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SYNTHESIS, STRUCTURE AND LABORATORY SCREENING OF GROWTH-STIMULATING, HERBICIDAL AND FUNGICIDAL ACTIVITIES OF DITHIOCARBOMATE AND ITS THIOANHIDRIDES BASED ON 2-OXOPYRROLIDINE

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Abstract. *Introduction.* The search for new and effective plant growth stimulants and chemical plant protection agents remains a pressing issue in modern agrochemistry. *This study aimed* to synthesize dithiocarbamate and its thioanhidrides based on pyrrolidin-2-one and evaluate their potential as plant growth regulators, herbicides and fungicides. *Results and Discussion:* Sodium dithiocarbamate based on 2-oxopyrrolidine and its butyric and benzoic 2-oxopyrrolidine-1-carbothioic thioanhydrides was synthesized with yields of 84%, 88%, and 67%, respectively. The structures of the synthesized compounds were established based on the analysis of elemental data, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy data. Primary laboratory screening for growth-stimulating, herbicidal, and fungicidal activity was carried out. *Conclusion:* High germination rates were observed when wheat seeds were treated with sodium 2-oxopyrrolidine-1-carbodithioate at a concentration of 100 mg/l, resulting in 90% laboratory germination compared to 70% in the control and 80% with treatment by the standards KN-2 and AN-16. Phytotoxicity assays demonstrated that compound 1, at concentrations of 0.01-1 mg/ml, did not negatively affect the sowing qualities of Agrostis and Lactuca seeds and instead promoted intensive growth. Furthermore, sodium dithiocarbamate and its thioanhdrides exhibited fungicidal activity comparable to the standard tetramethylthiuram disulfide (TMTD). The infection rate of wheat and barley seeds by phytopathogenic fungi in the untreated control was 100% and 77.3%, respectively. In contrast, treatment with compounds 1-3 at 0.001-0.1% reduced infection to 12.6-26% for wheat and 7.3-16% for barley, compared to 0.4% and 2.6% with TMTD.

Key words: 2-oxopyrrolidine, dithiocarbamate, thioanhydrides, growth-stimulating, herbicidal and fungicidal activity.

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1. Introduction

Among the diverse range of nitrogen-containing heterocyclic compounds that play a pivotal role in various domains of human activity, the class of pyrrolidone and its derivatives has attracted considerable scientific interest. A key factor contributing to the increased attention to the pyrrolidone scaffold is its incorporation into a number of pharmacologically active compounds, including hemodesis, enterodesis, levetiracetam, rolipram, among others.

In recent years, significant efforts have been directed toward the development of anticancer agents containing the pyrrolidone core, targeting various malignancies such as breast [1], colorectal (HCT116) [2], hepatic (SMMC-7721), and cervical (HeLa) cancers [3]. Furthermore, numerous pyrrolidone-based compounds have demonstrated a broad spectrum of biological activities, including antibacterial [4], antifungal [5], growth-stimulating, herbicide [6], antihypertensive [7], anticonvulsant [8], antiarrhythmic [9], and neuroprotective properties, notably in the context of Alzheimer's disease [10].

A critical analysis of the available literature reveals a marked scarcity of thioanhydride derivatives within this class of compounds. In light of this observation, the present study aims to synthesize novel thioanhydrides of dithiocarbamic acids derived from 2-oxopyrrolidine and to assess their potential as plant growth regulators and chemical agents for crop protection.

2. Experimental part

The reaction control and product purity were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates, with spot visualization performed using iodine vapor. The eluent consisted of a mixture of ethanol and acetone/hexane (1/4). Infrared (IR) spectra were recorded on a Nicolet 5700 FTIR spectrometer using KBr pellets and thin-layer films. Melting points were determined with a Hanon MP450 apparatus. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JNM-ECA 400 spectrometer (JEOL), operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C, using deuterated $CDCl_3$ and DMSO-d_6 as solvents. Elemental analysis was performed with a THERMO FlashSmart CHNS/O elemental analyzer (USA, 2024).

