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Synthesis and study of the fungicidal and growth-regulating activity of substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles

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Abstract

In vitro tests of substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles showed a fungicidal activity lower than the activity of the triadimefon, and spiroxamine. Studied compounds in the entire concentration range: from 0.001 to 10 mg/l showed noticeable retardant properties. The target compounds were derived by cyclization of substituted cyclohexanones with epichlorohydrin followed by alkylation of the derived 2-chloromethyl-1,4-dioxaspiro[4.5]decanes of sodium salts of imidazole or 1,2,4-triazole.

Keywords: alkylation, 1,3-dioxolane, 1,4-dioxaspiro[4.5]decane, growth-regulating activity, imidazole, fungicidal activity, ketalization, ketals, 1,2,4-triazole.

INTRODUCTION

Among numerous azole fungicides, substituted 2-azolylmethyl-1,3-dioxolanes: propiconazole and diphenoconazole occupy the most important place on the market [1].

In the mid-1990s, the full range of plant protection chemicals was supplemented by alkylaminomethyl-substituted 1,4-dioxaspiro[4.5]decane — *spiroxamine*, which, in terms of the mechanism of action, is also an inhibitor of steroid biosynthesis [2]

The combination of two fragments in a single molecule: toxophore azole, as well as relatively sensitive to hydrolysis 1,3-dioxolane, while preserving the fungicidal properties, reduces the hydrolytic stability and, therefore, accelerates the degradation of the drug in the environment. The use of the analog method [3] allows to develop and synthesize 4-azolylmethyl-1,3-dioxolanes with high fungicidal activity and reduced persistence.

It should be noted the earlier synthesized similar analogs substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles demonstrated a wide range of biological activities: mainly fungicidal [4-16] and antimycotic [13, 15], as well as antimycobacterial [18], growth-regulating [18,19], antiradical [20], antibacterial [21], cytotoxic [22].

A search for new biologically active compounds was carried out among analogues of spiroxamine – substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles, in which the ethylpropylamine group was replaced with 1,2,4-triazole or imidazole fragments, and alkyl substituents in cyclohexane ring were subjected to variation.

MATERIALS AND METHODS

^{1}H NMR spectra were recorded on Bruker AM-300 instrument (300.13 MHz). IR spectra were recorded on a Specord M-80 instrument (Nujol). The course of reaction was monitored and the purity of the compounds was checked by TLC (Silufol UV-254).

Substituted 2-chloromethyl-1,4-dioxaspiro[4.5]decanes. (general procedure). Boron trifluoride etherate (0,002 mol) was added to a stirred solution of substituted cyclohexanone **1-4** (0,1 mol), in CCl_4 (250 ml). The mixture was stirred at room temperature for 20 min. Then epichlorohydrin (0,08 mol) was added at 25-30 ^oC and stirring was continued at room temperature for 2 h. The reaction mixture was washed with 3% NaOH (100 ml) and water (100 ml) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was fractioned *in vacuo*.

2-Chloromethyl-1,4-dioxaspiro[4.5]decane (1a). Yield 67%, n_D^{20} 1.4755. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.41-1.59 (m, 10H, cycl.); 3.48 (d.d, 1H, CH_2Cl, ^3J = 8.0, ^2J = 8.4); 3.60 (d.d, 1H, CH_2Cl, ^3J = 6.6, ^2J = 8.4); 3.87 (d.d, 1H, CH_2O, ^3J = 5.0, ^2J = 8.0); 4.15 (d.d, 1H, CH_2O, ^3J = 6.4, ^2J = 8.0); 4.34 (q, 1H, CHO, ^3J = 5.9). IR (Nujol, ν/sm^{-1}): 1245, 1225, 1170, 1115, 1085 (COCOC); 768 (CCl).

2-Chloromethyl-8-methyl-1,4-dioxaspiro[4.5]decane (2a). Yield 45%, n_D^{20} 1.4685. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.92 (d, 3H, CH_3, ^3J = 6.2); 1.09-1.32 (m, 2H, cycl.); 1.32-1.51 (m, 2H, cycl.); 1.55-1.78 (m, 5H, cycl.); 3.46 (d.d, 1H, CH_2Cl, ^3J = 7.7, ^2J = 8.4); 3.59 (d.d, 1H, CH_2Cl, ^3J = 5.2, ^2J = 8.4); 3.89 (d.d, 1H, CH_2O, ^3J = 4.8, ^2J = 8.2); 4.11 (d.d, 1H, CH_2O, ^3J = 6.2, ^2J = 8.2); 4.31 (q, 1H, CHO, ^3J = 5.8).. IR (Nujol, ν/sm^{-1}): 1242, 1220, 1172, 1115, 1085 (COCOC): 772 (CCl).

