Bulgarian Chemical Communications, Volume 51, Issue 1, (pp. 73 – 79) 2019

Synthesis and biological activity of 2-alkylthio-5-(4-N-acetyl(N-chloroacetyl)aminophenyl)-1,3,4-oxadiazoles

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Received November 3, 2017; Revised November 13, 2018

New 2-alkylthio-5-(4-N-acetyl(N-chloroacetyl)aminophenyl)-1,3,4-oxadiazoles were synthesized. Optimal conditions for the synthesis were found. The physicochemical characteristics and structures of the synthesized compounds were established. On the example of compound **10** we carried out X-ray diffraction analysis (XRD). The antibacterial and antifungal activities of these compounds were investigated. The screening results showed that 2-alkylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazoles of **17**,**18**,**21**,**22** display an appreciable antibacterial activity against Gram-positive bacteria of *Bacillus subtilis* and *Staphylococcus aureus.*

Keywords: 2-alkylthio-5-(4-N-acetyl(N-chloroacetyl)aminophenyl)-1,3,4-oxadiazoles, X-ray analysis, crystal structure, antibacterial and antifungal activity.

INTRODUCTION

One of the most interesting representatives of five-membered heterocyclic compounds - 5-substituted-1,3,4-oxadiazole-2-thiones, along with great practical significance (a number of oxadiazolethione derivatives possess pesticide, pharmacological and other biological activities) represent theoretical interest for studying the relationship "structure - biological activity", which is well described in the reviews [1-4] and partly in our earlier work [5-8]. In contrast to the other oxadiazoliones, which we studied earlier [6,9,10], 5-(4-aminophenyl)-1,3,4-oxadiazol-2-thione, in addition to the two reaction centers (sulfur and nitrogen atoms) in the thioamide group NH-C=S has another reaction center - amino group in position 4 of the aromatic ring. It is known that the good reactivity of the amino group allows for carrying out chemical transformations with the formation of compounds with different substituents possessing different properties, including biological ones. A study of the literature showed that such compounds show appreciable biological activity. However, the data on such transformations and biological activity related to 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiones turned out to be very limited [11-13].

EXPERIMENTAL

IR spectra of the synthesized compounds were recorded on a Perkin Elmer-2000 Fourier spectrometer using KBr pellets, UV spectra recorded on a Perkin Elmer Lambda-16 spectrometer in ethanol. ^{1}H NMR spectra were recorded on the Unity-400+ spectrometer (400 MHz, $CDCl_3$ solvent, HMDS internal standard) at 20-25°C. The reactions and individuality of the synthesized compounds were monitored by TLC on Merck silicagel 60F254 plates using 10:1 $CHCI_3$-EtOH solvent system; developed plates were visualised under UV lamp and iodine tank, where necessary. The melting point of all synthesized substances was determined on a "Boetius" apparatus.

The unit cell parameters of the crystals were determined and refined with CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα-radiation, graphite monochromator (T=293 K).

Crystal growth. Single crystal of 2-butylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole **10** was grown from solutions of acetone by slow evaporation at room temperature.

X-ray structure determination. The unit cell parameters of the crystal were determined and refined with CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα-radiation, graphite monochromator (T=293 K). The three-dimensional set of reflections was obtained using the appropriate diffractometer. The amendment was introduced to the absorption by Multi-scan [14]. Table 1 shows the main parameters of the X-ray diffraction experiment and refinement calculations of the structure **10**.

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Table 1. Basic crystallographic parameters and characteristics of the X-ray diffraction for structure **10**.

Compound	10
Molecular formula	$C_{14}H_{17}N_3O_2S$
Mr	291.36
Crystal symmetry	Orthorhombic
Space group	Pbca
Z	8
a, Å	9.8091(3)
b, Å	9.2603(4)
c, Å	32.1709(14)
α, °	90
β, °	90
γ, °	90
V, $Å^3$	2922.2(2)
ρ, g/cm^3	1.325
Crystal dimension (mm)	0.35×0.48×0.55
Range scanned, 2θ°	5.282≤θ≤ 76.248o
μexp (cm^{-1})	2.017
No. reflection collected	3026
No. reflection with I>2σ(I)	2024
R1 (I>2σ(I) and total)	0.0457 (0.0772)
wR^2	0.1061 (0.1250)
GOOF	1.028
Largest diff. peak and hole (e $Å^{-3}$)	0.180 and –0.190
CCDC	1554510

The structure was solved by direct methods using SHELXS-2014 and refined using SHELXL-2014 programs [15]. All non-hydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters Uiso=nUeq, where n=1.5 for methyl hydrogens and 1.2 for others and Ueq is the equivalent isotropic thermal parameter of the corresponding C atoms.