Sodium 2-oxopyrrolidine-1-carbodithioate (1). A solution of 2.35 g (0.058 mol) of sodium hydroxide in 5 ml of water was added to a solution of 5.0 g (0.058 mol) of pyrrolidin-2-one in 30 ml of alcohol. Then, a solution of 4.47 g (0.058 mol) of carbon disulfide was added dropwise and stirred at room temperature. Upon complete addition of carbon disulfide, the reaction mixture was stirred at room temperature for an additional 4 hours. The solvent was then removed under reduced pressure using a water-jet vacuum pump, and the resulting solid was purified by recrystallization from acetonitrile. Yield 9.1 g (84 %), R_f 0.71 (ethanol). Found, %: C 32.66; H 3.21; N 7.57; O 8.67; S 35.12. $C_5H_6NNaOS_2$. Calculated, %: C 32.78; H 3.30; N 7.64; Na 12.55; O 8.73; S 35.00. IR spectra (KBr), ν, cm^{-1}: 675 (C–S), 1045 (C=S), 1673 (C=O). NMR ^{1}H spectra ($CDCl_3$), δ, ppm: 1.92-2.00 (m, 2H, CH_2, pyrrollidone); 2.27 (t, 2H, CH_2, pyrrollidone); 3.26

(t, 2H, CH_2, pyrrollidone). NMR ^{13}C spectra ($CDCl_3$), δ, ppm: 20.5 (CH_2, pyrrollidone); 30.4 (CH_2C=O, pyrrollidone); 42.8 (CH_2N-, pyrrollidone); 181.3 (C=O); 203.3 (C=S).

Butyric 2-oxopyrrolidine-1-carbothioic thioanhydride (2). A solution of 1.3 g (0.012 mol) of butyryl chloride was added dropwise to a stirred solution of 2 g (0.012 mol) sodium 2-oxopyrrolidine-1-carbodithioate in 25 ml of chloroform. The reaction mixture was stirred at room temperature (22 °C) for 2 hours. The solvent was then removed under reduced pressure using a water-jet vacuum pump, and the resulting product was purified by recrystallization from hexane. Yield 2.47 g (88%), R_f 0.34 (acetone/hexane, 1/4). Found, %: C 46.65; H 5.59; N 5.97; O 13.90; S 27.81. $C_9H_{13}NO_2S_2$. Calculated, %: C 46.73; H 5.66; N 6.05; O 13.83; S 27.72. IR spectra, ν, cm^{-1}: 688 (C–S), 1057 (C=S), 1711 (2 C=O, widened st.). NMR ^1H spectra (DMSO-d_6), δ, ppm: 0.85 (t, 3H, CH_3); 1.45-1.53 (m, 2H, CH_2); 1.92-1.98 (m, 2H, CH_2, pyrrollidone); 2.07 (t, 2H, CH_2, pyrrollidone); 2.15 (t, 2H, CH_2); 3.20 (t, 2H, CH_2, pyrrollidone). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 13.9 (CH_3); 18.3 (CH_2, pyrrollidone); 20.7 (CH_2); 30.2 (CH_2C=O, pyrrollidone); 43.9 (CH_2N-, pyrrollidone); 45.5 (CH_2CO); 174.8, 178.0 (C=O); 204.2 (C=S).

Benzoic 2-oxopyrrolidine-1-carbothioic thioanhydride (3) was synthesized by an analogous procedure. Yield 2.22 g (67%), R_f 0.52 (acetone/hexane, 1/4). Found, %: C 54.41; H 4.11; N 5.33; O 12.12; S 24.24. $C_{12}H_{11}NO_2S_2$. Calculated, %: C 54.32; H 4.18; N 5.28; O 12.06; S 24.17. IR spectra, ν, cm^{-1}: 715 (C–S), 1070 (C=S), 1704 (2 C=O, widened st.). NMR ^1H spectra (DMSO-d_6), δ, ppm: 1.92-1.98 (m, 2H, CH_2, pyrrollidone); 2.06 (t, 2H, CH_2, pyrrollidone); 3.19 (t, 2H, CH_2, pyrrollidone); 7.51 (t, 1H, CH, Ar); 7.62 (t, 1H, CH, Ar); 7.94 (d, 1H, CH, Ar). NMR ^{13}C spectra (DMSO-d_6), δ, ppm: 20.8 (CH_2, pyrrollidone); 30.3 (CH_2C=O, pyrrollidone); 41.8 (CH_2N-, pyrrollidone); 127.5, 129.0, 129.7, 131.1, 133.3 (Ar); 167.7, 177.6 (C=O); 203.0 (C=S).

