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# Synthesis and plant growth regulating activity of halo derivatives of 3,3'-(arylimino)dipropanoic acids

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Halogenation reactions of 3,3'-(phenylimino)dipropanoic acid were carried out, and the obtained products were transformed into dihydrazides and dihydrazones containing halogen atoms. The plant growth regulating effect of the synthesized compounds was evaluated.

**Key words:** amino acids, hydrazones, growth regulators

## INTRODUCTION

*N*-substituted β-amino acids and their derivatives are structural units of important natural compounds, such as alkaloids, co-enzymes and antibiotics. Carboxylic acid hydrazides and respective hydrazones have been shown to be biologically active compounds [1]. Isonicotinic acid hydrazide (isoniazid) is an anti-bacterial drug that has been used to prevent and treat tuberculosis since 1952. It has also an antide antidepressant effect and was one of the first antidepressants discovered. Hydrazones of various acids exhibit anticonvulsive [2], anti-inflammatory, and antithrombotic properties [3].

Previously, we have reported that certain dihydrazides and dihydrazones of *N*-aryl-*N*-carboxyethyl-β-alanines possess growth stimulating properties [4]. The presence of a halogen atom in the structure of organic compounds often enhances their biological activity or evokes new properties.

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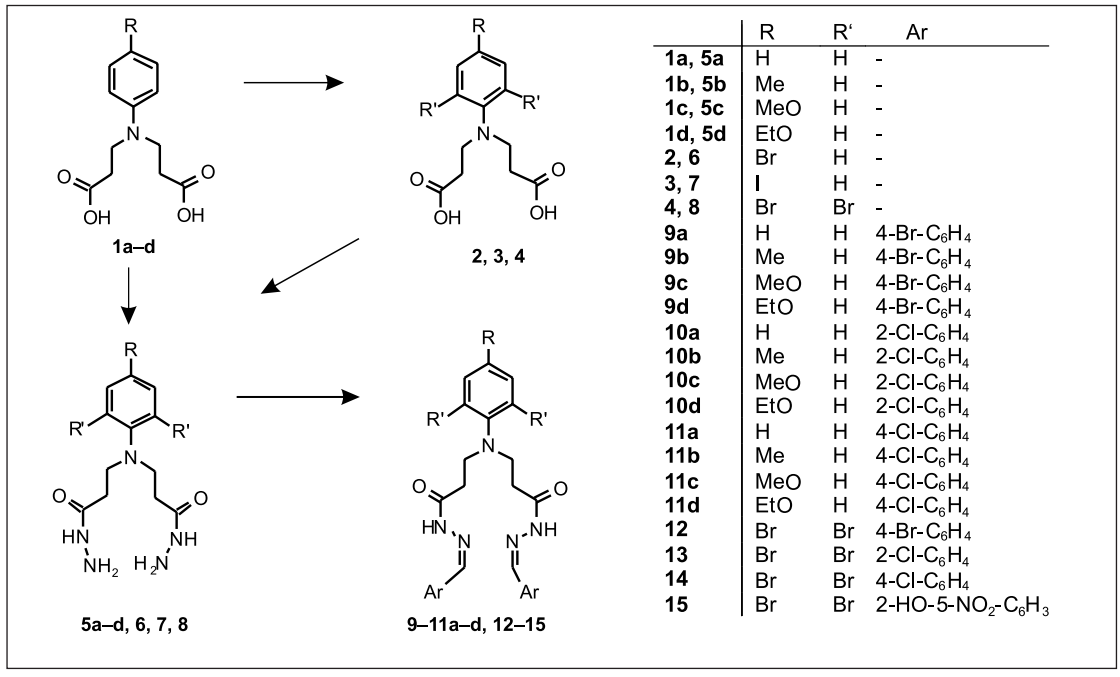
The aim of this work was synthesis of *N*-aryl-*N*-carboxyethyl-β-alanines, their dihydrazides and dihydrazones containing halogen atoms, and determination of the dependence of their biological activity (growth-regulating property) on their structure.