Materials X-ray diffraction as a CIF file were deposited at the Cambridge center of crystal data (CCDC), from which they can be obtained free on request at the following link: www.ccdc.cam.ac.uk/data_request/cif (CCDC number is 1554510).

Antimicrobial assay. The synthetic compounds were tested for antimicrobial activity by the agar disk-diffusion method [16-18]. The antimicrobial activity was evaluated using five species of microorganisms: Gram-positive bacteria *Bacillus subtilis* (RKMUz - 5) and *Staphylococcus aureus* (ATCC 25923); Gram-negative bacteria *Escherichia coli* (RKMUz - 221) and *Pseudomonas aeruginosa* (ATCC 27879) and the fungus *Candida albicans* (RKMUz - 247). The RKMUz microorganism cultures were obtained from the strain collection of the Institute of Microbiology, Academy of Sciences of the Republic of Uzbekistan. Sterile nutrient agar (25 g agar/l distilled water) was inoculated with bacterial cells (200 μl of bacterial cell in 2 ml of 0.9% NaCl suspension and 20 ml medium) and poured into Petri dishes to give a solid medium. *Candida albicans* ($1×10^6$ colony forming units per ml) was inoculated into sterile Mueller-Hinton-agar. Forty microliters of test material (0.2 mg/per disc of the compounds) was applied on sterile paper discs (Whatman No 1, 6 mm diameter). Ampicillin, ceftriaxone and nystatin (20 μg/disc) were used as positive controls and the solvents as negative controls. The solvents were allowed to evaporate in a stream of air. The discs were deposited on the surface of the inoculated agar plates. Plates were kept for 3 h in a refrigerator to enable the diffusion of the substances into the agar. Plates with bacteria were incubated for 24 h at 37°C and plates with yeasts for 48 h at 26°C. The inhibition zone (including the disc diameter) was measured and recorded after the incubation time. An average zone of inhibition was calculated for the three replicates in independent assays.

Interaction of 2-alkylthio-5-(p-aminophenyl)-1,3,4-oxadiazoles with acetyl and chloroacetyl chlorides (general procedure). 2-Alkylthio-5-(4-aminophenyl)-1,3,4-oxadiazole [8] (0.01 mol) was dissolved in 15 mL of benzene with continuous stirring, then triethylamine (0.015 mol) was added. A solution of acetyl chloride (0.011 mol) or chloroacetylchloride in 10 mL benzene was added dropwise to the resulting mixture at room

temperature. HCI was isolated as a white haze, the reaction mixture was left overnight, and then the resulting precipitate was filtered, washed with benzene, an alkali solution and water.

2-Propylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (9). Yield 97%, mp 166-167 °C, R_f = 0.46; UV spectrum (λ_{max}, nm): 298.9; ^{1}H NMR (δ, ppm, J/Hz): 0.99 (3H, t, J = 7.3, CH_3), 1.79 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.06 (3H, s, CH_3-CO), 3.24 (2H,t, J = 7.1, S-CH_2), 7.77 (2H, d, J = 8.8, H-3,5), 7.87 (2H, d, J = 8.9, H-2,6), 9.40(1H, brs, NH). IR spectrum(ν, cm^{-1}): 1694 (CH_3CO), 1523 (NH), 1179 (C-O-C, oxadiazole).

2-Butylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (10). Yield 89%, mp 162-163 °C, R_f = 0.51; UV spectrum(λ_{max}, nm): 298.7; ^{1}H NMR (δ, ppm, J/ Hz): 0.59 (3H, t, J = 7.4, CH_3), 1.15 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.49 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 1.98 (3H, CH_3-CO), 3.71 (2H, t, J = 7.3, S-CH_2) 7.45 (2H, d, J = 8.6, H-3,5), 7.68 (2H, d, J = 8.6, H-2, 6), 9.40 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1668 (CH_3CO), 1537 (NH), 1176 (C-O-C, oxadiazole).

