0.837	0.815	0.720	0.695	0.599	0.583	-
3f	0.707	0.657	-	-	-	-	0.541
3g	0.888	0.894	0.716	-	0.690	0.577	-
3h	0.576	0.555	-	0.606	-	-	0.575
3i	0.715	0.730	-	-	0.639	-	-
3j	-	-	0.546	-	0.635	-	0.521
3k	0.877	0.898	0.586	0.573	0.789	-	-

tion (STAT) inhibitors are widely discussed as important agents for cancer therapy (23). Abnormal activation of STAT signaling pathways is also implicated in inflammation, neurodegenerative diseases and auto-immunity (24,25). These data give us the reason to plan our further pharmacological investigation of the synthesized compounds **3a-k** as anti-cancer agents.

Recent investigations proved that 1,3,4-thiadiazoles possessed potent anticonvulsant activity in wide range preclinical *in vitro* and *in vivo* models (26). Thus, the reviewed literature data about 2-amino-5-mercapto-1,3,4-thiadiazole derivatives as anticonvulsant agents as well as results of our previous studies (27) allow us to anticipate their anticonvulsant properties that are tested at the moment.

CONCLUSION

New scaffold which represented by 2-amino-5-mercapto-1,3,4-thiadiazole basic structure bearing various substituents on both amino and mercapto groups has been proposed for perspective biologically active compounds. The effective method of their obtaining was developed via two-steps procedure that includes heterocyclization of acylated thiosemicarbazides with carbon disulfide and further alkylation of the intermediate 5-R-amino-1,3,4-thiadiazole-2-thioles. It opens the way to libraries of such derivatives through variation of alkylating reagents. The structures of the synthesized compounds were proved by elemental analysis, ¹H NMR and IR spectroscopy; their purity was determined by TLC. New 5-R-carbonylamino-1,3,4-thiadiazol-2-yl-sulfanyl-acetic acid derivatives are proposed as promising anticonvulsant and anti-cancer agents.

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