## RESULTS AND DISCUSSION

**Synthesis.** *N*-aryl-*N*-carboxyethyl-β-alanines **1a–d** were synthesized by stirring a reaction mixture of the respective amine and acrylic acid at room temperature until the target product precipitated as described previously [4] (Scheme).

4-Bromo derivative **2** was prepared by treating *N*-carboxyethyl-*N*-phenyl-β-alanine (**1a**) with a stoichiometric amount of bromine in acetic acid at room temperature, whereas a triple access of bromine was used in order to obtain tribromo derivative **4**. Acids **2** and **4** were isolated from the reaction mixture by diluting it with water. In the reaction of iodination, dimethyl sulfoxide was used as an oxidizing medium. 3,3'-[(4-Iodophenyl)imino]dipropanoic acid (**3**) was




| | R | R' | Ar |
|---|---|---|---|
| **1a, 5a** | H | H | - |
| **1b, 5b** | Me | H | - |
| **1c, 5c** | MeO | H | - |
| **1d, 5d** | EtO | H | - |
| **2, 6** | Br | H | - |
| **3, 7** | I | H | - |
| **4, 8** | Br | Br | - |
| **9a** | H | H | 4-Br-$C_6H_4$ |
| **9b** | Me | H | 4-Br-$C_6H_4$ |
| **9c** | MeO | H | 4-Br-$C_6H_4$ |
| **9d** | EtO | H | 4-Br-$C_6H_4$ |
| **10a** | H | H | 2-Cl-$C_6H_4$ |
| **10b** | Me | H | 2-Cl-$C_6H_4$ |
| **10c** | MeO | H | 2-Cl-$C_6H_4$ |
| **10d** | EtO | H | 2-Cl-$C_6H_4$ |
| **11a** | H | H | 4-Cl-$C_6H_4$ |
| **11b** | Me | H | 4-Cl-$C_6H_4$ |
| **11c** | MeO | H | 4-Cl-$C_6H_4$ |
| **11d** | EtO | H | 4-Cl-$C_6H_4$ |
| **12** | Br | Br | 4-Br-$C_6H_4$ |
| **13** | Br | Br | 2-Cl-$C_6H_4$ |
| **14** | Br | Br | 4-Cl-$C_6H_4$ |
| **15** | Br | Br | 2-HO-5-$NO_2$-$C_6H_3$ |

**Scheme.** Synthesis of hydrazones

isolated from the reaction mixture by scavenging unreacted iodine with $Na_2S_2O_3$, and purified by recrystalisation from alkaline solution. Attempts to introduce a higher number of iodine atoms into the molecule of **1a** failed.

Dicarboxylic acid dihydrazides **6–8** were obtained by heating diacids **2–4** under reflux with hydrazine in toluene with the subsequent removal of liquid fractions by distillation. Dihydrazides **5a–d** were obtained from the respective diacids **1a–d** according to the same synthesis procedure as described previously [4, 5].

Dihydrazones **9a–d**, **10a–d**, **11a–d**, and **12–15** were synthesized by heating under reflux dihydrazides **5a–d** and **6–8** with aromatic aldehydes containing bromine, chlorine or hydroxyl and nitro groups [4, 6]. The products were recrystallized from a dimethylformamide and water mixture.

$^1$H NMR spectra of hydrazones **9a–d**, **10a–d**, **11a–d**, and **12–15** registered in $d_6$-DMSO indicate that in the solutions these compounds exist as a mixture of isomers. The *s-E* and *s-Z* isomers can be formed due to the restricted rotation around the CO-NH bond, whereas the different spatial arrangement of phenyl radicals induces formation of the *E* and *Z* isomers. The spectra of these compounds are complicated due to the presence of two (amide and azomethine) isomerisation centers which cause formation of the sets of resonances corresponding to the time-averaged molecular structures. Methylene protons of $CH_2CO$ group resonated as multiplets in the range of 2.4–2.6, 2.80–2.95, and 2.80–3.00 ppm. The line intensity ratio was 0.4 : 0.6 and 0.5 : 0.5. Signals of methylene protons of $CH_2N$ group are present in the 3.51–3.71 ppm region. Multiplets of aromatic protons are observed in the range of 6.6–7.91 ppm. Some of them overlap with the signals of N=CH group protons. Two sets of signals (intensity ratio 0.4 : 0.6) in the region of 7.89–8.55 ppm ascribed to the protons of azomethine groups indicate the formation of *s-Z* and *s-E* isomers. The view of the spectral lines of NH groups also confirms the formation of isomers.