2-Amylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (11). Yield 92%, mp 135-136 °C, R_f = 0.46; UV spectrum(λ_{max}, nm): 299.2; ^{1}H NMR (δ, ppm, J/Hz): 0.84 (3H, t, J = 7.3, CH_3), 1.36 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.78 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 2.06 (3H, s, CH_3-CO), 3.26 (2H, t, J = 7.3, S-$C\underline{H}_2CH_2CH_2CH_2CH_3$), 7.77 (2H, d, J = 8.9, H-3, 5), 7.88 (2H, d, J = 8.9, H-2, 6), 9.42 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1674 (CH_3CO), 1536 (NH), 1173 (C-O-C, oxadiazole).

2-iso-Amylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (12). Yield 95%, mp 128-129 °C, R_f = 0.51; UV spectrum(λ_{max}, nm): 298.6; ^{1}H NMR (δ, ppm, J/Hz): 0.95 (6H, d, d, J = 7.3, J = 7.3, $2CH_3$), 1.64 (3H, m, $C\underline{H}_2C\underline{H}(CH_3)_2$), 2.08 (3H, s CH_3-CO), 3.27 (2H, t, J = 7.9, S-$C\underline{H}_2CH_2CH(CH_3)_2$), 7.77 (2H, d, J = 8.7, H-3, 5), 7.87 (2H, d, J = 8.7, H-2, 6), 9.48 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1676 (CH_3CO), 1542 (NH), 1174 (C-O-C, oxadiazole).

2-Hexylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (13). Yield 98%, mp 130-131 °C, R_f = 0.48; UV spectrum(λ_{max}, nm): 298.7; ^{1}H NMR (δ, ppm , J/Hz): 0.82 (3H, t, J = 7.1, CH_3), 1.27 (4H, m, $C\underline{H}_2CH_2CH_3$), 1.42 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 1.77 (2H, m, $C\underline{H}_2(CH_2)_3CH_3$), 2.06 (3H, s, CH_3-CO), 3.26 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_4CH_3$), 7.76 (2H, d, J = 8.9, H-3, 5), 7.87 (2H, d, J = 8.8, H-2, 6), 9.40 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1707 (CH_3CO), 1532 (NH), 1174 (C-O-C, oxadiazole).

2-Heptylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (14). Yield 98%, mp 105-106 °C, R_f = 0.51; UV spectrum(λ_{max}, nm): 299.5; ^{1}H NMR (δ, ppm J/Hz): 0.81 (3H, t, J = 6.7, CH_3), 1.24 (6H, m, $C\underline{H}_2C\underline{H}_2CH_2CH_3$), 1.42 (2H, m, $C\underline{H}_2(CH_2)_3CH_3$), 1.78 2H, m, $C\underline{H}_2(CH_2)_4CH_3$), 2.06 (3H, s, CH_3-CO), 3.26 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_5CH_3$), 7.78 (2H, d, J = 8.8 , H-3, 5), 7.86 (2H, d, J = 8.8, H-2, 6), 9.42 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1702 (CH_3CO), 1535 (NH), 1174 (C-O-C, oxadiazole).

2-Octylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (15). Yield 97%, mp 112-113 °C, R_f = 0.53; UV spectrum(λ_{max}, nm): 300.1; 1H NMR(δ, ppm, J/Hz): 0.80 (3H, t, J = 6.6, CH_3), 1.22 (8H, m, $C\underline{H}_2(C\underline{H}_2)_3CH_3$), 1.42 (2H, $C\underline{H}_2(CH_2)_4CH_3$), 1.78 (2H, m, $C\underline{H}_2(CH_2)_5CH_3$), 2.06 (3H, s, CH_3-CO), 3.27 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_6CH_3$), 7.77 (2H, d, J = 8.9, H-3, 5), 7.86 (2H, d, J = 8.8, H-2, 6), 9.42 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1698 (CH_3CO), 1530 (NH), 1176 (C-O-C, oxadiazole).

