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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Design, Synthesis, and Fungicidal Activity of 2-Alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles

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Abstract—A procedure was developed for preparing 2-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles by alkylation of 5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole-2-thione with β-bromophenetoles in the presence of triethylamine in acetone with up to 90% yield. The *in vitro* tests of the target compounds for fungicidal activity toward six species of phytopathogenic fungi of different taxonomic classes show that the S-halophenoxyethyl-substituted derivatives surpass a reference fungicide, Triadimefon, in the activity toward *Venturia inaequalis*, *Rhizoctonia solani*, and *Bipolaris sorokiniana*.

Keywords: alkylation, 1,3,4-oxadiazole-2-thione, 1,2,4-triazole, fungicidal activity

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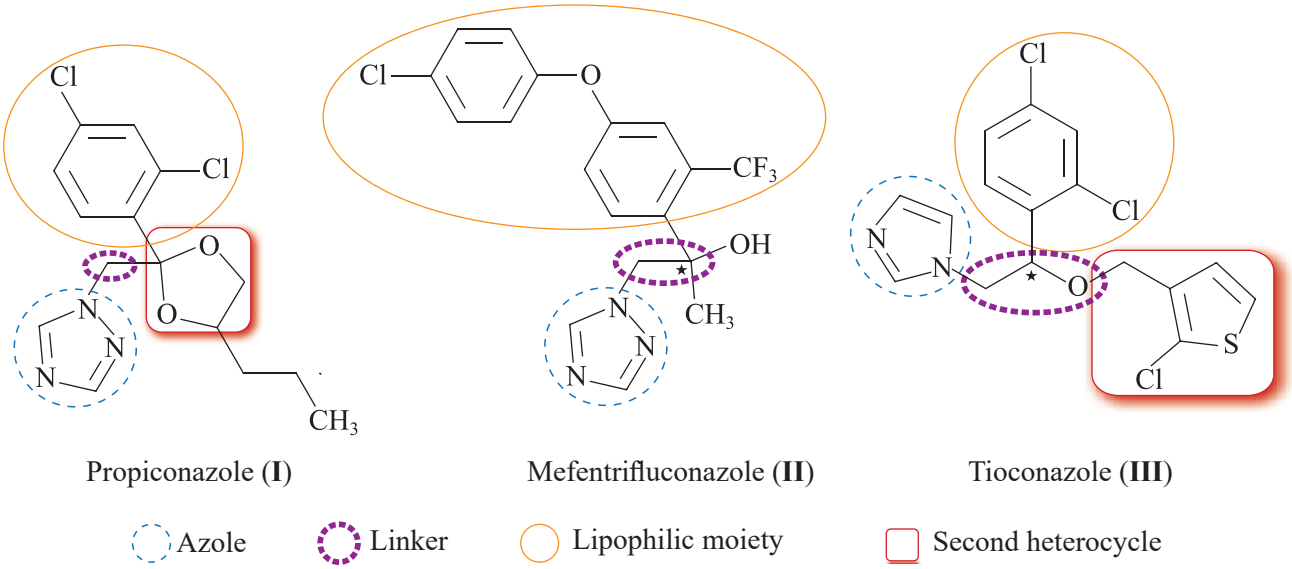
The use of fungicides allows preservation of crops, improvement of their quality, enhancement of their yield, and prevention of the contamination of the products with mycotoxins [1]. Contamination of agricultural products with mycotoxins leads to serious consequences for humans and animals: poisoning, allergic reactions, formation of malignant tumors, and weakening of the immunity [2]. Azoles are among the most important classes of fungicides. These are high-performance systemic agents with low consumption rates, low toxicity, and persistency. New effective agrochemical agents and drugs such as Prothioconazole, Efinaconazole, Izavuconazole, etc., appeared on the market in the recent years [3].

In the development of modern agents, there is a general trend toward combining several heterocycles in the structure of the acting compound [3]. The 1,2,4-triazole fragment acts as a pharmacophore group, and the second heterocycle bound through a linker (a fragment linking parts of the molecule and exerting no direct effect on the biological activity of the compound) ensures high performance of the agent owing to the formation of additional bonds in the enzyme active site. The liphophilic moiety of the acting compound is an aryl-containing fragment responsible for the modeling of lanosterol. This approach was used in the development of such fungicides as Propiconazole (I), Mefentrifluconazole (II), and Tioconazole (III) [4, 5].

The classical approach to the design of azole agents is used now. A typical example is Mefentrifluconazole, which is produced by BASF but is absent on the market of crop protection chemicals in Russia. It does not contain a second heterocyclic fragment in the structure but contains a long lipophilic fragment with an additional aromatic ring [6].



Propiconazole (**I**) Mefentrifluconazole (**II**) Tioconazole (**III**)

The molecular model of azole agents, based on introduction of additional heterocycles such as 1,2,4-triazole, pyrimidine, or thiazole instead of nonaromatic heterocycles, proved to be efficient, because such derivatives have found wide use in medicinal chemistry as drugs for mycosis treatment [7, 8]. Such design of azole agents led to the development of a new generation of agents for treatment of human and animal mycoses, but it has not yet led to the development of new crop protection chemicals.

