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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW MORPHOLIN-CONTAINING THIOANHYDRIDES

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Abstract. *Introduction.* Morpholine is a promising and versatile six-membered heterocycle, a popular pharmacophore with a wide spectrum of biological and pharmacological activity. *The purpose of this work* is the synthesis of biologically active compounds, based on 3-morpholinepropylamine, the determination of the structure and biological activity of the synthesized compounds. *Results and discussion*. Acetic, propionic, benzoic, 4-chlorobenzoic and 2,4-dichlorobenzoic 3-morpholinopropylcarbamothioic thioanhydrides have been synthesized as a result of acylation of sodium 3-morpholylpropylcarbadithioate with the corresponding acid's chlorides. The synthesis has been carried out in acetone at the room temperature for 2 – 3 h. The structure of the synthesized compounds has been established on the basis of the elemental analysis data, IR spectra, ^{1}H and ^{13}C NMR spectroscopy. *Conclusion.* As a result of the laboratory and field tests, it has been found that the use of morpholinopropylcarbamothioic thioanhydrides contribute to an increase in the seed shoot formation of wheat and spruce. Propionic 3-morpholinopropylcarbamothioic thioanhydride activates at a concentration of 0.01% the seedlings length of wheat seeds up to 5.1 cm and increases the germination of shoots up to 88%, and on spruce seeds, the seedlings length is 7.3 cm and the germination of shoots is 87% as compared with the control (4.4 cm, 86% and 4.0 cm, 84%), respectively. Benzoic (3-morpholinopropyl)carbamothioic thioanhydride has shown at a concentration of 0.01% a high shoot-forming ability, the length of shoots by cutting *Spiraea Vanhouttei* is on average 3.91 cm, as compared with the control (1.63 cm) and with the preparations Kornevin (2.58 cm) and KN-2 (3.59 cm).

Key words: sodium (3-morpholinopropyl) carbamodithioate, thioanhydrides, growth-stimulating and shoot-forming activity, wheat and spruce seeds

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1. Introduction

Compounds, containing a morpholine molecule, are still considered one of the most demanded structural pharmacophores for the creation of medicinal preparations with a wide spectrum of effects [1]. Morpholine derivatives are widely used in medicine, such as antibiotic Linezolid [2], psychostimulant Phenmetrazine [3], antidepressant Moclobemide and antitumor preparation Gefitinib [4].

For decades, scientists have been synthesizing compounds involving the morpholine ring, which has led to the synthesis of pharmacophore substances responsible for the anti-inflammatory, antiviral, antimicrobial, anticonvulsant, antioxidant and antitumor activities [5, 6].

Morpholine derivatives have found application as solar cells [7], fluorescent probes for the detection of HClO [8] and Hg^{2+} [9], surfactant as a collector for the reverse flotation separation of halite from carnallite ore [10, 11], and are also effective materials for protecting marine vessels from biocorrosion [12]. In addition, the preparation “Fenpropimorph” is widely used in agriculture as a fungicide for crops.

The analysis of scientific and technical literature shows that increased interest in morpholine derivatives is associated with a wide range of practically useful properties of these compounds, many of which are used both in the chemical industry and in medicine.

2. Experimental part

The progress of the reactions and the purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with the display of spots of the compounds with iodine vapor, eluent ethanol/benzene (1/3) and acetone/ hexane (1/4). The IR spectra were recorded on a Nicolet 5700 spectrometer in tablets with KBr. The melting points of the compounds were determined on a Hanon MP450 instrument. The ^{1}H and ^{13}C NMR spectra of the compounds were recorded on a JNM-ECA 400 spectrometer (Jeol) with the operating frequency of 400 (^{1}H) and 100 MHz (^{13}C) in the deuterated DMSO-d_6 solution. The elemental analysis was carried out on a Rapid Micro N Cube elemental analyzer (Elementar, Germany).

