The Synthesis of 1-Alkyl-3-polyfluoroalkyl-1,3-dihydrobenzimidazole-2-selenones as Potential Plant Growth Regulators

Abstract
Aim. To synthesize new 1-alkyl-3-polyfluoroalkyl-1,3-dihydrobenzimidazole-2-selenones and study their biological activity as potential plant growth regulators.

Results and discussion. 1-Alkyl-3-polyfluoroalkyl-1,3-dihydrobenzimidazole-2-selenones were obtained from the corresponding 1-alkyl-3-polyfluoroalkylbenzimidazolium iodides by the action of elemental selenium in the presence of a base. The preliminary biological tests for the growth-regulating activity of the compounds obtained were conducted.

Experimental part. The structure of the compounds synthesized was proven by $^1$H and $^{19}$F NMR spectroscopy methods, as well as by the elemental analysis. The biological studies were done on model plants of winter wheat of the “bezosta” variety.

Conclusions. A convenient method for obtaining 1-alkyl-3-polyfluoroalkyl-1,3-dihydro-benzimidazole-2-selenones has been developed. Biological studies have shown that the compounds synthesized have a diverse effect on the plant growth.

Keywords: N-polyfluoroalkylazoles; benzimidazole-2-selenones; plant growth regulation

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Синтез 1-алкіл-3-поліфлуороалкіл-1,3-дигідробензімідазол-2-селенонів як потенційних регуляторів росту рослин

Анотація
Мета. Синтезувати нові 1-алкіл-3-поліфлуороалкіл-1,3-дигідробензімідазол-2-селенони та вивчити їхню рістрегулювальну активність відносно рослин.

Результати та їх обговорення. Синтезовано нові 1-алкіл-3-поліфлуороалкіл-1,3-дигідробензімідазол-2-селенони дією елементарного селену на відповідні 1-алкіл-3-поліфлуороалкілбензімідазолій йодиди в присутності основи. Було проведено попередні біологічні випробування на рістрегулювальну активність отриманих сполук.

Експериментальна частина. Структуру одержаних сполук доведено методами $^1$H та $^{19}$F ЯМР, а також елементним аналізом. Біологічні дослідження виконували з використанням насіння озимої пшениці сорту Безоста.

Висновки. Розроблено зручний метод синтезу 1-алкіл-3-поліфлуороалкіл-1,3-дигідробензімідазол-2-селенонів. Біологічні випробування засвідчили, що отримані сполуки мають різноплановий вплив на ріст рослин.

Ключові слова: N-поліфлуороалкілазоли; benzimidazole-2-selenones; plant growth regulation

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Introduction

Selenium compounds play an important role in the physiological processes of many living organisms. It has been shown that selenium is contained (in the form of a selenocysteine fragment) in some enzymes, such as glutathione peroxidase, glycine reductase, and some others [1, 2]. Selenium was found to be incorporated into bacterial transfer RNA bases (probably following sulfur pathways) when Escherichia coli was growing in a medium containing [\(^{75}\)Se]selenite [3]. Natural nucleosides containing a selenouracil fragment were also isolated [4]. Additions of selenouracil derivatives increase the quality of strawberries and radishes [5]. It has been also found that selenium micro-additions to the soil increase the resistance of plants to UV radiation [6]. Although an excessive amount of selenium negatively affects the growth and development of plants, the effect of selenium compounds on the development of plant organisms, as well as the problem of selenium accumulation in food products, is the subject of Finbey's review [7]. There are no fluorinated preparations among the mentioned selenium-containing plant growth regulators. However, fluorine-containing compounds are widely used in agrochemistry, in particular, the known herbicides Sulfentrazone and Carfentrazone, which are difluoromethyl derivatives of triazole.

We previously studied the chemical properties of fluorine-containing imidazolium and benzimidazolium salts and showed the ways of their transformation through carbene intermediates into the corresponding thiones [8]. Since it is known that the introduction of fluorine atom into the molecule of a biologically active compound often leads to an increase in the biological activity, and imidazolium and benzimidazolium thiones, as well as selenones are structural analogs of the corresponding thioureas and thiouracils, the urgent task was to synthesize and study the effect of similar selenones on the plant development.