Based on the modern trends in the development of azole fungicides, we suggested a new molecular model of azoles, CYP51 inhibitor compounds, based on lengthy molecules containing 1,2,4-triazole bound through a linker to a second nitrogen-containing heterocycle and to a lipophilic moiety [9].

Our molecular model of azoles has already proved its efficiency in the development of new fungicides, 3-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,2,4-triazoles [10]. Low toxicity of such compounds is their important property [11, 12].

This study was aimed at the development of the design and synthesis of new fungicides based on substituted phenetoles, containing such structural fragments as 1,2,4-triazole, 1,3,4-oxadiazole-2-thione, and lipophilic sterol-modeling fragment.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker NMR spectrometer (300 MHz for ^{1}H).

The mass spectra were recorded using a QExactive liquid chromatograph coupled with a high-resolution mass spectrometer (Thermo Scientific) in the electrospray ionization mode at atmospheric pressure. Measurement conditions: HYPERSILGoldaQ column (Thermo Scientific) 150 mm long, 2.1 mm i.d., mobile phase acetonitrile–water–formic acid (99 : 1 : 0.1), voltage on the capillary 4000 V, total ion current registration, recording of positive ions in the range 80–750 Da, resolution 35000.

We used the following chemicals: triazole (99.5%, Acros Organics, catalog no. 139285000), ethyl chloroacetate (99%, Acros Organics, catalog no. 118220010), hydrazine hydrate (98%, Alfa Aesar, catalog no. A14005.36), carbon disulfide (99.5%, Panreac, catalog no. 161244.1611), triethylamine (99%, Acros Organics, catalog no. 157910010), methyl iodide (99%, Acros Organics, catalog no. 122375000), benzyl bromide (98%, Acros Organics, catalog no. 105871000), p-chlorobenzyl chloride (Acros Organics, catalog no. 150242500), 1-(2-bromoethoxy)-2-fluorobenzene (97%, BDLpharm, catalog no. BD49860), 1-(2-bromoethoxy)-4-chlorobenzene (98%, BDLpharm, catalog no. BD49870), 4-(2-bromoethoxy)-1-bromobenzene (98%, BDLpharm, catalog no. BD49876), 1-(2-bromoethoxy)-4-nitrobenzene (100%, Sigma–Aldrich, catalog no. PH010955), 4-(2-bromoethoxy)-1,2-dichlorobenzene (95%, BDLpharm, catalog no. BD01111988), 2-(2-bromoethoxy)-1,3,5-trichlorobenzene (95%, BDLpharm, catalog no. BD60944), 1-(2-bromoethoxy)-4-methylbenzene (Sigma–Al-

drich, catalog no. PH000131), 1-(2-bromoethoxy)-4-chloro-2-methylbenzene (98%, BDLpharm, catalog no. BD01792642), 2-(2-bromoethoxy)-1-chloro-4-methylbenzene (95%, BDLpharm, catalog no. BD275066), 1-(2-bromoethoxy)-2-methoxybenzene (97%, BDLpharm, catalog no. BD61130), 1-(2-bromoethoxy)-4-methoxybenzene (Sigma–Aldrich, catalog no. PH009793), hydrochloric acid (chemically pure grade, Komponent-Reaktiv, Russia, GOST (State Standard) 3118–77), KOH (chemically pure grade, EKOS-1, Russia), P_2O_5 (pure grade, Komponent-Reaktiv), K_2CO_3 (chemically pure grade, Komponent-Reaktiv), and anhydrous $MgSO_4$ (96%, Panreac, catalog no. 212486.1211).

As solvents we used acetonitrile (chemically pure grade, Komponent-Reaktiv), isopropanol (chemically pure grade, Komponent-Reaktiv), acetone (chemically pure grade, Komponent-Reaktiv), chloroform (chemically pure grade, Komponent-Reaktiv), diethyl ether (99.7%, Panreac, catalog no. 132770.0311), and ethanol (Khimmed, Russia, CP10288-08-1-BULK).

For fungicidal tests, we used agar-agar 900 (E406) (Zhenpai Hydrocolloids Co. Ltd, catalog no. ZP202108152).

Ethyl 1*H*-(1,2,4-triazol-1-yl)acetate. To a solution of 0.3 mol of 1,2,4-triazole in 180 mL of acetonitrile, 0.309 mol of potassium carbonate was added. The mixture was refluxed for 30 min, after which 0.295 mol of ethyl chloroacetate was added dropwise, keeping the reaction mixture temperature no higher than 60°C. Then, the mixture was refluxed for 5 h, the precipitate was filtered off, and the solvent was distilled off on a rotary film evaporator in a water-jet-pump vacuum. The residue was fractionated by distillation in a rough vacuum. 29.25 g (63%) of ethyl (1*H*-1,2,4-triazol-1-yl)acetate was obtained; T_b = 115–125°C (0.15 mm Hg); published data: T_b = 94–110°C (0.13 mmHg) [13]. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, ^3J = 7.4 Hz), 4.18 q(1H, CH_2CH_3, ^3J = 7.4 Hz), 5.21 s [2H, $CH_2C(O)$], 8.02 s (1H, C^5H_{Trz}), 8.54 s (1H, C^3H_{Trz}).