Acetic (3-morpholinopropyl)carbamothioic thioanhydride (1). A solution of 0.31 g (0.0036 mol) of acetic chloride was added dropwise to a solution of 1 g (0.0036 mol) sodium (3-morpholinopropyl)carbamodithioate in 20 ml of acetone with stirring. The mixture was stirred at the room temperature of 22°C for two hours. The solvent was distilled off in a water-jet pump vacuum, the product was isolated by recrystallization from hexane. Yield 0.5 g (50%), R_f 0.36 (ethanol/benzene, 1/3), m.p. 168 °C. Found, %: C 45.93; H 7.05; N 10.79; S 24.57. $C_{10}H_{18}N_2O_2S_2$. Calculated, %: C 45.77; H 6.91; N 10.68; S 24.44. IR spectra (KBr), ν, cm^{-1}: 618 (C–S), 1106 (C=S), 1645 (C=O), 3155 (NH). NMR ^{1}H spectra (DMSO-d_6), δ, ppm: 2.46 (s, 3H, CH_3); 1.77 (m, 2H, CH_2); 3.03 (t, 2H, $C\underline{H}_2NH$); 2.46 (t, 2H, $C\underline{H}_2N$-); 3.05 (t, 4H, $N(CH_2)_2$); 3.85 (t, 4H, $O(CH_2)_2$); 8.12

(s, 1H, NH). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 23.1 (CH_3); 23.0 (CH_2); 36.3 (CH_2NH); 40.6 (N-CH_2); 54.4 (N(CH_2)$_2$); 63.6 (O(CH_2)$_2$); 169.9 (C=O); 173.3 (C=S).

Propionic 3-morpholinopropylcarbamothioic thioanhydride (2) was synthesized in a similar way. Yield 0.7 g (70%), R_f 0.12 (ethanol/benzene, 1/3), m.p. 180ºC. Found, %: C 47.69; H 7.48; N 10.02; S 23.43. $C_{11}H_{20}N_2O_2S_2$. Calculated, %: C 47.80; H 7.29; N 10.13; S 23.20. IR spectra (KBr), ν, cm^{-1}: 626 (C–S), 1111 (C=S), 1663 (C=O), 3342 (NH). NMR ^{1}H spectra (DMSO-d_6), δ, ppm: 0.92 (s, 3H, CH_3); 1.76 (m, 2H, CH_2); 2.12 (m, 2H, $\underline{CH_2}CH_3$); 3.03 (t, 2H, C$\underline{H_2}$NH); 2.96 (t, 2H, C$\underline{H_2}$N-); 3.32 (t, 4H, N(CH_2)$_2$); 3.82 (t, 4H, O(CH_2)$_2$); 8.10 (s, 1H, NH). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 9.9 (CH_3); 23.1 (CH_2); 36.4 (N-CH_2); 51.5 (CH_2NH); 54.7 (N(CH_2)$_2$); 63.7 (O(CH_2)$_2$); 169.9 (C=O); 172.7 (C=S).

Benzoic (3-morpholinopropyl)carbamothioic thioanhydride (3) was synthesized in a similar way. Yield 0.7 g (57%), R_f 0.14 (ethanol/benzene, 1/3), m.p. 168ºC. Found, %: C 55.33; H 6.21; N 8.93; S 19.57. $C_{15}H_{20}N_2O_2S_2$. Calculated, %: C 55.01; H 6.01; N 9.13; S 19.11. IR spectra (KBr), ν, cm^{-1}: 682 (C–S), 1105 (C=S), 1690 (C=O), 3116 (NH). NMR ^{1}H spectra (DMSO-d_6), δ, ppm: 1.93 (m, 2H, CH_2); 3.32 (t, 2H, C$\underline{H_2}$NH); 2.45 (t, 2H, CH_2N-); 3.06 (t, 4H, N(CH_2)$_2$); 3.84 (t, 4H, O(CH_2)$_2$); 7.42 (t, 2H, Ar); 7.85 (t, 1H,Ar); 8.07 (d, 2H, Ar); 8.36 (s,1H, NH). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 23.7 (CH_2); 42.9 (CH_2NH); 51.4 (N-CH_2); 53.6 (N(CH_2)$_2$); 63.3 (O(CH_2)$_2$); 128.8, 130.2, 134.7 (Ph); 168.7 (C=O); 169.3 (C=S).