8-*Tert*-butyl-2-chloromethyl-1,4-dioxaspiro[4.5]decane (3a). Yield 88%, n_D^{20} 1.4763. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.85 (s, 9H, $C(CH_3)_3$), 1.02 (t, 1H, CH, ^3J = 11.9); 1.38-1.89 (m, 8H, cycl.); 3.47 (d.d, 1H, CH_2Cl, ^3J = 7.4, ^2J = 8.1); 3.58 (d.d, 1H, CH_2Cl, ^3J = 6.5, ^2J = 8.1); 3.80 (d.d, 1H, CH_2O, ^3J = 6.9, ^2J = 8.8); 4.10 (d.d, 2H, CH_2O, ^3J = 7.9, ^2J = 8.8), 4.45 (q, 1H, CHO, ^3J = 5.9). IR (Nujol, ν/sm^{-1}): 1245, 1225, 1170, 1118, 1088 (COCOC); 778 (CCl).

2-Chloromethyl-7,7,9-trimethyl-1,4-dioxaspiro[4.5]decane (4a). Yield 85%, n_D^{20} 1.4671. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.90 (s, 6H, $(CH_3)_2$); 1.01 (s, 3H, CH_3); 1.06-1.14 (m, 1H, cycl.); 1.15-1.30 (m, 2H, cycl.); 1.32-1.50 (m, 2H, cycl.); 1.32-1.50 (m, 2H, cycl.); 3.46 (d.d, 1H, CH_2Cl, ^3J =

7.3, ^2J = 8.2); 3.57 (d.d, 1H, CH_2Cl, ^3J = 5.1, ^2J = 8.0); 3.89 (d.d, 1H, CH_2O, ^3J = 4.6, ^2J = 8.3); 4.08 (d.d, 1H, CH_2O, ^3J = 6.4, ^2J = 8.3); 4.26 (q, 1H, CHO, ^3J =5.9). IR (Nujol, ν/sm^{-1}): 1245, 1220, 1175, 1115, 1085 (COCOC); 774 (CCl)

Substituted 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)-1*H*-1,2,4-triazoles and 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)-1*H*-imidazoles (general procedure).

A mixture of 0,03 mol a substituted 2-chloromethyl-1,4-dioxaspiro[4.5]decane (1a-4a) and 0,03 mol a sodium salt of 1,2,4-triazole or imidazole in was refluxed in 50 ml DMF for 16 h, filtered and evaporated. The residue was chromatographed on silica gel by gradient eluation in acetone-hexane with a concentration gradient of acetone from 10% to 40%.

1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)-1*H*-1,2,4-triazole (1b). Yield 12%, n_D^{20} 1.4874. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.32-1.44 (m, 2H, CH_2 cycl.); 3.77 (d.d, 1H, CH_2O, ^3J = 8.0, ^2J = 8.9); 4.11 (d.d, 1H, CH_2O, ^3J = 8.0, ^2J = 8.9); 4.32 (d, 2H, CH_2N, ^3J = 6.2); 4.46 (q, 1H, CHO, ^3J = 5.8); 7.94 (c, 1 H, C^{3}H triaz.); 8.19 (s, 1H C^{5}H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (β CH triaz.); 1248, 1228, 1172, 1120, 1072 (COCOC).

1-[(8-Methyl-1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazole (2b). Yield 44%, n_D^{20} 1.4930. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.90 (d, 3H, CH_3, ^3J = 6.2); 1.04-1.32 (m, 3H, CH, CH_2 cycl.); 1.33-1.82 (m, 6H, CH_2 cycl.); 3.77 (d.d, 1H, CH_2O, ^3J = 6.0, ^2J = 8.8); 4.09 (d.d, 1H, CH_2O, ^3J = 7.1, ^2J = 8.8); 4.31 (d, 2H, CH_2N, ^3J = 6.0); 4.42 (q, 1H, CHO, ^3J = 5.8); 7.94 (s, 1 H, C^{3}H triaz.); 8.16 (s, 0.6H C^{5}H triaz.); 8.18 (s, 0.4H C^{5}H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (β CH triaz.); 1243, 1223, 1171, 1128, 1078 (COCOC).