2-(1*H*-1,2,4-Triazol-1-yl)acetohydrazide (1). To a solution of 0.065 mol of ethyl (1*H*-1,2,4-triazol-1-yl)acetate in 25 mL of ethanol, 0.1625 mol of 98% hydrazine hydrate was added. The mixture was refluxed for 6 h. The solvent was removed on a rotary film evaporator in a water-jet-pump vacuum. The precipitate was recrystallized from isopropanol. 6.03 g (66%) of 2-(1*H*-1,2,4-triazol-1-yl)acetohydrazide (**1**) was obtained; T_m = 118–119°C; published data: T_m = 119–120°C [14]. ^{1}H NMR spectrum, δ, ppm: 4.85 s (2H, CH_2), 7.97 s (1H, C^5H_{Trz}), 8.51 s (1H, C^3H_{Trz}), 9.46 s (1H, NH).

Potassium 2-(1*H*-1,2,4-triazol-1-ylacetyl)hydrazinocarbodithioate (2). To a solution of 0.028 mol of 2-(1*H*-1,2,4-triazol-1-yl)acetohydrazide and 0.056 mol of 85% KOH in 100 mL of ethanol, a solution of 0.056 mol of carbon disulfide in 8 mL of ethanol was added dropwise. The reaction mixture was stirred for 2 h at room temperature, and the precipitate was filtered off and dried in a Fisher drying pistol over phosphorus pentoxide. 9.58 g (98%) of potassium 2-(1*H*-1,2,4-triazol-1-ylacetyl)hydrazinocarbodithioate (2) was obtained; T_m = 189–191°C. ^{13}C NMR spectrum, δ, ppm: 43.48 (CH_2), 151.50 (C^3_{Trz}), 151.62 (C^5_{Trz}), 159.81 (CS), 161.91 (C—S).

5-(1*H*-1,2,4-Triazol-1-ylmethyl)-1,3,4-oxadiazole-2-thione (3). A solution of 4 mmol of potassium 2-(1H-1,2,4-triazol-1-ylacetyl)hydrazinocarbodithioate (**2**) in 65 mL of мл ethnaol was refluxed for 9 h,. and the reaction mixture was acidified with 4.9 mL of a 3% HCl solution in isopropyl alcohol. The precipitate was filtered off and recrystallized from ethanol. 0.44 g (61%) of 5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole-2-thione (3) was obtained; T_m = 190–191°C; published data: T_m = 194–195°C [15]. ^{1}H NMR spectrum, δ, ppm: 3.28 br.s (1H, NH), 5.68 s (2H, CH_2), 8.09 s (1H, C_5H_{Trz}), 8.70 s (1H, C_3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 43.9 (C-6), 145.42 (C-2), 152.39 (C-3), 158.32 (C-10, C-7). High-resolution mass spectrum, electrospray ionization (ESI): calculated m/z [M^+] = 183.0215, found m/z [$C_5H_5N_5OS^+$] = 183.0222.

Preparation of 2-alkylthio5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (4) (general procedure). A mixture of 0.546 mmol of alkyl halide, 0.546 mmol of 5-(1*H*-1,2,4-triazol-1-methyl)-1,3,4-oxadiazole-2-thione (**3**), and 0.546 mmol of triethylamine in 3 mL of acetone was refluxed for 4–24 h (Table 1). The reaction mixture was cooled, the solvent was removed on a rotary film evaporator in a water-jet-pump vacuum, and 4 mL of water and 4 mL of chloroform were added to

Table 1. Yield of 2-alkylthio -5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4a–4n**)

Compound	Compound name	Yield, %
4a	2-Methylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	57
4b	2-Benzylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	64
4c	2-(4-Chlorobenzylthio)-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	42
4d	2-(2-Fluorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	85
4e	2-(4-Chlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	90
4f	2-(4-Bromophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	52
4g	2-(4-Nitrophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	79
4h	2-(3,4-Dichlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	64
4i	2-(2,4,6-Trichlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	55
4j	2-(4-Methylphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	64
4k	2-(2-Methyl-4-chlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	32
4l	2-(2-Chloro-5-methylphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	60
4m	2-(2-Methoxyphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	71
4n	2-(4-Methoxyphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	66

the residue. The organic phase was separated, and the aqueous layer was washed with chloroform (2 × 4 mL). The organic phases were combined and dried over magnesium sulfate, the desiccant was filtered off, and the chloroform was removed on a rotary film evaporator. 3 mL of diethyl ether was added to the residue. The crystals formed were filtered off and washed with diethyl ether.

2-Methylthio-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4a): yield 0.06 g (57%), T_m = 129–132°C. ^{1}H NMR spectrum, δ, ppm: 2.51 s (3H, (CH_3S), 5.82 s (2H, CH_2N), 8.06 s (1H, C^5H_{Trz}), 8.73 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 14.76 (C-13), 43.50 (C-6), 145.68 (C-2), 152.63 (C-3), 162.95 (C-10), 166.15 (C-7). High-resolution mass spectrum, ESI: calculated m/z [M + H^+] = 198.0449, found m/z [$C_6H_7N_5OS + H^+$] = 198.0455.