Preliminary laboratory evaluation of the synthesized compounds for growth-stimulating, herbicidal and fungicidal activities.

Growth-stimulating activity. The growth-stimulating activity of the synthesized compounds was assessed using wheat seeds. Experimental groups consisted of 10 seeds per replicate, with three replicates per treatment. The duration of the experiment ranged from 3 to 9 days. Seeds were pre-soaked in the test solutions for 8 hours and subsequently placed in Petri dishes lined with a sterile, four-layer gauze pad. Germination was conducted at an ambient temperature of 21-23 °C.

The experimental scheme included the following treatment groups:

1. Control: distilled water. 2. Standards: Akpinol KN-2 and AN-16 at concentrations of 10, 50, 100, and 200 mg/l. 3. Test sample: Compound 1 at concentrations of 10, 50, 100, and 200 mg/l.

Herbicidal activity. Herbicidal properties were evaluated using seeds of bent grass (Agrostis spp.) and lettuce (Lactuca sativa). Seeds were placed in 24-well plates, and the experiment was conducted over a 7-day period. Phytotoxic effects

were assessed based on visual indicators such as inhibition of root and shoot development and general plant morphology.

The experimental groups were as follows:

1. Standard: 2,4-dichlorophenoxyacetic acid (2,4-D) at concentrations of 0.01, 0.03, 0.1, 0.3, 0.5, and 1.0 mg/ml. 2. Test sample: Compound 1 at the same concentrations as the standard.

Fungicidal Activity. Fungicidal efficacy was examined on wheat and barley seeds, with three replicates of 50 seeds per treatment. The experiment lasted 3-7 days. Activity was assessed based on the degree of microbial growth, the number of infected seeds, seed germination energy, and overall germination rate.

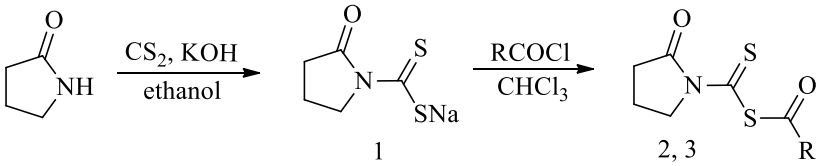
The experimental scheme included:

1. Control: distilled water. 2. Standard: tetramethylthiuram disulfide (TMTD) at a concentration of 0.04%. 3. Test samples: Compounds 1-3 at concentrations of 0.001%, 0.01%, and 0.1%.

3. Results and discussion

Heterocyclic sodium dithiocarbamate was synthesized by the reaction of a heterocyclic amine (2-oxopyrrolidine) with carbon disulfide in the presence of sodium hydroxide in ethanol at room temperature.

The subsequent acylation of sodium 2-oxopyrrolidine-1-carbodithioate was performed by its reaction with aliphatic (butyryl) and aromatic (benzoyl) acid chlorides in chloroform at room temperature, yielding the corresponding thioanhydrides.



1 2, 3

2: R = C_3H_7; 3: R = C_6H_5.

As a result of the synthesis, sodium dithiocarbamate and its thioanhydrides were obtained with yields ranging from 67% to 88%, respectively.

The composition and individuality of the synthesized sodium dithiocarbamate 1 and its thioanhydrides 2, 3 were confirmed by elemental analysis, thin-layer chromatography and physicochemical characteristics. The structure of compounds 1-3 were established based on the analysis of IR and NMR ^{1}H, ^{13}C spectroscopy data.

