Synthesis and spectral characteristics of *N*-(2,2,2-trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides

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In this work, we present the synthesis of a new series of 5-amino-1,3,4-thiadiazole-2-thiols containing a pharmacophore alkylamide fragment. The synthesis involved reacting the starting *N*-(2,2,2-trichloro-1-(2-(phenylcarbamothioyl)hydrazine-1-carbothioamido)ethyl)carboxamides with methyl iodide in ethanol under heating. The reaction proceeded through an *N,S*-alkylation step, followed by cyclization, which formed the thiadiazole ring. Yields ranged from 58% to 67%. The structures of the obtained compounds were confidently confirmed by spectral methods. The ^{1}H NMR spectra displayed clear signals for two NH protons (9.69-9.09 and 8.75-8.54 ppm), the methine proton of the alkylamide fragment (6.89-6.72 ppm), and the methylthiol group (2.64-2.62 ppm). In ^{13}C NMR spectra, characteristic signals included the carbon of the carboxamide group (169.0-166.5 ppm), the C=N atoms of the thiadiazole ring (166.5-155.1 ppm), the carbon of the CCl_3 group (101.0-100.7 ppm), the methine atom of the alkylamide fragment (70.3-69.9 ppm), and the methylthiol carbon (16.4 ppm).

Introduction

In recent years, there has been a steady rise in scientific interest in compounds with heterocyclic systems containing nitrogen and sulfur atoms. One of the most prominent examples of such structures is derivatives of 1,3,4-thiadiazole. The presence of a sulfur atom in these compounds determines the optimal level of lipophilicity, which helps ensure effective penetration through biological membranes and, consequently, high bioavailability [1-3]. Due to these properties, 1,3,4-thiadiazoles and their derivatives are widely used as key structural fragments in the development of biologically active molecules with a diverse range of therapeutic effects [1-5]. Among these derivatives, compounds with strong anti-inflammatory [6-9], anticonvulsant [10], diuretic [11,12], antidiabetic [13,14], antihyperlipidemic [15], and other pharmacological activities have been reported [1-5]. Important biological targets for 1,3,4-thiadiazole derivatives include

glycogen synthase kinase-3β [16], α-glucosidase [17], tyrosinase [18], urease [19], and acetyl- and butyrylcholinesterase [20], as well as telomerase [21], along with other enzymes and receptors that play crucial roles in regulating physiological processes [1-5]. Additionally, it has been shown that some compounds in this class exhibit significant antiviral [3], antitumor [3], and antibacterial [22,23] activities.

The use of 1,3,4-thiadiazole derivatives extends beyond the medical field. In agriculture, they are employed as pesticides [1], while in industry, they serve as catalysts [24], components of lithium-ion batteries [25], elements of polymeric materials [26, 27], films [28], and dyes [29, 30]. Notably, 1,3,4-thiadiazoles are considered promising semiconductor materials [31].

Several methods have been developed for synthesizing 1,3,4-thiadiazoles [1]. The most common methods include intramolecular cyclization of *N,N'*-diacylhydrazines, thiosemicarbazides, and dithiobisureas, as well as various types of intermolecular cyclization [1,32]. This work details the synthesis of some 5-amino-1,3,4-thiadiazole-2-thiol derivatives that contain an alkylamide fragment. It is known that compounds with an alkylamide fragment exhibit significant biological activity [33-37]. Combining this fragment with a 1,3,4-thiadiazole ring within a single molecule offers opportunities to develop new substances with a broad range of pharmacological effects.