**Investigation of biological activity.** The biological activity of the potential growth regulators was investigated by the laboratory screening method. Seeds of malting barley "Alsa" were germinated in Petri dishes on filter paper wetted with solutions of the study compounds in various concentrations (2–1800 mg/l) for 8 days. Distilled water was used to wet filter paper in the control. Light was on for 16 hours per day, the temperature was 18–20 °C, germination was repeated four times. After the exposure, the viability of seeds, the growth intensity of seedlings and roots and the average biomass of ten seedlings were evaluated. The obtained data are presented in Table. Only the concentrations at which the compounds gave positive results are provided.

As seen from the data, the presence of halogen atom in the phenyl moiety of *N*-carboxyethyl-*N*-phenyl-β-alanine increases the growth-stimulating properties of the compound. When the bromine atom is at the 4th position (compound **2**), the stimulating properties are observed in a wider range of concentrations (2–30 mg/l) in comparison with the activity of β-alanine **1a** which possesses no halogen atoms. Carboxyethylalanine **3** containing an iodine atom is active at 30–90 mg/l. The same tendency was observed in the series of hydrazides. The growth stimulating activity of 4-bromo derivative **6** was stronger than that of hydrazide **7** containing an iodine atom. Besides, hydrazone **12** containing a bromine atom in benzylidene moiety was more active than hydroxynitrobenzylidene derivative **15**. Hydrazone **10a** containing a chlorine atom was less active than the analogous bromine derivative **9a**.

Table. **Influence of compounds 1–3, 6–8, 9a, 10a, 12, and 15 on the growth of "Alsa" malting barley**