In the IR spectra of compounds 1-3, absorption bands corresponding to the stretching vibrations of the C–S group are observed in the range ν 675-715 cm^{-1}, along with stretching vibrations of the C=S bond in the region ν 1045-1070 cm^{-1}. In the IR spectrum of compound 1, an intense absorption band of the C=O group appears at ν 1673 cm^{-1}. In the IR spectra of compounds 2 and 3, a broadened

absorption band in the regions ν 1711 and ν 1704 cm^{-1}, respectively, corresponds to the C=O group, indicating the formation of thioanhydrides.

In the ^{1}H NMR spectra of compounds 1-3, the chemical shifts in the upfield region δ 1.92-2.00 ppm, δ 2.06-2.27 ppm, and δ 3.19-3.26 ppm are attributed to the protons of the pyrrolidine ring. The ^{1}H NMR spectrum of compound 2 shows characteristic signals in the upfield region, corresponding to the protons of the methyl and methylene groups at δ 0.85, δ 1.49, and δ 2.15 ppm. In the ^{1}H NMR spectrum of compound 3, the downfield region reveals the signals of the phenyl group protons at δ 7.51, δ 7.62, and δ 7.94 ppm.

The ^{13}C NMR spectra confirm the structure of compounds 1-3 by the presence of corresponding chemical shifts. The cyclic carbon atoms of the pyrolidine ring resonate in the strong field region at δ 18.3-20.8, 30.2-30.4, and 41.8-43.9 ppm. The ^{13}C NMR spectrum of compound 2 exhibits the following signals for the carbon atoms of the methyl and methene groups at δ 13.9, 18.3 and 45.5 ppm. The aromatic carbon signals in the ^{13}C NMR spectrum of compounds 3 appear in the downfield region at δ 127.3-133.3 ppm. The signals of the carbon atoms of the C=O and C=S groups in compound 1 are observed at δ 181.3 ppm and δ 203.3 ppm, respectively. The signals for the C=O carbon atoms in compounds 2 and 3 appear at δ 174.8, 178.0 and δ 167.7, 177.6 ppm, respectively, while the signal for the C=S carbon atom is located at δ 204.2 and 203.0 ppm.

As a result of the laboratory experiment investigating growth-stimulating activity, it was found that sodium dithiocarbamate 1 had a positive effect on the growth and development of wheat seeds (Figure 1).

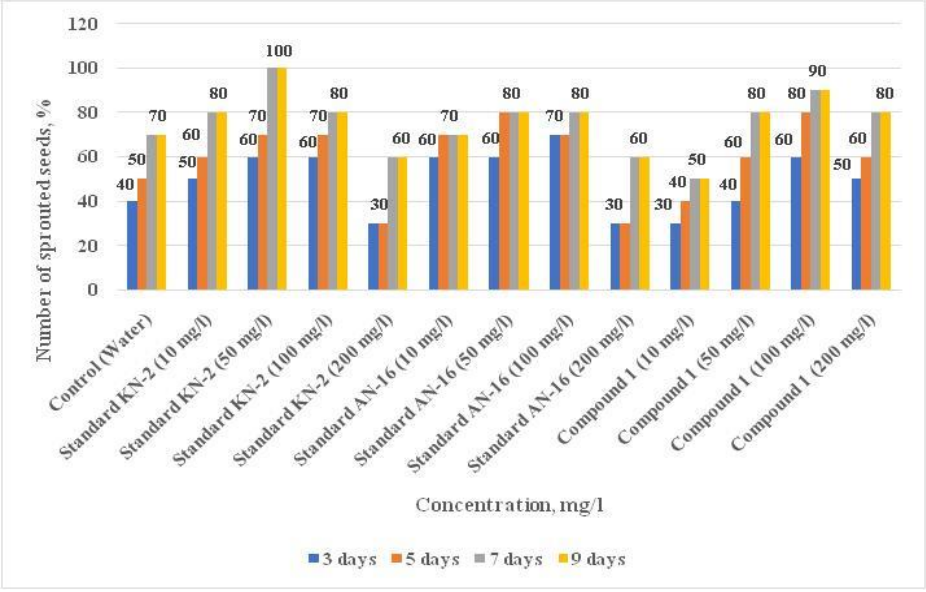


Figure 1 – The effect of compound 1 on the germination of wheat seeds at concentrations of 10-200 mg/l

From the graph data (Figure 1), it can be observed that compound 1 exhibited good activity on the germination of wheat seeds, with the concentration of the solution influencing both germination energy and overall germination.