2-Benzylthio-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4b): yield 0.09 g (64%), T_m = 87–90°C. ^{1}H NMR spectrum, δ, ppm: 4.48 s (2H, $SCH_2C_6H_5$), 5.83 s (2H, CH_2N_{Trz}), 7.31 m (3H, CH_{Ar}), 7.38 m (2H, CH_{Ar}), 8.08 s (1H, $CH^5{}_{Trz}$), 8.73 s (1H, $CH^3{}_{Trz}$). ^{13}C NMR spectrum, δ, ppm: 36.29 (C-13), 43.50 (C-6), 128.23 (C-15, C-19), 129.01 (C-16, C-18), 129.44 (C-17), 136.82 (C-14), 145.62 (C-2), 152.61 (C-3), 163.16 (C-7, C-10). High-resolution mass spectrum, ESI: calculated m/z [M + H^+] = 274.076, found m/z [$C_{12}H_{11}N_5OS + H^+$] = 274.078.

2-{[(4-Chlorophenyl)methyl]thio}-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4c), yield 0.07 g (42%), T_m = 97–100°C. ^{1}H NMR spectrum, δ, ppm: 4.47 s (2H, $SCH_2C_6H_4$), 5.82 s (2H, CH_2N), 7.39 m (2H, $4CH_{Ar}$), 8.07 s (1H, C^5H_{Trz}), 8.72 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 31.83 (C-13), 43.50 (C-6), 117.64 (C-16, C-18), 125.51 (C-15, C-19), 130.00 (C-17), 137.10 (C-14), 145.64 (C-2), 152.63 (C-3), 163.16 (C-10), 165.04 (C-7). High-resolution mass spectrum, ESI: calculated m/z [M + H^+] = 308.0373, found m/z [$C_{12}H_{10}ClN_5OS + H^+$] = 308.0380.

2-{[2-(2-Fluorophenoxy)ethyl]thio}-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4d): yield 0.15 g (85%), T_m = 79–82°C. ^{1}H NMR spectrum, δ, ppm: 3.69 t (2H, SCH_2CH_2O, J^3 = 6.2 Hz), 4.31 t (2H, SCH_2CH_2O, J^3 = 6.23 Hz), 5.83 s (2H, CH_2N_{Trz}), 7.1 m (4H, $4CH_{Ar}$), 8.04 s (1H, C^5H_{Trz}), 8.72 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 31.80 (C-1), 40.10 (C-7), 67.26 (C-14), 116.51 (C-18), 116.67 (C-21), 122.13 (C-19), 125.35 (C-20), 145.61 (C-3), 151.13

(C-16, C-17), 153.2 (C-4), 163.13 (C-12), 164.98 (C-8). High-resolution mass spectrum, ESI: calculated m/z $[M + H^+]$ = 322.0774, found m/z $[C_{13}H_{11}FN_5O_2S + H^+]$ = 322.0783.

2-{[2-(4-Chlorophenoxy)ethyl]thio}-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4e): yield 0.17 g (90%), T_m = 80–83°C. ^{1}H NMR spectrum, δ, ppm: 3.64 t (2H, SCH_2CH_2O J^3 = 5.86 Hz), 4.3 t (2H, SCH_2CH_2O, J^3 = 5.13 Hz), 5.83 s (1H, CH_2N_{Trz}), 6.95 d (2H, $2CH_{Ar}$, J^3 = 8.85 Hz), 7.32 d (2H, $2CH_{Ar}$, J^3 = 8.85 Hz), 8.05 s (1H, C^5H_{Trz}), 8.73 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 31.85 (C-1), 43.51 (C-7), 66.60 (C-14), 116.76 (C-21, C-17), 125.22 (C-19), 129.76 (C-18, C-20), 145.64 (C-3), 152.60 (C-4), 157.17 (C-16), 163.14 (C-12), 164.99 (C-8). High-resolution mass spectrum, ESI: calculated m/z $[M + H^+]$ = 338.0478, found *m/z* $[C_{13}H_{12}ClN_5O_2S + H^+]$ = 338.0476.

2-{[2-(4-Bromophenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4f): yield 0.11 g (52%), T_m = 84–87°C. ^{1}H NMR spectrum, δ, ppm: 3.62 d (2H, SCH_2CH_2O J^3 = 5.86 Hz), 4.30 d (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 5.83 s (2H, CH_2N_{Trz}), 6.89 d (2H, $2CH_{Ar}$, J^3 = 8.8 Hz), 6.95 d (2H, $2CH_{Ar}$, J^3 = 8.79 Hz), 8.06 s (1H, C^5H_{Trz}), 8.73 c (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 31.84 (C-1), 43.51 (C-7), 66.53 (C-14), 117.29 (C-19), 117.45 (C-17, C-21), 132.66 (C-18, C-20), 152.66 (C-3, C-4), 157.62 (C-16), 163.13 (C-12), 164.99 (C-8). High-resolution mass spectrum, ESI: calculated m/z $[M + H^+]$ = 381.9973, found m/z $[C_{13}H_{12}BrN_5O_2S + H^+]$ = 381.9975.