1-[(8-Methyl-1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazole (2c). Yield 39%, n_D^{20} 1.5035. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.88 (d, 3H, CH_3, ^3J = 6.2); 1.02-1.31 (m, 3H, CH, CH_2 cycl.); 1.31-1.80 (m, 6H, CH_2 cycl.); 3.70 (d.d, 1H, CH_2O, ^3J = 6.2, ^2J = 8.8); 4.05 (d.d, 1H, CH_2O, ^3J = 7.2, ^2J = 8.8); 4.28 (d.d, 2H, CH_2N, ^3J = 6.0, ^2J = 8.8); 4.38 (q, 1H, CHO, ^3J = 5.8); 6.97 (s, 1 H, C^{4}H imidaz.); 7.18 (s, 1H C^{5}H imidaz.); 7.68 (s, 1H C^{2}H imidaz.). IR (Nujol, ν/sm^{-1}): 1281 (β CH imidaz.); 1240, 1220, 1170, 1130, 1080 (COCOC).

1-[(8-*Tert*-butyl-1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazole (3b). Yield 44%, m.p. 57-59^{o}C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.84 (s, 9H, $C(CH_3)_3$); 0.99 (t, 1H, CH cycl., ^3J= 6.1); 1.09-1.22 (m, 2H, CH_2cycl.); 1.25-1.38 (m, 1H, CH_2cycl.); 1.39-1.54 (m, 2H, CH_2cycl.); 1.56-1.69 (m, 2H, CH_2cycl.); 1.71-1.80 (m, 1H, CH_2cycl.); 3.76 (d.d, 2H, CH_2O,^3J= 5.8, ^2J= 8.0); 4.02 (d.d, 2H, CH_2O,^3J= 5.6, ^2J= 8.0); 4.25-4.43 (m, 4H, CH_2N, CHO); 7.94 (s, 1 H, C^{3}H triaz.); 8.17 (s, 1HC^{5}H triaz.). IR (Nujol, ν/sm^{-1}): 1272 (βCH triaz.); 1245, 1225, 1170, 1125, 1075 (COCOC).

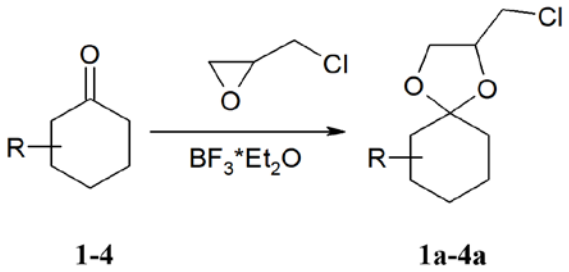
1-[(8-*Tert*-butyl-1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazole (3c). Yield 41%, n_D^{20} 1.4960. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.82 (s, 9H, $C(CH_3)_3$); 0.95 (t, 1H, CH cycl., ^3J= 6.1); 1.07-1.20 (m, 2H, CH_2 cycl.); 1.22-1.34 (m, 1H, CH_2 cycl.); 1.35-1.53 (m, 2H, CH_2 cycl.); 1.53-1.65 (m,2H, CH_2 cycl.); 1.69-1.78 (m, 1H, CH_2 cycl.); 3.72 (d.d, 2H, CH_2O, ^3J = 5.6, ^2J= 8.2); 4.00 (d.d, 2H, CH_2O, ^3J = 5.6, ^2J = 8.2); 4.22-4.40 (m, 4H, CH_2N, CHO); 6.92 (s, 1 H, C^{4}H imidaz.); 7.28 (s, 1H C^{5}H imidaz.); 7.78 (s, 1H C^{2}H imidaz.). IR (Nujol, ν/sm^{-1}): 1280 (β CH imidaz.); 1245, 1225, 1172, 1127, 1080 (COCOC).