Results and discussion

We chose benzimidazole derivatives – 1-difluoromethylbenzimidazole (1a) [9] and 1-(2,2-dichloro-1,1,2-trifluoromethyl)benzimidazole (1b) [10] as starting compounds. The latter were introduced into the interaction with iodoalkanes – iodomethane, iodoethane, and 2-iodopropane (Scheme). Only the reactions of similar imidazolium salts were studied earlier [8]. It has turned out that, as in the case of fluorine-containing imidazole derivatives, the alkylation of 1-polyfluoroalkylbenzimidazoles takes place during the prolonged period of reflux in acetonitrile. The reaction time is significantly reduced in the case of 1-difluoromethylbenzimidazole compared to 1-(2,2-dichloro-1,1,2-trifluoromethyl)benzimidazole since the latter contains a more electron-withdrawing substituent near the nitrogen atom, and therefore, it is a weaker base. The interaction of 1-(2,2-dichloro-1,2,2-trifluoromethyl)benzimidazole with the least reactive 2-iodopropane under the reaction conditions was extremely slow, so we were unable to obtain the corresponding salt in preparative quantities.

The 1-alkyl-3-polyfluoroalkylbenzimidazolium iodides 2a-e synthesized were introduced into the interaction with elemental selenium in pyridine in the presence of potassium carbonate. Although the reaction was accompanied by the substantial tar formation, the target products were easily purified by flash chromatography of organic extracts. Thus, the target 1-alkyl-3-polyfluoroalkylbenzimidazolium-2-selenones 3a-e were obtained with the yields of 50–60%. They are

\[
\begin{align*}
\text{1a, b} & : RF = CF_2H \\
\text{1b} & : RF = CF_2CFCl_2 \\
\text{2a–e} & : RF = CF_2H, R = Me (a) \\
\text{2b, 3b} & : RF = CF_2H, R = Et (b) \\
\text{2c, 3c} & : RF = CF_2H, R = iPr (c) \\
\text{2d, 3d} & : RF = CF_2CFCl_2, R = Me (d) \\
\text{2e, 3e} & : RF = CF_2CFCl_2, R = Et (d)
\end{align*}
\]

Scheme. Synthesis of 1-alkyl-3-polyfluoroalkyl-1,3-dihydrobenzimidazole-2-selenones
stable crystalline compounds that are well soluble in most organic solvents and can be crystallized from hexane.

We conducted screening studies of the compounds synthesized for plant growth regulating and herbicidal effects. The tests were carried out on model plants of winter wheat of the “bezosta” variety according to the Sergiyeva method [11]. Experiments were performed in Petri dishes in the agar medium. Solutions of the compounds synthesized with a mass fraction of the test compound of $1 \times 10^{-2}$, $1 \times 10^{-3}$, and $1 \times 10^{-4}$% were studied. The same amount of nutrients was added to the control samples as in the test plants, but without the test compounds. Experiments were performed in four repetitions. The results of the experiment were calculated on the 9th day from the experiment start. Experimental data are presented in Table.

The analysis of the results shows that all compounds synthesized affect the growth and development of plants. Judging by the results of the study, selenone 3a containing methyl and difluoromethyl groups exhibits the growth-regulating activity. At the concentration of $1 \times 10^{-4}$%, this preparation increases the growth of the root system of winter wheat of the “bezosta” variety by 26% and increases the total weight compared to control plants, practically without affecting seed germination. The patented drug Ivin (2,6-dimethylpyridine-1-oxide) when applied to the soil in the same concentration leads to an increase in the growth of the plant root system (on beans) by 21% [12]; therefore, it can be argued that compound 3a is close in its activity to the known drug.

<table>
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<tr>
<th>Cmp</th>
<th>Concentration, %</th>
<th>Root, % to control</th>
<th>Stem length, % to control</th>
<th>Plant mass, % to control</th>
<th>Germination % to control</th>
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<td>78.6</td>
<td>73.2</td>
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<td>99.3</td>
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<tr>
<td></td>
<td>$1 \times 10^{-4}$</td>
<td>126.3</td>
<td>98.9</td>
<td>105.9</td>
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<tr>
<td>3b</td>
<td>$1 \times 10^{-2}$</td>
<td>33.3</td>
<td>76.6</td>
<td>45.4</td>
<td>101.7</td>
</tr>
<tr>
<td></td>
<td>$1 \times 10^{-3}$</td>
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<td>94.1</td>
<td>88.2</td>
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<tr>
<td></td>
<td>$1 \times 10^{-4}$</td>
<td>97.4</td>
<td>98.0</td>
<td>92.3</td>
<td>103.4</td>
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<tr>
<td>3c</td>
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<td>88.3</td>
<td>95.5</td>
<td>91.6</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>$1 \times 10^{-3}$</td>
<td>89.6</td>
<td>93.2</td>
<td>93.7</td>
<td>101.4</td>
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<td>97.4</td>
<td>93.2</td>
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<td>95.6</td>
<td>83.2</td>
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<td></td>
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<td>93.4</td>
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<td>98.8</td>
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<tr>
<td>3e</td>
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<td>98.6</td>
<td>98.4</td>
<td>92.6</td>
<td>101.7</td>
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</table>