A high germination rate was achieved when treating with compound 1 at a concentration of 100 mg/l, with laboratory germination of wheat reaching 90% on the seventh and ninth days. For the standard substances, KN-2 and AN-16, germination rates were 80% and 80%, respectively. Increasing the concentration to 200 mg/l led to a decrease in seed germination and growth development, with germination rates for the standards KN-2 and AN-16 dropping to 60%, and for compound 1, to 80%.

The phytotoxic (herbicidal) activity of sodium 2-oxopyrrolidine-1-carbodithioate (compound 1) was evaluated under laboratory conditions using the seeds of Agrostis (bent grass) and Lactuca (lettuce). The results showed that at concentrations ranging from 0.01 to 1 mg/ml, compound 1 did not exhibit herbicidal activity on Agrostis seeds, but rather promoted intensive seed growth. However, on Lactuca seeds, compound 1 at concentrations of 0.3 to 1 mg/ml inhibited growth by 20%, in contrast to the standard herbicide 2.4-D, which caused a 100% inhibition. At lower concentrations, compound 1 did not exhibit any herbicidal activity (Table 1, Figure 2).

The results of phytotesting of wheat and barley seeds treated with compounds 1-3 at concentrations of 0.001%, 0.01%, and 0.1% showed that in most cases, the number of germinated seeds was comparable to the control and standard groups (Figure 3, 4).

For wheat, at the concentrations of compounds 1-3, the germination energy on the 3rd day ranged from 93.3% to 97.3%, and the laboratory germination ranged from 93.3% to 98%, compared to the control (95.3%) and the TMTD standard (91.3% and 96.0%). The damage caused by phytopathogenic fungi to wheat seeds in the control group (without treatment) was 100%. However, when compounds 1-3 were applied at concentrations of 0.001-0.1%, seed infection was reduced to 12.6%-26%, while the TMTD standard resulted in a 0.6% infection rate.

Table 1 - Herbicidal activity of standard 2.4 D and compound 1 at concentrations of 0.01-1 mg/ml

Variants	Concentration, mg/ml	Inhibition of Agrostis bentgrass seeds, %	Inhibition of lettuce seeds Latuc, %
2.4 D (standard)	0.01	20	80
	0.03	40	80
	0.1	60	100
	0.3	60	100
	0.5	80	100
	1	100	100
Compound 1	0.01	0	0
	0.03	0	20
	0.1	0	0
	0.3	0	20
	0.5	0	20
	1	0	20