2-Nonylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole (16). Yield 97%, mp 151-116 °C, R_f = 0.49; UV spectrum (λ_{max}, nm): 298.9; ^{1}H NMR (δ, ppm, J/Hz): 0.80 (3H, t, J = 6.7, CH_3), 1.22 (10H, m, $C\underline{H}_2(C\underline{H}_2)_4CH_3$), 1.42 (2H, m, $C\underline{H}_2(CH_2)_5CH_3$), 1.78 (2H, m, $C\underline{H}_2(CH_2)_6CH_3$), 2.06 (3H, s, CH_3-CO), 3.27 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_7CH_3$), 7.77 (2H, d , J = 8.7, H-3, 5), 7.86 (2H, d, J = 8.8, H-2, 6) 9.41 (1H, brs, NH). IR spectrum(ν, cm^{-1}): 1697 (CH_3CO), 1529 (NH), 1178 (C-O-C, oxadiazole).

2-Propylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (17). Yield 85%, mp 111-112 °C, R_f = 0.66; UV spectrum (λ_{max}, nm): 297.7; ^{1}H NMR (δ, ppm, J/Hz): 1.01 (3H, t, J = 7.3, CH_3), 1.81 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.21 (2H, t, J = 7.1, S-CH_2) 4.16 (2H, s, CH_2-CO), 7.67 (2H, d, J = 8.7, H-3,5), 7.93 (2H, d, J = 8.8, H-2,6), 8.43 (1H, brs, NH). IR spectrum (ν, cm^{-1}): 1703 (-CH_2CO), 1537 (NH), 1177 (C-O-C, oxadiazole).

2-Butylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (18). Yield 96%, mp 142-143 °C, R_f = 0.60; UV spectrum (λ_{max}, nm): 301.5; ^{1}H NMR δ, ppm J/Hz): 0.90 (3H, t, J = 7.3, CH_3), 1.43 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.76 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 3.20 (2H, t, J = 7.3, S-CH_2), 4.16 (2H, s, CH_2-CO), 7.66 (2H, d, J = 8.5, H-3, 5), 7.93 (2H, d, J = 8.9, H-2, 6), 8.41 (1H, brs, NH). IR spectrum (ν, cm^{-1}: 1675 (-CH_2CO), 1550 (NH), 1176 (C-O-C, oxadiazole).

2-Amylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (19). Yield 98%, mp 165-166 °C, R_f = 0.63; UV spectrum(λ_{max}, nm): 298.8; ^{1}H NMR (δ, ppm, J/Hz): 0.84 (3H, t, J = 7.3, CH_3), 1.34 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.78 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 3.23 (2H, t, J = 7.3, S-$C\underline{H}_2CH_2CH_2CH_2CH_3$), 4.23 (2H, s, CH_2-CO), 7.83 (2H, d, J = 8.7, H-3,5), 7.89 (2H, d, J = 8.8, H-2, 6), 9.75 (1H, brs, NH). IR spectrum (ν, cm^{-1}): 1659 (-CH_2CO), 1540 (NH), 1176 (C-O-C, oxadiazole).

2-Hexylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (20). Yield 93%, mp 107-108 °C, R_f =0.57; UV spectrum(λ_{max}, nm): 298.3; 1H NMR δ, ppm, J/Hz): 0.82 (3H, t, J = 7.1, CH_3), 1.27 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.42 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 1.78 (2H, m, $C\underline{H}_2(CH_2)_3CH_3$), 3.27 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_4CH_3$), 4.23 (2H, s, CH_2-CO), 7.82 (2H, d, J = 8.9, H-3, 5), 7.92 (2H, d, J = 8.8, H-2, 6), 9.69 (1H, brs, NH). IR spectrum (ν, cm^{-1}): 1681 (-CH_2CO), 1542 (NH), 1177 (C-O-C, oxadiazole).

2-Heptylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (21). Yield 95%, mp 96-97 °C, R_f = 0.58; UV spectrum (λ_{max}, nm): 298.0; ^{1}H NMR (δ, ppm, J/Hz): 0.81 (3H, t, J = 6.9, CH_3), 1.24 (6H, m, $C\underline{H}_2C\underline{H}_2CH_2CH_3$), 1.41 (2H, m, $C\underline{H}_2(CH_2)_3CH_3$), 1.78 (2H, m, $CH_2(CH_2)_4CH_3$), 3.27 (2H, t, J = 7.3, S-$CH_2(CH_2)_5CH_3$), 4.23 (2H, s, CH_2-CO), 7.82 (2H, d, J = 8.9 , H-3, 5), 7.91 (2H, d, J = 8.8, H-2, 6), 9.68 (1H, brs, NH). IR spectrum (ν, cm^{-1}): 1675 (-CH_2CO), 1545 (NH), 1176 (C-O-C, oxadiazole).