Thus, 1-methyl-3-difluoromethyl-1,3-dihydro-benzimidazole-2-selenone (3a) can be regarded as a potential plant growth regulator. In high concentrations compound 3a along with other selenones synthesized displayed an inhibiting effect on the plant growth. An increase in the size of both alkyl and polyfluoroalkyl radicals in the selenone molecule leads to undesirable changes in the biological activity. In these cases, the selenones obtained lose their growth-stimulating properties and behave only as plant growth inhibitors. For example, compound 3b, with difluoromethyl and ethyl groups in the concentration of $1 \times 10^{-2}$% exhibits herbicide properties, reducing the rate of the root system development by three times. Selenones with a dichlorotrifluoroethyl group show a low biological activity.

The acute toxicity of the compounds obtained was also studied on white mice weighing 20–23 g by oral administration of solutions of the compounds under research in DMSO. The research results were calculated in 24 hours. It has been shown that selenones 3a–e have approximately the same toxicity – they are moderately toxic substances ($LD_{50} = 400–450$ mg kg$^{-1}$).

**Conclusions**

Thus, one of the fluorine-containing benzimidazole-2-selenone derivatives (1-methyl-3-difluoromethyl-1,3-dihydro-benzimidazole-2-selenone) studied has been shown to exhibit a high growth-stimulating activity. This compound shows activity at the level of well-known patented preparations and can be considered as a promising...
Experimental part

Melting points were measured in open capillary tubes and were given uncorrected. 1H NMR (300 MHz, CDCl3 or DMSO-d6) and 19F NMR (288 MHz, CDCl3 or DMSO-d6) spectra were recorded on a Varian-Mercury-300 spectrometer using TMS and CCl3F as internal standards, respectively. The elemental analysis was performed in the Analytical Chemistry Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. The reaction progress was controlled by TLC on Silufol 254 plates by UV light.

The procedure for biological tests

The studies were carried out according to the method [11]. Quartz sand (2–3 mm) previously washed with hydrochloric acid and distilled water was placed on the bottom of Petri dishes, agar-agar (2–3 mm) was added and placed on top of 4 awned wheat seeds of the “bezosta” variety and covered with filter paper. The filter paper was impregnated with an emulsion of a test drug in water at the test concentration. In parallel, the control experiment was carried out by impregnating filter paper with distilled water. The Petri dishes were covered with glass and distilled water, or an emulsion of the test preparation was periodically added for 9 days, ensuring that the sand and agar-agar were constantly wet. Nine days later, measurements were taken by finding the arithmetic mean of the four seeds under study.

The general procedure for the synthesis of 1-alkyl-3-polyfluoroalkylbenzimidazolium iodides (2a–e)

A mixture of the corresponding 1-polyfluoroalkylbenzimidazole (0.05 mol) and iodoalkane (0.1 mol) in 50 mL of anhydrous acetonitrile was boiled for: 2a – 5 hours, 2b – 18 hours, 2c – 30 hours, 2d – 12 hours, 2d – 56 hours. The precipitate formed upon cooling was filtered off, washed with diethyl ether, and dried giving an analytically pure product.

1-Methyl-3-difluoromethylbenzimidazolium iodide (2a)

A white solid. Yield – 93%. M. p. 227–229 ºC. Anal. Calcd for C11H6F2IN, %: I 30.90. Found, %: 31.15. 1H NMR (300 MHz, DMSO-d6), δ, ppm: 4.05 (3H, s, CH3); 7.62–7.75 (2H, m, ArH); 7.79–7.85 (2H, m, ArH); 7.88 (1H, t, JHH = 59 Hz, CF3I); 10.02 (1H, s, CH). 19F NMR (288 MHz, DMSO-d6), δ, ppm: -97.6 (2F, d, JHF = 59 Hz, CF3I).

1-Ethyl-3-difluoromethylbenzimidazolium iodide (2b)

A white solid. Yield – 82%. M. p. 202–204 ºC. Anal. Calcd for C11H7F2IN, %: I 31.20. Found, %: I 30.96. 1H NMR (300 MHz, DMSO-d6), δ, ppm: 1.37 (3H, t, JHF = 5 Hz, CH3); 7.45–7.54 (2H, m, ArH); 7.65–7.77 (2H, m, ArH); 7.88 (1H, t, JHF = 59 Hz, CF3I); 9.79 (1H, s, CH). 19F NMR (288 MHz, DMSO-d6), δ, ppm: -98.1 (2F, d, JHF = 59 Hz, CF3I).