2-{[2-(4-Nitrophenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4g): yield 0.15 g (79%), T_m = 97–100°C. ^{1}H NMR spectrum, δ, ppm: 3.68 t (2H, SCH_2CH_2O, J^3 = 5.9 Hz), 4.47 t (3H, SCH_2CH_2O, J^3 = 5.9 Hz), 5.84 s (2H, CH_2N), 7.15 d (2H, $2CH_{Ar}$, J^3 = 9.5 Hz), 8.07 s (1H, C^5H_{Trz}), 8.21 d (2H, $2CH_{Ar}$, J^3 = 9.5 Hz), 8,74 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 31.65 (C-1), 43.50 (C-7), 67.20 (C-14), 115.55 (C-17, C-21), 126.34 (C-18, C-20), 141.64 (C-19), 145.61 (C-3), 152.61 (C-4), 163.19 (C-12), 163.55 (C-16), 164.87 (C-8). High-resolution mass spectrum, ESI: calculated m/z $[M + H^+]$ = 349.0719, found *m/z* $[C_{13}H_{11}N_6O_4S + H^+]$ = 349.0722.

2-{[2-(3,4-Dichlorophenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4h): yield 0.13 g (64%), T_m = 68–71°C. ^{1}H NMR spectrum, δ, ppm: 3.71 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 4.4 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 5.83 s (2H, CH_2N_{Trz}), 7.22 m (2H, $2CH_{Ar}$), 7.36 s (1H, $1CH_{Ar}$), 8.06 s (1H, C^5H_{Trz}), 8.73 (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 31.66 (C-1), 43.51 (C-7), 67.66 (C-14), 115.77 (C-21), 116.03 (C-17), 125.45 (C-19), 129.82 (C-18), 145.59 (C-3), 152.52 (C-4), 152.85 (C-16), 163.07 (C-12), 164.95 (C-8). High-resolution mass spectrum, ESI: calculated *m/z* $[M + H^+]$ = 372.0089, found *m/z* $[C_{13}H_{10}Cl_2N_5O_2S + H^+]$ = 372.0095.

2-[(1H-1,2,4-Triazol-1-yl)methyl]-5-{[2-(2,4,6-trichlorophenoxy)ethyl]thio}-1,3,4-oxadiazole (4i): yield 0.12 g (55%), T_m = 101–104°C. ^{1}H NMR spectrum, δ, ppm: 3.66 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 4.38 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 5.83 s (2H, CH_2N_{Trz}), 7.71 s (2H, $2CH_{Ar}$), 8.05 s (1H, C^5H_{Trz}), 8.72 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 32.34 (C-1), 43.50 (C-7), 71.58 (C-14), 129.42 (C-19), 129.71 (C-17, C-18, C-20, C-21), 145.58 (C-3), 149.93 (C-16), 152.58 (C-4), 163.10 (C-12), 164.90 (C-8). High-resolution mass spectrum, ESI: calculated m/z $[M + H^+]$ = 405.9699, found *m/z* $[C_{13}H_9Cl_3N_5O_2S + H^+]$ = 405.9698.

2-{[2-(4-Methylphenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4j): yield 0.11 g (64%), T_m = 96–99°C. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, $CH_3C_6H_4O$, J^3 = 5.86 Hz), 3.61 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 4.26 t (3H, SCH_2CH_2O, J^3 = 5.86 Hz), 5.82 s (2H, CH_2N_{Trz}), 6.81 m (2H, $2CH_{Ar}$), 7.08 m (2H, $2CH_{Ar}$), 8.06 s (1H, C^5H_{Trz}), 8,72 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 20.53 (C-22), 32.00 (C-1), 43.50 (C-7), 66.19 (C-14), 115.01 (C-17, C-21), 130.33 (C-18, C-20), 145.59 (C-3), 152.60 (C-4), 156.20 (C-16), 163.12 (C-8), 165.82 (C-8). High-resolution mass spectrum, ESI: calculated *m/z* $[M + H^+]$ = 318.1025, found m/z $[C_{14}H_{15}N_5O_2S + H^+]$ = 318.1032.

5-{[2-(4-Chloro-2-methylphenoxy)ethyl]thio}-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4k): yield 0.06 g (32%), T_m = 83–86°C. ^{1}H NMR spectrum, δ, ppm: 2.04 s (3H, $CH_3C_6H_3$), 3.66 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 4.31 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 5.82 s (2H, $2CH_2N_{Trz}$), 6.97 d (1H, CH_{Ar}, J^3 = 8.06 Hz), 7.2 m (2H, $2CH_{Ar}$), 8.06 s (1H, C^5H_{Trz}), 8.72 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 15.93 (C-23), 32.04 (C-1), 43.47 (C-7), 66.69 (C-14), 113.58 (C-21), 124.73 (C-20), 126.90 (C-19), 128.83 (C-17), 130.43 (C-18), 145.62 (C-3), 152.50 (C-4, C-16), 155.29 (C-12), 163.09 (C-8). High-resolution mass spectrum, ESI: calculated m/z $[M + H^+]$ = 352.0635, found *m/z* $[C_{14}H_{13}ClN_5O_2S + H^+]$ = 352.0641.