4-Chlorobenzoic (3-morpholinopropyl)carbamothioic thioanhydride (4) was synthesized in a similar way was synthesized in a similar way.Yield 2.0 g (67%), R_f 0.52 (acetone/hexane, 1/4), m.p. 104ºC. Found, %: C 50.33; H 5.43; N 7.93; S 17.57. $C_{15}H_{19}ClN_2O_2S_2$. Calculated, %: C 50.20; H 5.34; Cl 9.88; N 7.81; S 17.87. IR spectra (KBr), ν, cm^{-1}: 705 (C–S), 1068 (C=S), 1647 (C=O), 3123 (NH). NMR ^{1}H spectra (DMSO-d_6), δ, ppm: 1.90 (s 2H, CH_2); 3.28 (t, 2H, C$\underline{H_2}$NH); 2.96 (t, 2H, CH_2N-); 3.04 (t, 4H, N(CH_2)$_2$); 3.78 (t, 4H, O(CH_2)$_2$); 7.46 (d, 2H, Ar); 7.86 (d, 2H, Ar); 8.74 (s,1H, NH). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 24.0 (CH_2); 37.2 (C$\underline{H_2}$NH); 54.6 (CH_2N-); 51.7 (N(CH_2)$_2$); 64.0 (O(CH_2)$_2$); 129.6, 130.3, 131.6, 133.5, 136.5, 138.2 (Ar); 165.7 (C=O); 166.9 (C=S).

2,4-Dichlorobenzoic (3-morpholinopropyl)carbamothioic thioanhydride (5) was synthesized in a similar way. Yield 1.0 g (64%), R_f 0.56 (acetone/hexane, 1/4), m.p. 92ºC. Found, %: C 45.95; H 4.73; N 7.27; S 16.48. $C_{15}H_{18}Cl_2N_2O_2S_2$. Calculated, %: C 45.80; H 4.61; Cl 18.03; N 7.12; S 16.30. IR spectra (KBr), ν, cm^{-1}: 667 (C–S), 1049 (C=S), 1693 (C=O), 3152 (NH). NMR ^{1}H spectra (DMSO-d_6), δ, ppm: 1.77 (m, 2H, CH_2); 3.25 (t, 2H, C$\underline{H_2}$NH); 2.70 (t, 2H, CH_2N-); 2.66 (t, 4H, N(CH_2)$_2$); 3.66 (t, 4H, O(CH_2)$_2$); 7.42 (dd, 1H, Ar); 7.58 (t, 2H, Ar); 8.52 (s, 1H, NH). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 25.1 (CH_2); 37.5 (C$\underline{H_2}$NH); 55.4 (C$\underline{H_2}$N-); 52.7 (N(CH_2)$_2$); 65.3 (O(CH_2)$_2$); 127.8, 129.6, 131.6, 132.6, 134.6, 136.3 (Ar);165.9 (C=O); 168.9 (C=S).

Biological studies of the compounds were carried out at Zh. Zhiyembayev Kazakh Research Institute of Quarantine and Plant Protection LLP and RSE Institute of Botany and Phytointroduction Forestry and Wildlife Committee of the Ministry of Ecology and Natural Resources of the Republic of Kazakhstan.

Laboratory experiment.

Object of the study: seeds of wheat and spruce. The experimental samples were laid in 3-fold repetition of 50 seeds. The duration of the experiment was 3 - 7 days. The experiment was carried out according to the scheme: 1. Control (water). 2. Compound 2 at a concentration of 0.01%.

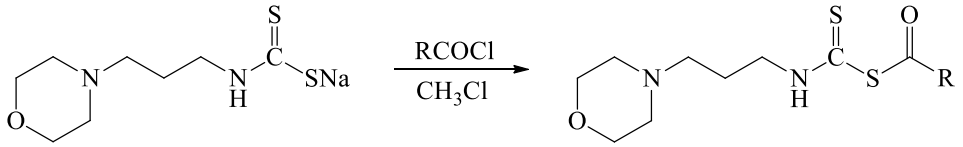
Field experiment.

In the experiment, semi-lignified cuttings of *Spiraea Vanhouttei* 8–9 cm long, with three buds in an amount of 65 pieces, were soaked in a solution of compound 3 with concentrations (0.001%, 0.01%) for 6 hours. The cuttings were planted in a greenhouse with a prepared substrate (soil:sand). The duration of the experiment was 4 months. Within 4 months, the cuttings were watered.

3. Results and discussion

One of the promising branches of the study of nitrogen-containing heterocyclic compounds is the synthesis, transformations and biological activity of morpholine derivatives.