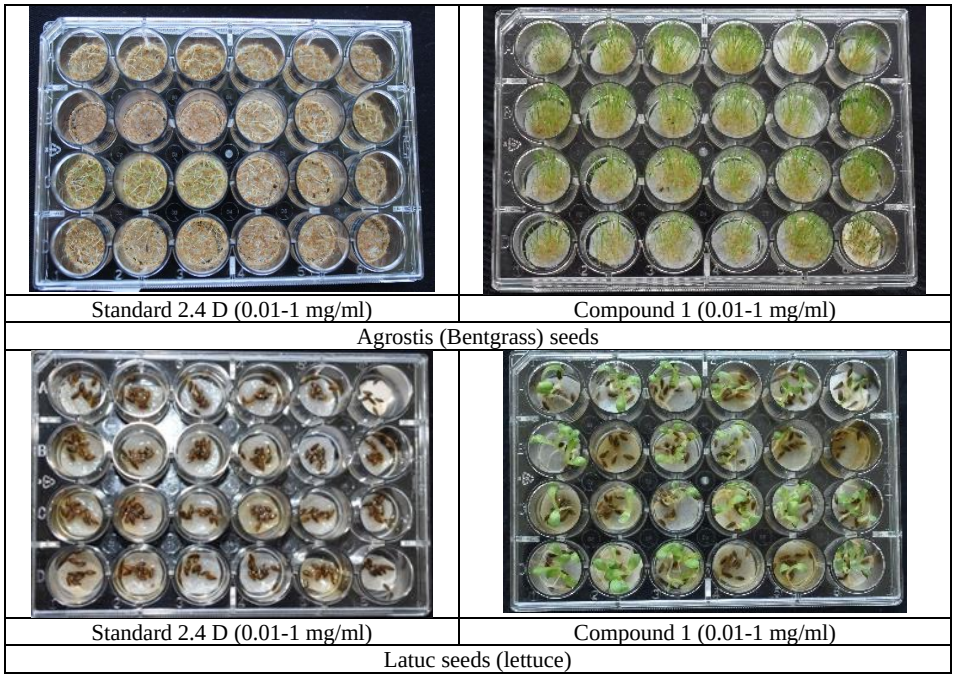


Figure 2 – Herbicidal activity of standard 2.4 D and compound 1 at concentrations of 0.01-1 mg/ml on seeds of Agrostis (bent grass) and Latuc (lettuce).

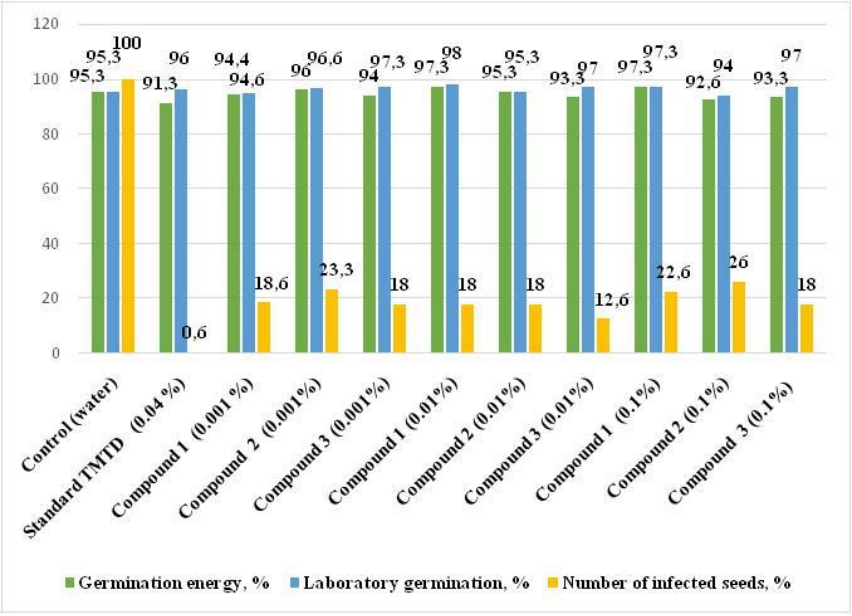


Figure 3 – The effectiveness of treatment with compounds 1-3 on the sowing qualities and microflora of wheat seeds at a concentration of 0.001-0.1%.

In all experimental variants, both the germination energy and laboratory germination were higher than those in the control and standard groups. Additionally, a decrease in fungal and bacterial microflora in barley seeds was observed. Regarding mold fungi (such as Mucor, Alternaria, Penicillium), the highest percentage of damage was observed in the control group (77.3%), while in the TMTD standard, the damage was 2.6%, and in the tested compounds 1-3, the fungal damage ranged from 7.3% to 16%, respectively (Figure 4).