2-{[2-(1-Chloro-4-methylphenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4l): yield 0.12 g (60%), T_m = 74–77°C. ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, CH_3), 3.61 t (2H, SCH_2CH_2O, J^3 = 5.9 Hz), 4.27 t (2H, SCH_2CH_2O, J^3 = 5.9 Hz), 5.83 s (2H, CH_2N_{Trz}), 6.74 d (1H, CH_{Ar}, J^3 = 8.8 Hz), 6.93 m (1H, $1CH_{Ar}$), 7.27 d (1H, $1CH_{Ar}$, J^3 = 8.8 Hz), 8.06 s (1H, C^5H_{Trz}), 8.73 c (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 20.19 (C-23), 31.84 (C-1), 43.53 (C-7), 68.46 (C-14), 117.66 (C-21), 117.88 (C-17), 125.51 (C-19), 129.98 (C-18), 137.07 (C-20), 145.61 (C-3), 152.52 (C-4), 157.07 (C-16), 163.13 (C-12), 165.01 (C-8). High-resolution mass spectrum, ESI: calculated m/z [M + H$^+$] = 352.0635, found *m/z* [$C_{14}H_{13}ClN_5O_2S + H^+$] = 352.0641.

2-{[2-(2-Methoxyphenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4m): yield 0.13 g (71%), T_m = 87–90°C. ^{1}H NMR spectrum, δ, ppm: 3.62 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 3.75 s (3H, $CH_3OC_6H_4$), 4.27 t (2H, SCH_2CH_2O, J^3 = 5.86 Hz), 5.83 s (2H, CH_2N_{Trz}), 6.69 m (3H, $3CH_{Ar}$), 6.96 m (1H, CH_{Ar}), 8.06 s (1H, C^5H_{Trz}), 8.73 s (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 25.43 (C-23), 31.80 (C-1), 40.15 (C-7), 67.56 (C-14), 116.59 (C-18), 116.67 (C-21), 122.14 (C-19), 125.39 (C-20), 145.54 (C-3), 151.11 (C-16, C-17), 153.22 (C-4), 163.39 (C-12), 164.99 (C-8). High-resolution mass spectrum, ESI: calculated m/z [M + H$^+$] = 322.0774, found *m/z* [$C_{14}H_{14}N_5O_3S + H^+$] = 322.0776.

2-{[2-(4-Methoxyphenoxy)ethyl]thio}-5-[(1H-1,2,4-triazol-1-yl)methyl]-1,3,4-oxadiazole (4n): yield 0.12 g (66%), T_m = 56–59°C. ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, $CH_3OC_6H_4$), 3.77 t (2H, SCH_2CH_2O, J^3 = 5.13 Hz), 4.25 t (2H, SCH_2CH_2O, J^3 = 5.13 Hz), 5.83 s (2H, CH_2N_{Trz}), 6.88 m (4H, $4CH_{Ar}$), 8.06 s (1H, C^5H_{Trz}), 8.73 c (1H, C^3H_{Trz}). ^{13}C NMR spectrum, δ, ppm: 25.23 (C-23), 31.12 (C-1), 43.45 (C-7), 67.00 (C-14), 115.04 (C-17, C-21), 126.50 (C-18, C-20), 142.64 (C-19), 145.99 (C-3), 152.60 (C-4), 163.11 (C-12), 163.22 (C-16), 164.49 (C-8). High-resolution mass spectrum, ESI: calculated *m/z* [M + H$^+$] = 334.0974, found *m/z* [$C_{14}H_{14}N_5O_3S + H^+$] = 334.0977.

The 1,2,4-triazol-1-ylmethylazoles synthesized were tested for the fungicidal activity *in vitro* using a common procedure [16] with six pathogenic fungi: *Sclerotinia sclerotiorum* (white rot pathogen), *Fuzarium oxysporum*, *Fuzarium moniliforme* (fusariosis pathogens), *Rhizoctonia solani* (rhizoctoniosis pathogen), *Bipolaris sorociniana* (root rot pathogen), and *Venturia inaequalis* (apple scab pathogen). The fungus cultures were obtained from the Center for Shared Use "State Collection of Phytopathogenic Microorganisms and Identifier Sorts (Differentiators) of Pathogenic Microorganism Strains," All-Russia Research Institute of Phytopathology. Potato–sucrose agar (agar-agar 900, E406) was used as a cultural medium. The action of the agents on the radial growth of mycelium was determined by dissolving the compound in acetone and introducing an aliquot into a sterile potato–sucrose agar under aseptic conditions at 50°C to obtain the acting compound concentration of 30 mg L^{-1}. The media thus obtained were poured into Petri dishes. The final acetone concentration in control solutions with acting compounds was 1%. Into Petri dishes containing 15 mL of the agar medium, we introduced with a needle the fungus cultures onto the agar surface. The samples were kept in an incubator at 25°C for 3 days, and the radial growth of the mycelium was measured. The action of the compounds on the radial mycelium growth was studied in comparison with a widely used fungicide, Triadimefon. The mycelium growth inhibition percentage (inh, %) was calculated according to Abbot:

$$\text{inh} = [(D_c - D_t)/D_c] \times 100,$$

where D_c is the diameter of fungus colonies in the control medium, and D_t is the diameter of fungus colonies in a medium with a test compound (**4a–4n**).