Synthesis of thioanhydrides, based on sodium 3-morpholinopropyldithiocarbamates was carried out by acylation of dithiocarbamate with the corresponding acid chlorides (acetic, propyl, benzoic, 4-chlorobenzoic, and 2,4-dichlorobenzoic) in acetone at the room temperature.



1 R= CH_3; 2 R = C_2H_5; 3 R = C_6H_5; 4 R = 4-ClC_6H_4; 5 R = 2,4-$Cl_2C_6H_3$.

As a result of processing the reaction mixtures in the individual form of morpholine thioanhydrides of dithiocarbamic acid 1-5 were obtained with the corresponding yields of 50-70%.

The structure and the composition of the synthesized compounds 1-5 was determined, based on the IR spectra and ^{1}H and ^{13}C NMR spectroscopy and elemental analysis data.

In the IR spectra of the compounds 1-5, an absorption band of stretching vibrations of the NH group appears in the region 3116-3342 cm^{-1}. The absorption band of stretching vibrations of the C=S group is present in the region of 1106-1111 cm^{-1}. There is an absorption band of the C-S bond in the region of 618-705 cm^{-1}. The formation of thioanhydrides was evidenced by the presence in the IR

spectra of an intense absorption band of the C=O group in the region of 11645-1693 cm^{-1}.

There are signals of carbon atoms of the methyl group in the region of the spectrum δ 23.0-55.4 ppm in the ^{13}C NMR spectrums of compounds 1-5. The cyclic carbon atoms of morpholine $–(CH_2)_2N-$ and $–O(CH_2)_2$ resonate in the region of δ 51.7-54.7 ppm and δ 63.3-65.3 ppm, respectively. The signal of the carbon atom of the C=O group appears in the low field region δ 165.7-169.9 ppm. The carbon atom of the C=S group resonates in the weak field δ 166.3-173.3 ppm.

The biological study was carried out to investigate the effect of thioanhydride 2 on the sowing qualities of wheat and spruce seeds under the laboratory conditions. The growth-stimulating activity of the studied compound 2 is evaluated by two parameters: the length of the seedlings and the germination of the shoots. Compound 2 activates at a concentration of 0.01% the length of wheat seedlings up to 5.1 cm and increases the germination of shoots up to 88%, as compared with the control. Thus, compound 2 activates on spruce seeds the length of seedlings up to 7.3 cm and increases the germination of shoots up to 87%. (Table 1).

Table 1 – Growth-stimulating activity of the compound 2

Preparation concentration, %	Seedling length, cm	Shoot germination, %
Wheat seeds		
Control (Water)	4.4	86
Compound 2, 0.01%	5.1	88
Spruce seeds		
Control (Water)	4.0	84
Compound 2, 0.001%	7.3	87

The field experiment was carried out to identify the root-forming activity of the obtained substances and to determine the effect of compounds on the growth and development of the shoots and the root system of spirea cuttings (Figures 1, 2).

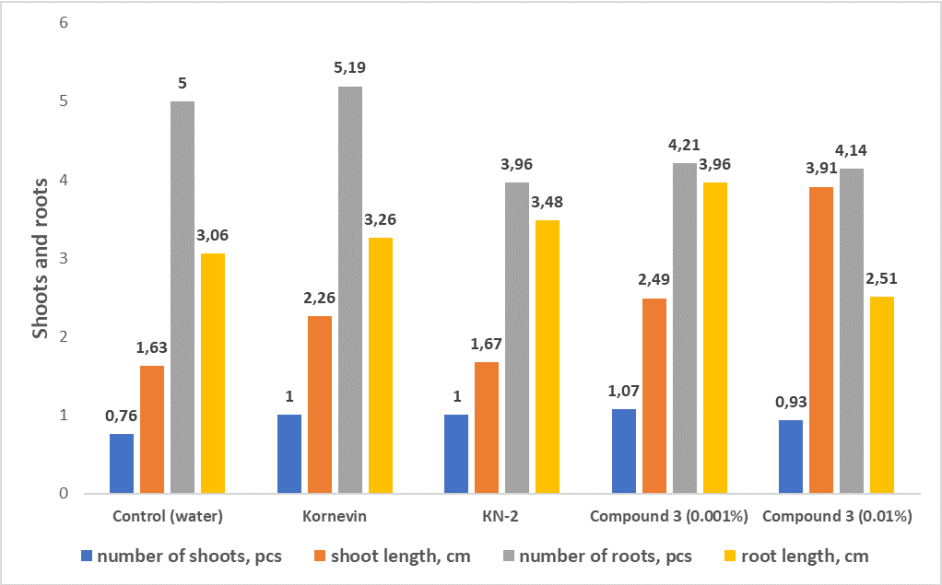


Figure 1 – Shoot- and root-forming activity of compound 3.