| Concentration of the test solution | Viability, % | Root length, cm | Difference from control, cm | Hight of seedlings, cm | Difference from control, cm | Biomass of ten seedlings, g | Difference from control, g |
|---|---|---|---|---|---|---|---|
| Compound **1a** | | | | | | | |
| Control ($H_2O$) | 70 | 8.17 | – | 10.66 | – | 3.721 | – |
| 30 mg/l | 70 | 9.25 | +1.08 | 10.20 | –0.46 | 2.651 | –1.07 |
| Compound **2** | | | | | | | |
| Control ($H_2O$) | 75 | 9.39 | – | 12.33 | – | 3.625 | – |
| 2 mg/l | 70 | 9.58 | +0.19 | 12.59 | +0.26 | 3.732 | +0.107 |
| 5 mg/l | 79 | 10.69 | +1.30 | 13.83 | +1.50 | 4.735 | +1.110 |
| 10 mg/l | 75 | 10.62 | +1.23 | 13.87 | +1.54 | 4.661 | +1.036 |
| 30 mg/l | 65 | 8.69 | –0.70 | 13.21 | +0.88 | 4.545 | +0.920 |
| 60 mg/l | 50 | 8.28 | –1.11 | 12.68 | +0.35 | 3.263 | –0.362 |
| 90 mg/l | 39 | 6.81 | –2.58 | 12.14 | –0.19 | 3.341 | –0.284 |
| Compound **3** | | | | | | | |
| Control ($H_2O$) | 69 | 6.15 | – | 9.50 | – | 3.12 | – |
| 10 mg/l | 73 | 8.95 | +2.80 | 9.25 | –0.25 | 3.30 | + 0.18 |
| 30 mg/l | 80 | 11.25 | +5.10 | 9.84 | +0.34 | 3.91 | +0.79 |
| 60 mg/l | 80 | 11.50 | +5.35 | 9.72 | +0.22 | 3.92 | +0.80 |
| 90 mg/l | 78 | 11.05 | +4.90 | 9.70 | +0.20 | 3.65 | +0.53 |
| 125 mg/l | 82 | 10.38 | +4.23 | 9.65 | + 0.15 | 3.52 | +0.40 |
| Compound **6** | | | | | | | |
| Control ($H_2O$) | 70 | 6.00 | – | 9.30 | – | 3.05 | – |
| 2 mg/l | 62 | 6.15 | +0.15 | 9.15 | –0.15 | 2.72 | –0.33 |
| 5 mg/l | 58 | 6.82 | +0.82 | 9.49 | +0.19 | 2.80 | –0.25 |
| 10 mg/l | 65 | 7.35 | +1.35 | 9.50 | +0.20 | 3.26 | +0.21 |
| 30 mg/l | 60 | 7.20 | +1.20 | 9.38 | +0.08 | 2.91 | –0.14 |
| 60 mg/l | 52 | 6.63 | +0.63 | 9.18 | –0.12 | 2.58 | –0.47 |
| 90 mg/l | 45 | 6.12 | +0.12 | 8.75 | –0.55 | 2.36 | –0.69 |
| Compound **7** | | | | | | | |
| Control ($H_2O$) | 68 | 9.0 | – | 12.3 | – | 3.84 | – |
| 90 mg/l | 68 | 13.5 | +4.5 | 16.3 | +4.0 | 4.61 | +0.77 |
| Compound **8** | | | | | | | |
| Control ($H_2O$) | 68 | 9.0 | – | 12.3 | – | 3.84 | – |
| 90 mg/l | 68 | 5.6 | –3.4 | 13.7 | +1.4 | 3.07 | –0.77 |
| Compound **9a** | | | | | | | |
| Control ($H_2O$) | 65 | 8.5 | – | 12.0 | – | 3.62 | – |
| 90 mg/l | 70 | 12.8 | +4.3 | 15.9 | +3.5 | 4.69 | +1.07 |
| Compound **10a** | | | | | | | |
| Control ($H_2O$) | 65 | 8.5 | – | 12.0 | – | 3.62 | – |
| 90 mg/l | 56 | 8.1 | –0.4 | 10.3 | –1.7 | 3.81 | +0.19 |
| Compound **12** | | | | | | | |
| Control ($H_2O$) | 70 | 6.00 | – | 9.30 | – | 3.05 | – |
| 5 mg/l | 76 | 7.55 | +1.55 | 10.25 | +0.95 | 2.67 | –0.38 |
| 10 mg/l | 72 | 8.95 | +2.95 | 10.62 | +1.32 | 2.75 | –0.30 |
| 30 mg/l | 80 | 9.30 | +3.30 | 10.75 | +1.45 | 3.15 | +0.10 |
| 60 mg/l | 82 | 9.32 | +3.32 | 11.20 | +1.90 | 3.33 | +0.28 |
| 90 mg/l | 76 | 9.45 | +3.45 | 11.30 | +2.00 | 3.50 | +0.45 |
| 125 mg/l | 78 | 9.18 | +3.18 | 10.55 | +1.25 | 3.53 | +0.48 |
| 250 mg/l | 78 | 8.54 | +2.54 | 10.48 | +1.18 | 3.26 | +0.21 |
| 375 mg/l | 72 | 8.35 | +2.35 | 9.96 | +0.66 | 3.21 | +0.16 |
| 500 mg/l | 70 | 8.05 | +2.05 | 9.60 | +0.30 | 3.15 | +0.10 |
| Compound **15** | | | | | | | |
| Control ($H_2O$) | 69 | 6.15 | – | 9.50 | – | 3.12 | – |
| 90 mg/l | 72 | 8.39 | +2.24 | 8.80 | –0.70 | 3.02 | –0.10 |
| 125 mg/l | 68 | 9.15 | +3.00 | 8.78 | –0.72 | 3.39 | +0.27 |
| 250 mg/l | 74 | 9.30 | +3.15 | 8.90 | –0.60 | 3.33 | +0.21 |
| 375 mg/l | 70 | 9.51 | +3.36 | 8.94 | –0.56 | 3.45 | +0.33 |
| 500 mg/l | 72 | 9.45 | +3.30 | 9.02 | –0.48 | 3.47 | +0.35 |
| 625 mg/l | 62 | 9.27 | +3.12 | 8.85 | –0.65 | 3.27 | +0.15 |
| 750 mg/l | 58 | 8.85 | +2.70 | 8.60 | –0.90 | 3.04 | –0.08 |