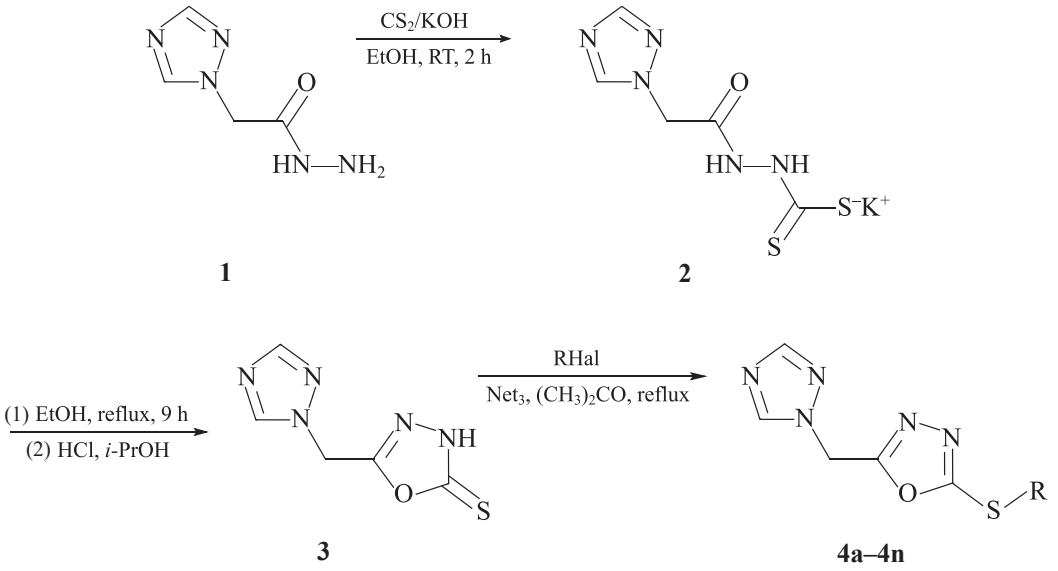
The lipophilicity of the target compounds (log *P*) was calculated using the ACD Labs program package [ACD/ChemSketch (Freeware) 2022.2.3, ACD/ Labs 2022.2.3 (File version C45E41, Build 130928, 16 Dec 2022)] in the automatic mode.

RESULTS AND DISCUSSION

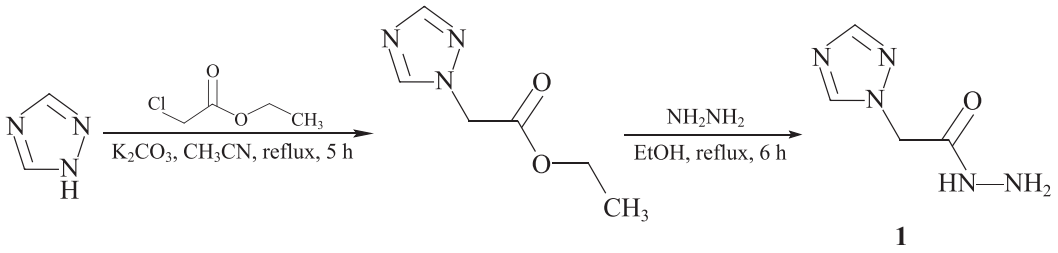
To obtain the desired 2-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4a–4n**), we developed a three-step scheme (Scheme I) starting from 2-(1,2,4-triazol-1-yl)acetohydrazide (**1**) prepared by the known procedure [13, 14].

The starting acetohydrazide (**1**) can be prepared in two steps with the overall yield of 41% by alkylation of 1,2,4-triazole with ethyl chloroacetate in the presence of a base, followed by the reaction of the intermediate ethyl

Scheme I.



Scheme II.



(1*H*-1,2,4-triazol-1-yl)acetate with hydrazine hydrate to form hydrazide (**1**) (Scheme II).

The reaction of 2-(1,2,4-triazol-1-yl)acetohydrazide (**1**) with carbon disulfide in the presence of potassium hydroxide in absolute ethanol gives potassium 2-(1*H*-1,2,4-triazol-1-ylacetyl)hydrazinocarbodithioate (**2**) in 98% yield. Then, potassium salt (**2**) is refluxed in ethanol for 20 h until the hydrogen sulfide evolution ceases. The subsequent acidification with a 3% HCl solution in isopropyl alcohol gives the key intermediate, 5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole-2-thione (**3**) in 61% yield.

Further alkylation of compound **3** with primary alkyl halides in the triethylamine–acetone system gives a series of 2-alkylthio-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4a–4n**) in up to 90% yield. The alkylation with benzyl halides occurs somewhat more slowly than the alkylation with β-bromophenetoles. The benzylation is complicated by the formation of low-molecular-mass products but allows obtaining the target compounds in up to 90% yield (Table 1). The use of strong bases such as alkali metal alcoholates in protic and aprotic solvents in this reaction leads to the tarring of the starting 1,3,4-oxadiazole-2-thione (**3**).