Figure 1 shows that compound 3 exhibits moderate root-forming activity as compared with the control and standard preparations Kornevin and KN-2, which showed a higher activity.

The shoot-forming ability of the studied preparation was determined by two parameters: the number and length of the formed shoots.

Compound 3 at the concentration of 0.01% showed a good shoot length of 3.91 cm compared to the control (1.63 cm) and the standard preparations Kornevin (2.58 cm) and KN-2 (3.59 cm), respectively (Figure 1). The number of shoots formed on the semi-lignified cuttings of spirea was at the concentration of 0.01% in the same range of 0.76-1.12 pcs depending on experience.

Figure 2 shows that the percentage of the root formation of cuttings at the concentration of 0.01% has a similar interval between indicators from 42% to 45%, depending on the variant of the experiment. Thus, preparation 3, developed by us, contributes to the growth of the crown of *Spiraea Vanhouttei* shrubs.

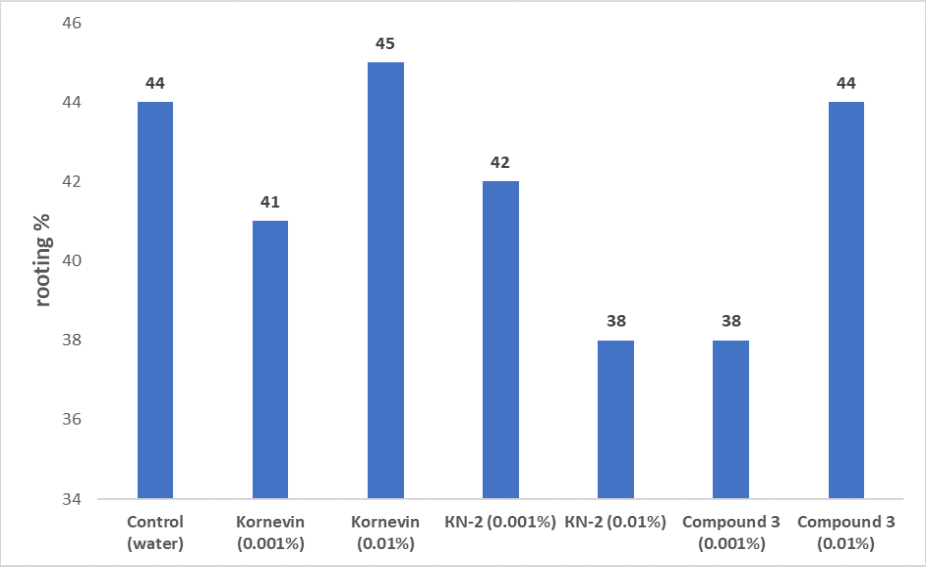


Figure 2 – The effect of compound 3 on the number of the rooted cuttings of *Spiraea Vanhouttei* at the concentrations of 0.01 and 0.001%.

4. Conclusion

An acylation reaction of heterocyclic amine dithiocarbamate based on 3-morpholinopropan-1-amine has been studied, new heterocyclic acetyl, propyl, benzoic, 4-chloro- and 2,4-dichlorobenzoic thioanhydrides of carbamothioic acid have been synthesized.

The stimulating effect of the studied thioanhydrides at the concentration of 0.01% on the processes of germination and shoot formation based on the laboratory and field tests has been determined. A total positive effect on the morphometric parameters of seeds (wheat, spruce) and on semi-lignified cuttings of *Spiraea Vanhouttei* has been shown.

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Conflict of Interest: All authors declare that they have no conflict of interest.