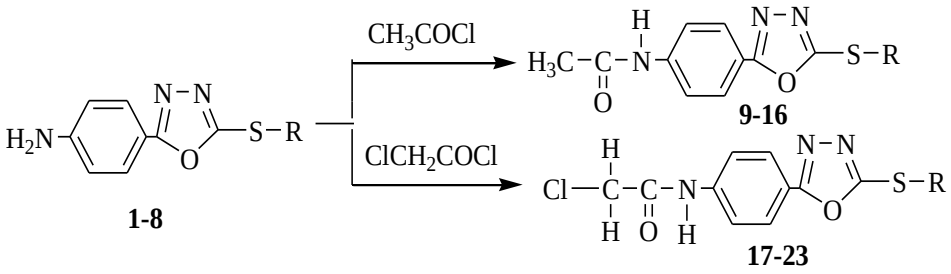
2-Octylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (22). Yield 98%, mp 100 - 101 °C, R_f = 0.61; UV spectrum(λmax, nm) 298.3; ^{1}H NMR (δ, ppm J/Hz): 0.81 (3H, t, J = 6.8, CH_3), 1.22 (8H, m, $C\underline{H}_2(C\underline{H}_2)_3CH_3$), 1.42 (2H, $C\underline{H}_2(CH_2)_4CH_3$), 1.78 (2H, m, $C\underline{H}_2(CH_2)_5CH_3$), 3.27 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_6CH_3$), 4.23 (2H, s, CH_2-CO), 7.82 (2H, d, J = 8.8, H-3, 5), 7.91 (2H, d, J = 8.9, H-2, 6), 9.68 (1H, brs, NH). IR spectrum (ν, cm^{-1}): 1684 (-CH_2CO), 1539 (NH), 1177 (C-O-C, oxadiazole).

2-Nonylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazole (23). Yield 87%, mp 71-77 °C, R_f = 0.61; UV spectrum (λ_{max}, nm): 298.7; ^{1}H NMR (δ, ppm, J/ Hz): 0.80 (3H, t, J = 6.7, CH_3), 1.23 (10H, m, $C\underline{H}_2(CH_2)_4CH_3$), 1.43 (2H, m, $C\underline{H}_2(CH_2)_5CH_3$), 1.78 (2H, m, $C\underline{H}_2(CH_2)_6CH_3$), 3.27 (2H, t, J = 7.3, S-$C\underline{H}_2(CH_2)_7CH_3$), 4.24 (2H, s, CH_2-CO), 7.34 (2H, d , J = 8.9, H-3, 5), 7.91 (2H, d, J = 8.9, H-2,6), 9.79 (1H, brs, NH). IR spectrum (ν, cm^{-1}): 1677 (-CH_2CO), 1539 (NH), 1179 (C-O-C, oxadiazole).

RESULTS AND DISCUSSION

With the aim to synthesize new derivatives on the functional amino group of 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thione and to study their physico-chemical characteristics and antimicrobial activity, acylation reactions of the previously synthesized 2-alkylthio-5-(4-aminophenyl)-1,3,4-oxadiazoles **1-8** [8] with acetyl chloride (AC) and chloroacetyl chloride (CAC) were carried out. The experiments were carried out in acetone, benzene at room temperature and at the boiling point of the solvents. Also, the influence of the ratio of chemical reagents - alkyl substituted compounds **1-8**, acylating agent and HCl acceptor triethylamine (TEA) on product yield was studied. Optimal reaction conditions were established at which the highest yields (85-98%) of the desired products were achieved.