Introduction of substituents to the exocyclic sulfur atom considerably enhances the activity of 2-alkylthio-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4a–4n**) and makes them more lipophilic. Unfortunately, we failed to reveal any correlation between the fungitoxicity and lipophilicity (varies from 0.84 to 2.7) in the series of compounds (**4a–4n**). Compounds of this series exhibit the highest fungitoxicity toward Rhizoctonia solani phytopathogen, in some cases fully suppressing the growth of its mycelium (**4b**, **4e–4g**, **4n**). Some compounds also surpass the reference Triadimefon in the fungicidal activity toward pathogens of apple scab

Table 2. Fungicidal tests of compounds (**3**, **4a–4n**) *in vitro* (c = 30 mg L^{-1})

Compound	Compound name	Suppresson of the growth of phytopathogenic fungi, %						Calculated lipophilicity (log P)[a]
		Venturia inaequalis	*Rhizoctonia solani*	*Fusarium oxysporum*	*Fusarium moniliforme*	*Bipolaris sorokiniana*	*Sclerotinia sclerotiorum*	
3	5-(1,2,4-Triazol-1-ylmethyl)-1,3,4-oxadiazole-2-thione	1	28	6	9	25	5	0.26 ± 0.72
4a	2-Methylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	25	97	18	25	6	24	0.97 ± 0.63
4b	2-Benzylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	33	100	20	30	41	9	0.81 ± 0.64
4c	2-(4-Chlorobenzylthio)-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	39	47	19	31	64	13	1.40 ± 0.64
4d	2-(2-Fluorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	24	50	10	25	45	13	0.95 ± 0.67
4e	2-(4-Chlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	43	100	23	39	31	13	1.63 ± 0.64
4f	2-(4-Bromophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	90	100	54	67	34	27	1.98 ± 0.67
4g	2-(4-Nitrophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	55	100	33	50	58	18	0.84 ± 0.64
4h	2-(3,4-Dichlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	52	92	49	60	80	55	2.34 ± 0.73
4i	2-(2,4,6-Trichlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	60	98	51	59	60	24	2.76 ± 0.76
4j	2-(4-Methylphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	29	40	16	21	25	13	1.41 ± 0.64
4k	2-(2-Methyl-4-chlorophenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	51	82	44	55	50	21	2.09 ± 0.64
4l	2-(2-Chloro-5-methylphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	61	92	36	57	74	21	1.95 ± 0.66
4m	2-(2-Methoxyphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	34	39	9	27	42	11	0.77 ± 0.64
4n	2-(4-Methoxyphenoxyethyl)thio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole	45	100	23	46	33	15	0.91 ± 0.65
Triadimefon		41	43	77	87	44	61	2.77 ± 0.80

(*Venturia inaequalis*) and barley leaf spot (*Bipolaris sorokiniana*) (compounds **4c**, **4g–4i**, **4l**). It should be noted that S-halophenoxyethyl-substituted derivatives (**4e**, **4f**, **4h**, **4i**) exhibit the highest activity toward all the three above-mentioned phytopathogens (Table 2). The aryloxyethyl fragment is present in the molecules of Prochloraz fungicide, phenoxyethyltriazoles, etc., considerably enhancing their fungitoxicity [17]. It can be expected that testing for the fungicidal activity toward other pathogenic fungi will allow more complete characterization of the 2-alkylthio-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles synthesized, and the most active compounds among them will find use as plant protection chemicals. We assume that the compounds obtained act similarly to other azole-type fungicides, selectively inhibiting CYP51 enzyme.

CONCLUSIONS

2-Alkylthio-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles can be prepared by the reaction of 5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazole-2-thione with alkyl halides in the presence of triethylamine in refluxing acetone in 32–90% yield. Their fungicidal activity toward six phytopathogenic fungal species was studied *in vitro*. 2-Alkylthio-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles surpass the reference fungicide, Triadimefon, in the activity toward such phytopathogens as *Venturia inaequalis*, *Rhizoctonia solani*, and *Bipolaris sorokiniana*. The aryloxyalkyl substituent in the target compounds plays an important role, considerably enhancing the fungicidal activity of 2-alkylthio-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles.

The compound series synthesized is an important example of our approach to designing azoles with fungicidal activity. It demonstrates the efficiency of the given chemotype, based on successive linking of the pharmacophore group, linker, second heterocycle, and lipophilic moiety.

AUTHOR CONTRIBUTION

G.V. Tsaplin: synthesis of the target 2-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4a–4d**); S.A. Kazakov: synthesis of the target 2-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4e–4g**); M.I. Semchukova: synthesis of the target 2-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4h–4j**); E.A. Alekseeva: synthesis of the target 2-alkylthio-5-(1,2,4-triazol-1-ylmethyl)-1,3,4-oxadiazoles (**4k–4n**); A.L. Alekseenko: fungicidal tests; I.M. Chernega: preparation of starting compound and intermediates (**1–3**); S.V. Popkov: development of the concept of the study, formulation of its goals.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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