СИНТЕЗ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ НОВЫХ МОРФОЛИНСОДЕРЖАЩИХ ТИОАНГИДРИДОВ

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Резюме. *Введение.* Морфолин является перспективным и универсальным шестичленным гетероциклом, востребованным фармакофором с широким спектром биологической и

фармакологической активности. *Целью данной работы* является синтез биологически активных соединений на основе 3-морфолинпропиламина, установление строения и биологической активности синтезированных соединений. *Результаты и обсуждение.* В результате ацилирования 3-морфолинопропилкарбамодитиоата натрия с хлорангидридами соответствующих кислот синтезированы уксусный, пропионовый, бензойный, 4-хлорбензойный и 2,4-дихлорбензойный 3-морфолинопропилкарбамотиоевые тиоангидриды. Синтез проводили в среде ацетона при комнатной температуре в течение 2–3 ч. Строение синтезированных соединений установлено на основании данных элементного анализа, ИК спектров, спектроскопии ^{1}H и ^{13}C ЯМР. *Заключение.* В результате лабораторных и полевых испытаний установлено, что применение морфолинопропилкарбамотиоевых тиоангидридов способствует повышению побегообразования семян пшеницы и ели. Пропионовый (3-морфолинопропил) карбамотиовый тиоангидрид при концентрации 0.01% активирует длину проростков семян пшеницы до 5.1 см и увеличивает всхожесть побегов до 88 %, на семенах ели длина проростков составляет 7.3 см и всхожесть побегов - 87 % по сравнению с контролем (4.4 см, 86% и 4.0 см, 84%), соответственно. Бензойный (3-морфолинопропил) карбамотиовый тиоангидрид при концентрации 0.01% показал высокую побегообразующую способность, длина побегов при черенковании спиреи Вангутта составляет в среднем 3.91 см по сравнению с контролем (1.63 см) и с препаратами Корневин (2.58 см) и КН-2 (3.59 см).

Ключевые слова: (3-морфолинопропил) карбамодитиоат натрия, тиоангидриды, ростстимулирующая и побегообразующая активность, семена пшеницы и ели

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ЖАҢА МОРФОЛИНҚҰРАМДАС ТИОАНГИДРИДТЕРДІҢ СИНТЕЗІ ЖӘНЕ БИОЛОГИЯЛЫҚ БЕЛСЕНДІЛІГІ

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Түйіндеме. *Кіріспе.* Морфолин – тиімді және әмбебап алты мүшелі гетероцикл, биологиялық және фармакологиялық белсенділіктің кең спектрлігі негеізінде сұранысқа ие фармакофор. Жұмыстың *мақсаты* 3-морфолинпропиламина негізінде биологиялық белсенді қосылыстарды синтездеу, синтезделген қосылыстардың құрылымы мен биологиялық белсенділігін анықтау. *Нәтижелер және оларды талдау.* Натрий 3-морфолинопропилкарбамодитиоатының сәйкес хлорангидридтермен ацилдеу нәтижесінде сірке, пропион, бензойлы, 4-хлорбензойлы және 2,4-дихлорбензойлы 3-морфолинопропилкарбамотио тиоангидридтер синтезделінді. Синтез ацетонды ортада бөлме температурасында 2-3 сағат жүргізілді.Синтезделген қосылыстардың құрылымы элементтік талдау, ИҚ спектрлері және ^{1}H және ^{13}C ЯМР спектроскопиясы негізінде анықталды. *Қорытынды.* Зертханалық және далалық сынақтардың нәтижесінде морфолинопропилкарбамотио тиоангидридтерін қолдану бидай мен шырша тұқымдарының өркен түзілуін арттыратыны анықталды. Пропионды (3-морфолинопропил)карбамотио тиоангидрид 0.01% концентрацияда бақылаумен салыстырғанда (тиісінше 4.4 см, 86% және 4.0 см, 84%) бидай тұқымдарының өскіндерінің ұзындығын 5.1 см-ге дейін белсендіреді және өркендердің өнуін 88%-ға дейін арттырады, шырша тұқымдарында өскіндердің ұзындығы 7.3 см және өркендердің өнуі 87% құрады. Бензойлы (3-морфолинопропил)карбамотио тиоангидрид 0.01% концентрацияда жоғары өскінтүзуші қабілетін көрсетті, Вангуттың спирея кесінділерінің өскін ұзындықтары бақылаумен (1.63 см), Корневин (2.58 см) және КН-2 (3.59 см) препараттарымен салыстырғанда орта есеппен 3.91 см құрады.

Түйін сөздер: натрий (3-морфолинопропил)карбамодитиоаты, тиоангидридтер, өсуді ынталандырғыш және өскінтүзгіш белсенділік, бидай және шырша тұқымдары

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