1-[(7,7,9-Trimethyl-1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazole (4b). Yield 27%, n_D^{20} 1.4885. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.82-1.06 (m, 9H, $(CH_3)_3$); 1.07-1.27 (m, 3H, CH, CH_2 cycl.); 1.29-1.61 (m, 2H, CH_2 cycl.); 1.66-1.93 (m, 2H, CH_2 cycl.); 3.69 (d.d, 0.44H, CH_2O, ^3J = 6.4, ^2J = 8.4); 3.79 (d.d, 0.56H, CH_2O, ^3J = 5.8, ^2J = 8.4); 4.0-4.15 (m, 1H, CH_2O); 4.22-4.49 (m, 2H, CHO, CH_2N); 7.94 (s, 1 H, C^{3}H triaz.); 8.16 (s, 0.56H C^{5}H triaz.); 8.18 (s, 0.44H C^{5}H triaz.).

RESULTS AND DISCUSSION

For the synthesis of the target compounds, a two-stage scheme was selected, by which ketalization of the source cyclohexanones with epichlorohydrin during catalysis by trifluoride boron etherate synthesized intermediate 2-chloromethyl-1,4-dioxaspiro[4.5]decanes **1a-4a**, which then alkylated 1,2,4-triazole or imidazole sodium salts.

For the synthesis of 2-chloromethyl-1,4-dioxaspiro[4.5]decanes, the Petrov method [23] served as the prototype. We tested this method on 4-methylcyclohexanone **2**, however, having reduced the excess of 4-methylcyclohexanone to twofold. The yield of the target 8-methyl-2-chloromethyl-1,4-dioxaspiro[4.5]decane **2a** was only 16%, and the main share among the reaction products was a resin of unidentified structure, apparently formed during the polymerization of epichlorohydrin, since the conversion of 4-methylcyclohexanone **2** almost coincided with the yield of **2a** (fig. 1). When epichlorohydrin was added to the mixture of ketone and catalyst, the reaction temperature increased sharply, possibly due to the side reaction of polymerization of epichlorohydrin. In this regard, the methodology has been modified: 4 mol% of boron trifluoride etherate were added to a twofold excess of ketone with stirring, cooled to 10–15^{o}C, after which epichlorohydrin dropwise at 30-40^{o}C. With this method, the yield increased to 34% and the proportion of by-products of polymerization of epichlorohydrin decreased.



1-4 **1a-4a**

Fig. 1

Due to the fact that various authors describing the use of boron trifluoride etherate as a catalyst in the synthesis of 1,3-dioxolanes, varied its amount from 1 to 10 mol%, we conducted an additional study to identify the effect of the amount of catalyst on the yield of chloromethyldioxolane **2a**. It was found that the highest yield of **2**a – 45% was achieved in the case of reducing the amount of catalyst from 4% to 2%. Further reducing the amount of catalyst to 1 mol% led to a decrease in the yield to 38%:

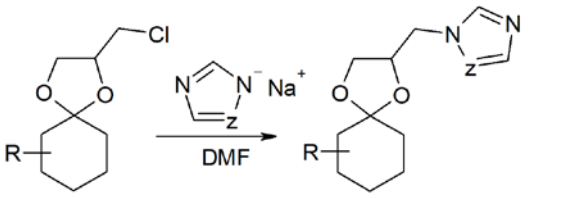
According to the method modified for the product **2a**, 2-chloromethyl-1,4-dioxaspiro[4.5]decanes **1a**, **3a, 4a** were synthesized with average yields of 67%, 88% and 85% respectively. In the case of the synthesis of 8-*tert*butyl-2-chloromethyl-1,4-dioxaspiro[4.5]decane **3a** from crystalline 4-*tert*butylcyclohexanone, the reaction was carried out in a solvent, carbon tetrachloride, as in [24].

In the ^{1}H NMR spectra of 2-chloromethyl-1,4-dioxaspiro[4.5]decanes **1a-4a**, protons of the cyclohexane fragment were present in the form of several multiplets at 1.01–1.89 ppm, and characteristic signals of 2,2,4-tri-substituted dioxolane were observed: two doublets of doublets of protons of the chloromethyl group at 3.47–3.48 and 3.57–3.60 ppm, as a rule, two doublets of doublets of the dioxolane ring methylene protons at 3.80-3.89 and 4.08–4.15 ppm, and dioxolane methine proton quintets at 4.26–4.45 ppm.

In the IR spectra of chloromethyldioxolanes **1a-4a**, there was no signal from the carbonyl group of the source ketone, and

five characteristic bands of the dioxolane ring were observed in the range of 1085–1245 cm^{-1}.