The optimal reaction conditions were established at which the highest yields (85-98%) of the desired products of 2-alkylthio-5-(4-N-acetyl(N-chloroacetyl)aminophenyl)-1,3,4-oxadiazoles **9-23** (Scheme 1) were achieved (in benzene at room temperature, the ratio of 2-alkylthio-5-(4-aminophenyl)-1,3,4-oxadiazoles **1-8**: AC or CAC : TEA - 1: 1.1: 1.5 respectively):



R=C_3H_7(**1**,**9**,**17**), C_4H_9(**2**,**10**,**18**), C_5H_{11}(**3**,**11**,**19**), i-C_5H_{11}(**4**,**12**), C_6H_{13}(**5**,**13**,**20**), C_7H_{15}(**6**,**14**,**21**), C_8H_{17}(**7**,**15**,**22**), C_9H_{19}(**8**,**16**,**23**)

Scheme 1. Synthesis of 2-alkylthio-5-(4-N-acetyl(N-chloroacetyl)aminophenyl)-1,3,4-oxadiazoles **9-23**

Reactions were monitored by TLC. All synthesized compounds are solids. The structure of the obtained derivatives is proved and characterized by ^{1}H NMR, IR and UV spectra. So in the ^{1}H NMR spectra, substituted amino group (NH) proton signals are seen at 9.40-9.48 ppm in 2-alkylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazoles **9-16** and at 8.41-9.75 ppm in 2-alkylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazoles **17-23**. They are very different from the chemical shifts of the unchanged NH_2 group of the initial alkyl derivatives **1-8** where the signals are observed in a

stronger field of 3.72-4.11 ppm [8] that indicates that the acylation reaction proceeds through this amino group. Also the signals at 1.98-2.08 ppm are observed in spectra in the form of singlet corresponding to the protons of the acetyl group (CH_3CO-) of 2-alkylthio-5-(4-N-acetylamino-phenyl)-1,3,4-oxadiazoles **9-16** and at 4.06-4.24 ppm corresponding to the protons of $Cl\text{-}CH_2$ fragment of 2-alkylthio-5-(4-N-chloroacetylamino-phenyl)-1,3,4-oxadiazoles **17-23**. The appearance of absorption bands in the interval of 1674-1707, 1523-1542 cm^{-1} in IR spectra of compounds **9-16** and for **17-23** in the interval of 1659-1703, 1537-1550 cm^{-1}, respectively, corresponding to C=O and NH groups, confirms the production of acyl derivatives on the amino group.

The results of X-ray diffraction analysis of 2-butylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole also confirm the previously established structures of the synthesized compounds. A crystal of 2-butylthio-5-(4-N-acetylaminophenyl)-1,3,4-oxadiazole **10** was grown from solutions of acetone by slow evaporation at room temperature.

The five-membered heterocyclic ring in molecular structure **10** is flat (within ± 0.002 Å) (Fig.1.). The phenyl ring is also flat (within ± 0.001 Å). The location of phenyl ring relative to the plane of the oxadiazole nucleus is characterized with a value of torsion angle O1-C5-C6-C7 of 5.15°. The location of the acetamido fragment relative to the plane of the phenyl ring is characterized with a value of torsion angle C8-C9-N12-C13 -8.94°.

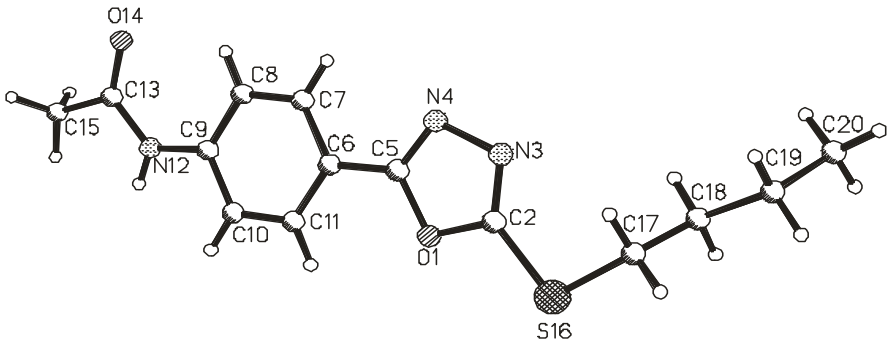


Fig. 1. Numbering of the atoms in the structure **10**.