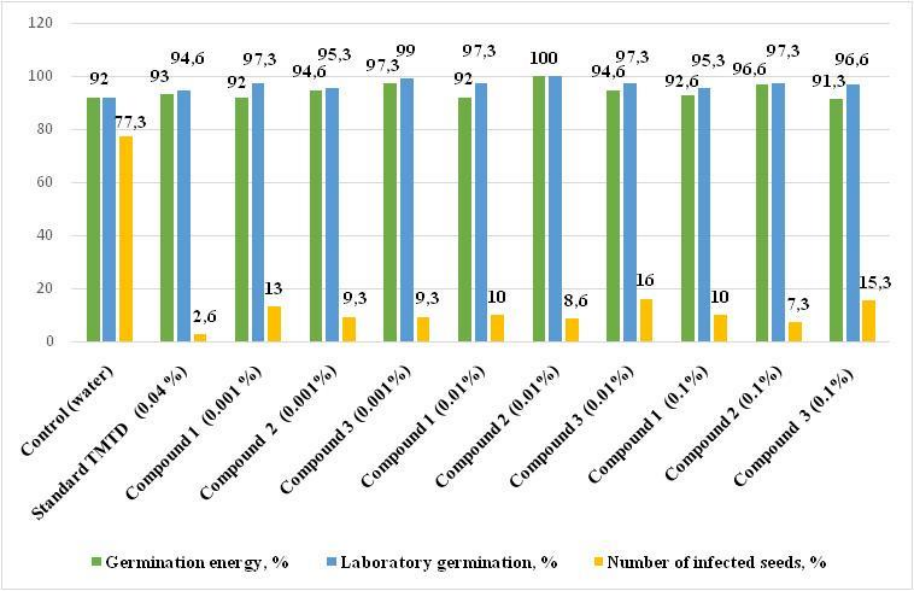


Figure 4 – The effectiveness of treatment with compounds 1-3 on the sowing qualities and microflora of barley seeds at a concentration of 0.001-0.1%.

As shown in Figure 4, compound 2 at a concentration of 0.01% exhibited high laboratory germination of 100% in barley seeds, compared to the control (92.0%) and the TMTD standard (94.6%). The number of affected seeds in compound 2 treatment was 8.6%, whereas in the control (without treatment) it was 73.3%, and with the TMTD standard, it was 2.6%.

4. Conclusion

As a result of the synthesis, a new N-heterocyclic dithiocarbamate and its corresponding thioanhydrides of dithiocarbamic acids based on 2-oxopyrrolidine were obtained. Their structures were confirmed by IR and ^{1}H, ^{13}C NMR spectroscopy. Laboratory screening demonstrated that the synthesized compounds exhibited no phytotoxicity with respect to the sowing qualities of seeds; on the contrary, they promoted the growth of plant shoots and roots. The study further revealed that the heterocyclic thioanhydrides derived from 2-oxopyrrolidine-based dithiocarbamate possess fungicidal activity and inhibit fungal and bacterial

microflora. Notably, butyric 2-oxopyrrolidine-1-carbothioic thioanhydride showed the highest laboratory germination rate for barley seeds at a concentration of 0.01% (100%), with mold infection limited to 8.6%, compared to untreated seeds (92.0% germination and 77.3% infection) and those treated with the TMTD standard (94.6% germination and 2.6% infection).

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

2-ОКСОПИРРОЛИДИН НЕГІЗІНДЕГІ ДИТИОКАРБАМАТ ЖӘНЕ ОНЫҢ ТИОАНГИДРИДТЕРІНІҢ СИНТЕЗІ, ҚҰРЫЛЫМЫ ЖӘНЕ ӨСУДІ ЫНТАЛАНДЫРАТЫН, ГЕРБИЦИДТІК ЖӘНЕ ФУНГИЦИДТІК БЕЛСЕНДІЛІГІНІҢ БИОСКРИНИНГІ