Target substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles **1b; 2b,c; 3b,c, 4b** were synthesized with a yield of from 12 to 44% by alkylation of the sodium salt of 1,2,4-triazole or imidazole with 2-chloromethyl-1,4-dioxaspiro[4.5]decanes **1a-4a** with boiling in dimethylformamide for 16–20 h (fig. 2).



1a-4a **1b, 2b, 2c, 3b, 3c, 4b Z=N, CH**

Fig. 2.

The alkylation reaction of sodium azolates with 2-chloromethyl-1,4-dioxaspiro[4.5]decanes in lower boiling solvents: acetonitrile or tetrahydrofuran, did not lead to the formation of the target azole derivatives. No positive results have been achieved when using imidazole as a base and imidazole melt solvent, or in the case of using potassium carbonate as a base.

According to ^{1}H NMR spectroscopy and chromatography-mass spectrometry, the reaction masses contained in addition to target substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles up to 10% of substituted 4-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles, 15% of the mixture of hydrolyzates of the target derivatives 3-(1*H*-azol-1-yl)propan-1,2-diols and source cyclohexanones. Since the derivatives **1b; 2b,c; 3b,c, 4b** in the technical condition were viscous oily liquids with high boiling points; it was not possible to purify them by recrystallization or vacuum distillation. Therefore, we used column chromatography to isolate individual 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles. For this purpose, a column with a diameter of 30 mm was used; Acros silica gel (particle size 35–70 μm) was eluted with chloroform: methanol (10:1) system. With this method, the target derivatives were successfully separated from the impurities of the source cyclohexanones, by-products of 4-substitution, bis-alkylation, as well as 3-(azol-1-yl)propane-1,2-diols.

In ^{1}H NMR spectra of substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles **1b; 2b,c; 3b,c, 4b**, characteristic signals of the protones of 2,2,4-trisubstituted dioxolane are observed: at 3.69-3.77 and 4.02–4.11 ppm, there are two doublets of doublets of methylene protons of the dioxolane cycle, at 4.22–4.49 ppm, there are two doublets of doublets of the azolylmethyl group and the quintet of the methine proton of dioxolane, both in the form of separate signals and in the form of multiplets [25]. In comparison with 2-chloromethyl-1,4-dioxaspiro[4.5]decanes, the signals of the protons of the exocyclic methylene group of substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles are shifted to a weaker field, and their chemical shift values are greater than those of protons.

The target compounds were tested for fungicidal activity *in vitro* according to the procedure of [26] on six common fungal phytopathogens: *Sclerotinia sclerotiorum (S.s.)* – causative agent of white rot, *Fusarium oxysporum (F.o.), Fusarium moniliforme (F.m.)* – causative agent of Fusarium wilt, *Bipolaris sorokiniana (B.s.)* – causative agent of helminthosporium root rot, *Rhizoctonia solani (R.s.)* – causative agent of brown rot – Rhizoctonia rot and *Venturia inaequalis (V.i.)* – causative agent of apple scab. Effect of compounds on the radial growth of mycelium was studied at a concentration of 30 mg/l. Solutions of the test substances were prepared in acetone, their aliquots were added to the molten sterile potato-sucrose agar, and the resulting media were poured into aseptic conditions in Petri dishes, in which case a final concentration of acetone in all media, including test medium, did not exceed 1%. Pieces of fungus mycelium were placed on the consolidated nutrient medium, thermostated in the dark at 25±0.5^{o}C, and the radial growth was measured after 72 h. The experiment was repeated three times. The percent of mycelial growth inhibition (I) was calculated by Abbott:

$$I = \frac{D_c - D_t}{D_c} \cdot 100\,\%$$

D_c – is the diameter of the fungus colonies in the test medium (control), D_t – is the diameter of the fungal colonies in the medium with the test substance.

The known 1,2,4-triazole fungicide – *triadimefon* and the prototype – dioxaspirodecane – *spiroxamine* were used as standards. The research results are presented in table 1.

Investigated 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles showed a fungicidal activity, significantly lower than the activity of the widely triazole fungicide triadimefon, and the closest to them in the structure of dioxaspirodecane – spiroxamine. Compounds **3b** and **3c**, differing from spiroxamine only by the fact that the propylethylamine group is replaced with a 1,2,4-triazole or imidazole group, also showed activity significantly lower than the standards.

A series 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles was tested for growth-regulating activity on germs of cucumber (one of the recommended test cultures [28]) of Zozulya variety (hybrid F_1).