Experimental part

Material and methods

NMR spectra of ^{1}H and ^{13}C were recorded for solutions of the studied compounds in DMSO-d_6. The spectra were taken at external magnetic field strengths of 400 MHz and 100 MHz, respectively, using a Varian VXR-400 spectrometer. Residual solvent signals served as internal standards. IR spectra were recorded in KBr tablets on a Spectrum BX II instrument. Elemental analysis was performed with a LECO CHNS-900 instrument. Melting points were measured in open capillaries using an Electrothermal 9100 Digital Melting Point instrument; the values obtained were not corrected. R_f determination, reaction monitoring, and purity assessment of the synthesized compounds were conducted via thin-layer chromatography on Silufol UV-254 plates, using a mixture of chloroform and acetone in a 3:1 ratio as the eluent.

Synthesis

Synthesis of N-(2,2,2-trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides (3a-d). A threefold excess of methyl iodide was added to a suspension of 10 mmol of dithiourea **1a-d** [38] in 50 mL of ethanol. The mixture was refluxed for 30 minutes and then kept at 20°C for 24 hours. The resulting precipitate was filtered, washed with 15 mL of chilled ethanol, and purified by recrystallization from methanol.

N-(2,2,2-Trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)cinnamamide (3a). White crystals, yield 58% (2.46 g); m.p.: 222-224 °C (MeOH); R_f = 0.24. IR (KBr) ν_{max}: 3407, 3270, 3237, 3184 (NH), 3098, 3003, 2986, 2919, 2853, 2866 (CH), 1661 (C=O), 1630, 1564, 1519, 1469, 1345, 1194, 1108, 1023, 994, 984, 866, 825, 768, 718, 680, 628, 585, 553, 514, 485 cm^{-1}. NMR ^1H (DMSO-d_6), δ, ppm: 9.09 (d, *J* = 8.8 Hz, 1H, NH), 8.75 (d, *J* = 9.3 Hz, 1H, NH), 7.59-7.54 (m, 3H, $2H_{arom.}$+$C_6H_5C\underline{H}$=CH), 7.45-7.38 (m, 3H, $H_{arom.}$), 6.90 (d, *J* = 15.7 Hz, 1H, C_6H_5CH=$C\underline{H}$), 6.79 (dd, *J* = 8.8, 9.3 Hz, 1H, CH), 2.62 (s, 3H, SCH_3). NMR ^{13}C (DMSO-d_6), δ, ppm: 166.5 (C=O), 164.8 (C=N), 155.1 (C=N), 141.1 ($C_6H_5\underline{C}$H=CH), 134.5, 129.9, 129.0, 127.7 ($C_{arom.}$), 120.7 (C_6H_5CH=$\underline{C}$H), 100.9 (CCl_3), 69.9 (CH), 16.4 (SCH_3). Anal. Calcd (%) for: $C_{14}H_{13}Cl_3N_4OS_2$ (423.76): C, 39.68; H, 3.09; N, 13.22; S, 15.13. Found: C, 39.61; H, 3.12; N, 13.28; S, 15.19.

N-(2,2,2-Trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (3b). White crystals, yield 62% (2.47 g); m.p.: 232-234 °C (MeOH); R_f = 0.53. IR (KBr) ν_{max}: 3434, 3298 (NH), 3069, 3000, 2979, 2926, 2853, 2813 (CH), 1652 (C=O), 1602, 1580, 1541, 1505, 1483, 1434, 1418, 1341, 1272, 1233, 1203, 1140, 1116, 1091, 1054, 1026, 984, 970, 877, 841, 815, 767, 690, 676, 635, 569, 521, 458 cm^{-1}. NMR ^1H (DMSO-d_6), δ, ppm: 9.36 (d, *J* = 8.3 Hz, 1H, NH), 8.54 (d, *J* = 9.3 Hz, 1H, NH), 7.87 (d, *J* = 7.3 Hz, 2H, $H_{arom.}$), 7.60-7.57 (m, 1H, $H_{arom.}$), 7.52-7.48 (m, 2H, $H_{arom.}$), 6.89 (dd, *J* = 9.3, 8.3 Hz, 1H, CH), 2.62 (s, 3H, SCH_3). NMR ^{13}C (DMSO-d_6), δ, ppm: 166.8 (C=O), 166.5 (C=N), 155.7 (C=N), 133.0, 132.1, 128.4, 127.7 ($C_{arom.}$), 100.9 (CCl_3), 70.3 (CH), 16.4 (SCH_3). Anal. Calcd (%) for: $C_{12}H_{11}Cl_3N_4OS_2$ (397.72): C, 36.24; H, 2.79; N, 14.09; S, 16.12. Found: C, 36.29; H, 2.72; N, 14.13; S, 16.20.