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Түйіндеме. *Кіріспе.* Жаңа тиімді өсімдіктер өсуін ынталандырғыштар және өсімдіктерді қорғаудың химиялық құралдарын іздеу қазіргі агрохимияның өзекті міндеті болып қала береді. Жұмыстың *мақсаты* 2-оксопирролидин негізінде дитиокарбамат және оның тиоангидридтерін синтездеу және өсімдіктер өсуін реттегіштер, гербицидтер мен фунгицидтер ретінде олардың әлеуетін бағалау. *Нәтижелер және талқылау.* 2-оксопирролидин негізінде натрий дитиокарбаматы, оның бутил және бензой 2-оксопирролидин-1-карботио тиоангидридтері 84%, 88% және 67% шығыммен синтезделді. Синтезделген қосылыстардың құрылымы элементтік талдау, ИҚ спектрлері, ^{1}H және ^{13}C ЯМР спектроскопиясы деректері негізінде анықталды. Синтезделген қосылыстардың өсуді ынталандырғыш, гербицидтік және фунгицидтік белсенділікке бастапқы зертханалық скринингі жүргізілді. *Қорытынды.* Бидай тұқымын натрий 2-оксопирролидин-1- карбодитиоатымен 100 мг/л концентрациясында өңдеу өнудің жоғары көрсеткіштерін, бақылаумен салыстырғанда 70% және KN-2 және AN-16 стандарттарымен өңдеумен салыстырғанда 80% зертханалық өнгіштік 90% жоғарылағанын көрсетті. Фитоуыттылықты талдау нәтижелері 0.01-1 мг/мл концентрацияда 1 қосылыс Agrostis және Lactuca тұқымдарының тұқым себу сапасына теріс әсер етпейтінін, керісінше қарқынды өсуіне ықпал ететінін көрсетті. Сонымен қатар, натрий дитиокарбаматы және оның тиоангидридтері тетраметилтиурамдисульфид (ТМТД) стандартымен салыстырғанда фунгицидтік белсенділік көрсетті. Өңделмеген бақылауда бидай мен арпа тұқымдарының фитопатогенді саңырауқұлақтармен зақымдану деңгейі сәйкесінше 100% және 77.3% құрады. Ал ТМТД пайдаланған кезде 0.4% және 2.6% болса, 0.001-0.1% концентрациясында 1-3 қосылыстармен өңдеу бидай үшін 12.6-26% және арпа үшін 7.3-16% дейін зақымдану деңгейін төмендетті.

Түйін сөздер: 2-оксопирролидин, дитиокарбамат, тиоангидридтер, өсуді ынталандыратын, гербицидтік және фунгицидтік белсенділік.

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СИНТЕЗ, СТРУКТУРА И БИОСКРИНИНГ РОСТСТИМУЛИРУЮЩЕЙ, ГЕРБИЦИДНОЙ И ФУНГИЦИДНОЙ АКТИВНОСТИ ДИТИОКАРБАМАТА И ЕГО ТИОАНГИДРИДОВ НА ОСНОВЕ 2-ОКСОПИРРОЛИДИНА

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Резюме. *Введение.* Поиск новых эффективных стимуляторов роста растений и химических средств защиты растений остается актуальной задачей современной агрохимии. *Целью данной работы* являлся синтез дитиокарбамата и его тиоангидридов на основе 2-оксопирролидина и оценка их потенциала в качестве регуляторов роста растений, гербицидов и фунгицидов. *Результаты и обсуждение.* Синтезированы дитиокарбамат натрия на основе 2-оксопирролидина, его бутиловый и бензойный 2-оксопирролидин-1-карботиоевые тиоангидриды с выходами 84%, 88% и 67%, соответственно. Строение синтезированных соединений установлено на основании данных элементного анализа, ИК спектров, спектроскопии ЯМР ^{1}H и ^{13}C. Проведен первичный лабораторный скрининг синтезированных соединений на ростстимулирующую, гербицидную и фунгицидную активность. *Заключение.* Высокие показатели прорастания наблюдались при обработке семян пшеницы 2-оксопирролидин-1-карбодитиоатом натрия в концентрации 100 мг/л, что привело к 90% лабораторной всхожести по сравнению с 70% в контроле и 80% при обработках стандартами KN-2 и AN-16. Анализ фитотоксичности показал, что соединение 1 в концентрациях 0.01-1 мг/мл не оказывает отрицательного влияния на посевные качества семян Agrostis и Lactuca, а наоборот способствует интенсивному росту. Кроме того, дитиокарбамат натрия и его тиоангидриды проявили фунгицидную активность, сопоставимую со стандартом тетраметилтиурамдисульфид (ТМТД). Уровень заражения семян пшеницы и ячменя фитопатогенными грибами в необработанном контроле составил 100% и 77,3%, соответственно. Тогда как, обработка соединениями 1-3 в концентрации 0.001-0.1% снизила уровень заражения до 12.6-26% для пшеницы и 7.3-16% для ячменя по сравнению с 0.4% и 2.6% при использовании ТМТД.

Ключевые слова: 2-оксопирролидин, дитиокарбамат, тиоангидриды, ростстимулирующая, гербицидная и фунгицидная активность.

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