Table 1. Inhibition (I) of mycelial growth of phytopathogenic fungi under the action of test compounds.

Compound	I, %						logP*
	V.i.	***R.s.***	***F.o.***	***F.m.***	***B.s.***	***S.s.***	
1b	7	1	5	16	7	10	0.64±0,60
2b	0	14	8	21	2	9	1.13±0,60
2c	0	7	8	16	11	8	1.78±0,46
3b	26	0	9	0	13	8	2.36±0,61
3c	21	0	14	26	16	17	3.01±0,47
4b	26	0	15	12	1	12	2.16±0,62
triadimefon	58	40	82	89	54	57	
spiroxamine	81	70	16	59	70	59	

* calculated values of logP [27];

Table 2. Growth-regulating activity on germs of cucumber under the action of test compounds.

№	Conc., mg/l	length of the root system		length of the aboveground part		wet weight		dry weight	
		ℓ, cm	Δℓ,%	ℓ, cm	Δℓ,%	m, g	Δm,%	m, g	Δm,%
3b	0,001	2,1±0,4	**-40,0**	7,5±1,2	-16,7	3,99	-0,5	0,21	-47,5
	0,01	0,7±0,3	**-80,0**	5,2±1,0	-42,2	2,89	-27,9	0,47	17,5
	0,1	2,1±0,5	**-40,0**	7,3±1,2	-18,9	3,52	-12,2	0,34	-15,0
	1,0	1,6±0,6	**-48,5**	8,1±1,1	-10,0	3,99	-0,5	0,41	2,5
	10,0	1,5±0,4	**-57,1**	7,0±1,0	-22,2	3,16	-21,2	0,39	-2,5
4b	0,001	1,6±0,3	**-48,5**	10,3±2,0	14,4	2,63	-34.4	0,31	-22,5
	0,01	0,6±0,2	**-82,8**	3,3±0,6	-63,3	2,21	-44.9	0,27	-32,5
	0,1	1,9±0,6	**-45,7**	4,5±1,3	-50,0	3,54	-11.7	0,47	17,5
	1,0	1,3±0,5	**-62,8**	5,6±0,9	-37,7	2,61	-34.9	0,28	-30,0
	10,0	1,0±0,2	**-71,4**	5,5±0,6	-38,9	2,71	-32.4	0,32	-20,0
Control (water)		3,5±0,4	0	9,0±1,1	0	4,01	0	0,40	0

In the work, an express method was used, which consisted in growing cucumber seeds *in vitro* for 8 days. The seeds were cultivated on Murashige and Skoog (MS) agar medium free of substances belonging to the auxin and cytokinin classes. The drugs were subjected to cold sterilization (solutions were passed through bacterial filters) and then they were added to the pre-autoclaved nutrient medium MS, and poured into sterile culture bottles. Cucumber seeds were superficially sterilized with a 0.1% solution of mercuric chloride for 10 minutes, then washed three times with sterile distilled water and placed on the nutrient medium MS. The bottles with plant material were covered with foil and transferred to the light room, where the temperature of 22^{o}C, constant illumination with white fluorescent lamps, with an intensity of 3 thousand lux, at a humidity of 70% were maintained. In the experiment, each drug was studied in 5 concentrations: 0.001; 0.01; 0.1; 1 and 10 mg/l. Control was a variant that did not contain the drug. For each variant, 50 seeds were sown.

At the end of the 8th day, the linear and weight indicators of cucumber germ plants were studied: the length of the root system (cm), the length of the aboveground part of the germ plant (cm), dry and wet weight of the germ plant (g). The experimental results were statistically processed using Straz and Excel software packages. The analysis of variance was carried out and the standard error or the error of the sample mean was found.

The growth-regulating activity of compounds was judged by the following criteria: the length of the aboveground part of the germ plant and root, the dry mass of the aboveground part of the germ plant and root. The research results of the growth-regulating activity are presented in table 2.

Most of the studied compounds in the entire concentration range: from 0.001 to 10 mg/l showed noticeable retardant properties, reducing the length of the aboveground part with significantly less inhibitory effect on root growth.

CONCLUSIONS

The substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles showed no fungicide activity, but proved good retardant properties. That is why new substituted 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,4-dioxaspiro[4.5]dec-2-yl)methyl]-1*H*-imidazoles synthesis and their retardant activity evaluation is to be done further.

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