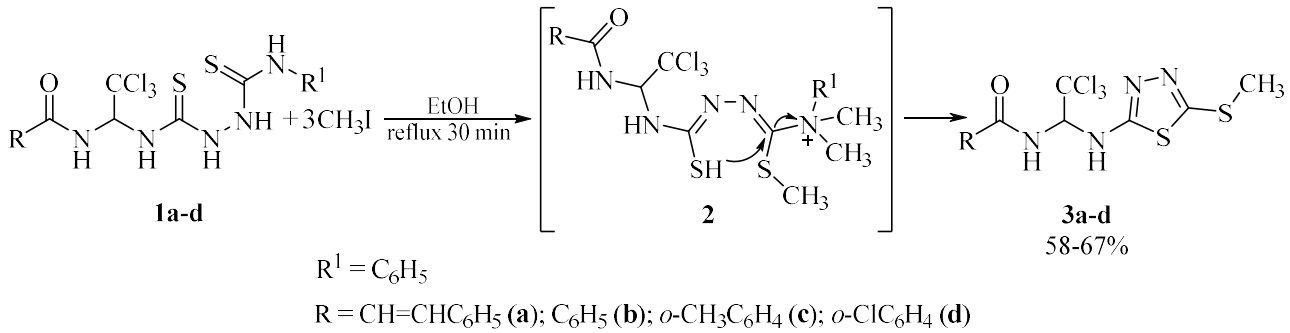
2-Methyl-N-(2,2,2-trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (3c). White crystals, yield 65% (2.68 g); m.p.: 226-228 °C (MeOH); R_f = 0.58. IR (KBr) ν_{max}: 3388, 3259 (NH), 3097, 3005, 2961, 2925, 2854 (CH), 1656 (C=O), 1557, 1511, 1467, 1416, 1377, 1328, 1273, 1216, 1152, 1114, 1026, 971, 817, 740, 691, 627, 581, 519 cm^{-1}. NMR ^1H (DMSO-d_6), δ, ppm: 9.43 (d, *J* = 8.8 Hz, 1H, NH), 8.63 (d, *J* = 9.3 Hz, 1H, NH), 7.38-7.23 (m, 4H, $H_{arom.}$), 6.83 (dd, *J* = 8.8, 9.3 Hz, 1H, CH), 2.64 (s, 3H, SCH_3), 2.33 (s, 3H, CH_3). NMR ^{13}C (DMSO-d_6), δ, ppm: 169.0 (C=O), 166.5 (C=N), 155.3 (C=N), 135.9, 130.4, 129.7, 127.2, 125.4 ($C_{arom.}$), 101.0 (CCl_3), 70.0 (CH), 19.3 (CH_3), 16.4 (SCH_3). Anal. Calcd (%) for: $C_{13}H_{13}Cl_3N_4OS_2$ (411.74): C, 37.92; H, 3.18; N, 13.61; S, 15.57. Found: C, 37.86; H, 3.11; N, 13.70; S, 15.62.