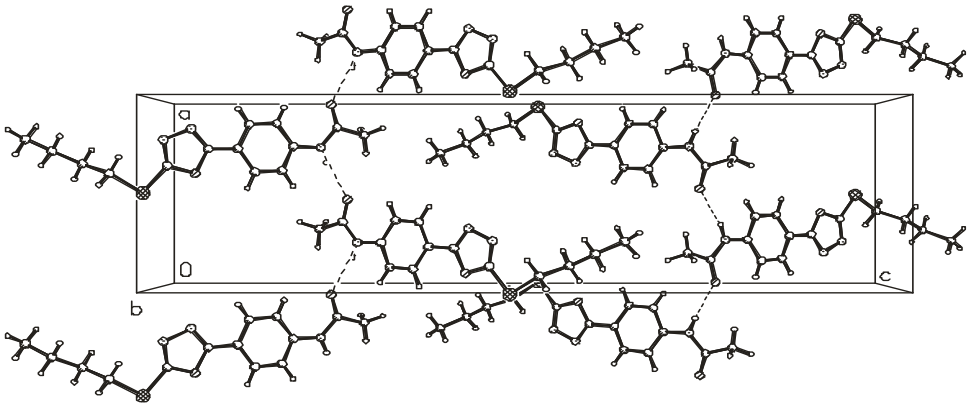


Fig. 2. Packing structure **10**.

In the crystal structure of **10** C=O group and NH group form intermolecular H-bonds. In the crystal between molecules related by glide plane are formed N-H...O type H-bonded chains along *a* axis with graph set motifs of $C_1^1(4)$ [19] (Fig. 2.). Parameters of H-bond are as follows: N-H 0.86 Å, H…O 2.12 Å, N…O 2.934(3) Å, angle N-H…O 159°, symmetry *-1/2+x,y,3/2-z*.

In the structure **10** a weak π...π interaction was observed between the five- and six-membered aromatic rings (atoms O1, C2, N3, N4, C5 and C6, C7, C8, C9, C10, C11) of molecules related by symmetry *3/2-x,-1/2+y,z* and with centroid-centroid distance of 3.6766(15) Å [20].

Herein, the antimicrobial activity of the compounds **9-23** against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli* as well as the fungus *Candida albicans* was assessed using the agar disk-diffusion method [17,18]. The results of the current research are displayed in Table 2 and show that Gram-positive bacteria were susceptible to the studied compounds. *B. subtilis* and *S. aureus* are more susceptible to the antimicrobial activity of the

compounds **17**, **18**, **21** and **22** displaying inhibition zone diameters between 8-14 mm at a concentration of 200 μg/per disc. All tested compounds showed no inhibitory activity against Gram-negative bacteria and *C. albicans* fungus.

Table 2. Antimicrobial effect evaluated by diameter of inhibition zone (mm) for compounds 9-23 using agar disk-diffusion assay

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungus
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*	*C. albicans*
9	NA	NA	NA	NA	NA
10	NA	NA	NA	NA	NA
11	NA	NA	NA	NA	NA
12	NA	NA	NA	NA	NA
13	NA	NA	NA	NA	NA
14	NA	NA	NA	NA	NA
15	NA	NA	NA	NA	NA
16	NA	NA	NA	NA	NA
17	14	11	NA	NA	NA
18	10	8	NA	NA	NA
19	6	6	NA	NA	NA
20	6	6	NA	NA	NA
21	10	12	NA	NA	NA
22	9	11	NA	NA	NA
23	NA	NA	NA	NA	NA
Ampicillin (20μg/disc)	26	25	NT	26	NT
Ceftriaxone (20 μg/disc)	NT	NT	25	NT	NT
Nystatin (20 μg /disc)	NT	NT	NT	NT	20

NA- not active; NT – not tested

CONCLUSION

The new 2-alkylthio-5-(4-N-acetyl (N-chloroacetyl) aminophenyl)-1,3,4-oxadiazoles **9-23** were synthesized by the reaction of 2-alkylthio-5-(4-aminophenyl)-1,3,4-oxadiazoles with acetyl and chloroacetylchlorides. Optimal conditions for the synthesis were found; the physicochemical characteristics and structures of the synthesized compounds were established. X-ray diffraction analysis was carried out using compound **10** as an example, which confirmed the structures of the substances obtained. The 2-alkylthio-5-(4-N-chloroacetylaminophenyl)-1,3,4-oxadiazoles **17-22** showed appreciable antibacterial activity against Gram-positive bacteria.

Acknowledgment: *Authors are thankful to the Academy of Sciences of the Republic of Uzbekistan for supporting this study (grant VA-FA-F-7-006 and VA-FA-F-6-009).*

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