1-iso-Propyl-3-difluoromethylbenzimidazolium iodide (2c)

A white solid. Yield – 72%. M. p. 182–184 ºC. Anal. Calcd for C11H8F2IN, %: I 37.86. Found, %: I 38.02. 1H NMR (300 MHz, DMSO-d6), δ, ppm: 1.42 (6H, d, JHH = 4 Hz, CH3); 5.18 (1H, m, CH3); 7.45–7.54 (2H, m, ArH); 7.65–7.77 (2H, m, ArH); 7.87 (1H, t, JHF = 59 Hz, CF3I); 9.98 (1H, s, CH). 19F NMR (288 MHz, DMSO-d6), δ, ppm: -98.1 (2F, d, JHF = 59 Hz, CF3I).

1-Methyl-(2,2-dichloro-1,1,2-trifluoroethyl)-benzimidazolium iodide (2d)

A white solid. Yield – 87%. M. p. 218–220 ºC. Anal. Calcd for C11H6Cl2F3IN, %: I 30.90. Found, %: I 31.20. 1H NMR (300 MHz, DMSO-d6), δ, ppm: 4.20 (3H, s, CH3); 7.64–7.72 (2H, m, ArH); 7.76–7.84 (2H, m, ArH); 10.45 (1H, s, CH). 19F NMR (288 MHz, DMSO-d6), δ, ppm: -75.2 (1F, s, CFCl3), -92.6 (2F, s, NCF3I).

1-Ethyl-(2,2-dichloro-1,1,2-trifluoroethyl)-benzimidazolium iodide (2e)

A white solid. Yield – 52%. M. p. 205–207 ºC. Anal. Calcd for C11H7ClF3IN, %: I 29.81. Found, %: I 30.02. 1H NMR (300 MHz, DMSO-d6), δ, ppm: 1.37 (3H, t, JHH = 5 Hz, CH3); 4.14 (2H, q, JHF = 5 Hz, CH2); 7.45–7.54 (2H, m, ArH); 7.65–7.77 (2H, m, ArH); 10.07 (1H, s, CH). 19F NMR (288 MHz, DMSO-d6), δ, ppm: -75.6 (1F, s, CFCl3), -92.7 (2F, s, NCF3I).

The general procedure for the synthesis of 1-alkyl-3-polyfluoroalkylbenzimidazole-2-selenones (3a–d)

Finely ground selenium (0.8 g, 0.015 mol) and potassium carbonate (1.4 g, 0.01 mol) were added to a solution of the corresponding salt 2a–d (0.01 mol) in 15 mL of pyridine. The reaction mixture was heated with intensive stirring, gradually increasing the temperature to 115 ºC, and then the reaction mixture was refluxed for an hour. Water (100 mL) was then added, and
the resulting precipitate was extracted with chloroform (2×50 mL), washed with water, and dried over MgSO₄. After filtering the solution, the solvent was evaporated to a residual volume of 10 mL and chromatographed on a column (MN-Kieselgel-60) to isolate the first compound with the highest Rₓ. The eluent is chloroform.

1-Methyl-3-difluoromethyl-1,3-dihydrobenzimidazole-2-selenone (3a)

A white solid. Yield – 61%. M. p. 151–153 ºС. Anal. Calcd for C₁₆H₁₄F₂N₁Se, %: Se 30.27. Found, %: Se 30.21. ¹H NMR (300 MHz, CDCl₃), δ, ppm: 1.38 (3H, t, 3JHF = 5 Hz, CH₂); 4.52 (2H, q, 3JHF = 5 Hz, CH₂); 7.33–7.45 (2H, m, ArH); 7.71–7.84 (2H, m, ArH); 8.25 (1H, CF, t, 3JHF = 59 Hz).

¹³F NMR (288 MHz, CDCl₃), δ, ppm: -102.9 (2F, d, 3JHF = 59 Hz, NCF₂).

1-Ethyl-3-difluoromethyl-1,3-dihydrobenzimidazole-2-selenone (3b)

A white solid. Yield – 42%. M. p. 71–72 ºС. Anal. Calcd for C₁₆H₁₄F₂N₁Se, %: Se 21.01. Found, %: Se 21.02. ¹H NMR (300 MHz, CDCl₃), δ, ppm: 1.39 (3H, t, 3JHF = 5 Hz, CH₂); 4.70 (2H, q, 3JHF = 5 Hz, CH₂); 7.25–7.34 (2H, m, ArH); 7.55–7.64 (2H, m, ArH); 7.68–7.79 (2H, m, ArH); 8.24 (1H, t, 3JHF = 59 Hz CF₂).

¹³F NMR (288 MHz, CDCl₃), δ, ppm: -103.7 (2F, d, 3JHF = 59 Hz, NCF₂).

References


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