2-Chloro-N-(2,2,2-trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)benzamide (3d). White crystals, yield 67% (2.90 g); m.p.: 200-202 °C (MeOH); R_f = 0.51. IR (KBr) ν_{max}: 3434, 3252 (NH), 3094,

3003, 2925, 2853 (CH), 1663 (C=O), 1593, 1557, 1515, 1467, 1434, 1415, 1327, 1291, 1274, 1260, 1214, 1125, 1110, 1099, 1054, 1026, 968, 945, 884, 838, 817, 781, 745, 721, 690, 649, 626, 577, 519, 491, 462 cm^{-1}. NMR ^1H (DMSO-d_6), δ, ppm: 9.69 (d, *J* = 8.8 Hz, 1H, NH), 8.71 (d, *J* = 9.3 Hz, 1H, NH), 7.52-7.38 (m, 4H, $H_{arom.}$), 6.84 (dd, *J* = 9.3, 8.8 Hz, 1H, CH), 2.64 (s, 3H, SCH_3). NMR ^{13}C (DMSO-d_6), δ, ppm: 166.5 (C=O), 166.3 (C=N), 155.2 (C=N), 135.7, 131.2, 130.0, 129.6, 129.0, 127.0 ($C_{arom.}$), 100.8 (CCl_3), 69.9 (CH), 16.4 (SCH_3). Anal. Calcd (%) for: $C_{12}H_{10}Cl_4N_4OS_2$ (432.16): C, 33.35; H, 2.33; N, 12.96; S, 14.84. Found: C, 33.30; H, 2.39; N, 13.01; S, 14.92.

Results and discussion

The starting *N*-(2,2,2-trichloro-1-(2-(phenylcarbamothioyl)hydrazine-1-carbothioamido)ethyl)carboxamides (**1a-d)** were previously obtained using the method described in [38]. When compounds **1a-d** reacted with methyl iodide in ethanol, they formed the corresponding *N*-(2,2,2-trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides (**3a-d**). This reaction was performed under reflux for 30 minutes. It most likely proceeded through an *N,S*-alkylation step, producing intermediate **2**. Subsequently, the SH group attacked the sp^2 hybridized carbon atom, leading to the elimination of the tertiary amine and the formation of the 1,3,4-thiadiazole ring (see Scheme 1). The yields of the reaction products ranged from 58% to 67%.



Scheme1. Synthesis of *N*-(2,2,2-trichloro-1-((5-(methylthio)-1,3,4-thiadiazol-2-yl)amino)ethyl)carboxamides. (**3a-d**).

^1H, ^{13}C NMR and IR spectroscopic data confirmed the structure of the synthesized compounds. In the ^1H NMR spectra of compounds **3a-d**, the signals of two NH protons, the CH of the alkylamide fragment, and the methylthiol group were characteristic. The amine and amide NH protons appeared as doublets in the regions of 9.69-9.09 and 8.75-8.54 ppm, respectively. The methine proton of the alkylamide fragment appeared as a doublet-doublet at 6.89-6.72 ppm, and the protons of the methylthiol group appeared as a singlet at 2.64-2.62 ppm. In the ^{13}C NMR spectra, the signals of the carbon atom of the carboxamide group,

which appeared in the region of 169.0-166.5 ppm, as well as the signals of two C=N bonds of the thiadiazole ring, which appeared at 166.5-155.1 ppm, were characteristic. The signals of the carbon atoms of the CCl_3 group and the CH of the alkylamide fragment appeared at 101.0-100.7 ppm and 70.3-69.9 ppm, respectively. The signal of the carbon atom of the methylthiol group was observed at approximately 16.4 ppm. In the IR spectra of compounds **3**, intense broad bands are observed in the 3435-3100 cm^{-1} region, corresponding to the N-H stretching vibrations, as well as a band at 1665-1650 cm^{-1} assigned to the C=O group.

Conclusions

We can conclude that we have developed a preparative method for synthesizing new amidoalkylated derivatives of 5-amino-1,3,4-thiadiazole-2-thiol **3** at the exocyclic nitrogen atom. Comprehensive spectral studies have reliably confirmed the structure of these synthesized compounds. The substances obtained are promising candidates for exploring their potential applications in the synthesis of fused heterocycles, as well as in pharmacy and medicine.

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