## EXPERIMENTAL

NMR spectra were recorded on a Varian Unity Inova (300 MHz) spectrometer using $d_6$-DMSO as a solvent. Chemical shifts (δ) are reported in parts per million (ppm) calibrated from TMS (0 ppm) for $^1$H NMR, and $d_6$-DMSO (39.5 ppm) for $^{13}$C NMR. The IR spectra were measured as potassium bromide pellets using a Perkin–Elmer 1600 series FT-IR spectrometer. Mass spectra were obtained on a Waters (Micromas) ZQ 2000 spectrometer. Melting points were determined on the Auto probe analyzer APA 1. Elemental analyses (C, H, N) were performed on a CE-440 elemental analyzer. The monitoring of the reaction course and the purity of the synthesized compounds was carried out using TLC on Silufol 254 and Silufol UV-254 plates.

**3,3'-[(4-Bromophenyl)imino]dipropanoic acid (2).** To a solution of β-alanine **1a** (23.7 g, 0.1 mol) in acetic acid (20 ml), a bromine (5.16 ml, 0.1 mol) solution in acetic acid (20 ml) was added dropwise. Then water (50 ml) was added, and the crystals formed were filtered off. Yield 20.91 g (66%). M. p. 138–139 °C. $^1$H NMR δ: 2.35 (t, 4 H, $J$ = 7.2 Hz, $CH_2CO$); 3.50 (t, 4 H, $J$ = 7.2 Hz, $CH_2N$); 6.60 (d, 2 H, $J$ = 9 Hz, 2, 6-$H_{Ar}$); 7.25 (d, 2 H, $J$ = 9 Hz, 3, 5-$H_{Ar}$); 7.55 (br. s, 2 H, OH). $^{13}$C NMR δ: 33.76 ($CH_2CO$); 46.65 ($CH_2N$); 106.31 (C-4); 113.59 (C-2,6); 131.54 (C-3,5); 146.21 (C-1); 173.89 (CO). IR ν ($cm^{-1}$): 1703 C=O; 3527–3646 OH. MS (APCI$^+$, 20 V), *m/z* (%): 318 $[M + 2H]^+$ (90). Anal. calcd. for $C_{12}H_{14}BrNO_4$, %: C, 45.59; H, 4.46; N, 4.43. Found, %: C, 45.45; H, 4.40; N, 4.45.

**3,3'-[(4-Iodophenyl)imino]dipropanoic acid (3).** A solution of β-alanine **1a** (11.85 g, 0.05 mol) in DMSO (20 ml) was cooled down to 3–4 °C, and iodine (25.4 g, 0.1 mol) was added. The reaction mixture was stirred at room temperature for 20 h, and then a saturated $Na_2S_2O_3$ solution (20 ml) was added. The crystals formed were filtered off, the filtrate was extracted with $CHCl_3$, volatile fractions were removed from the extract with a rotary evaporator, the slurry was dissolved in 5% NaOH solution (40 ml), the solution obtained was filtered and acidified with acetic acid to pH 4. The crystals formed were filtered off, dissolved in 5% NaOH solution, the solution was filtered and acidified, the crystals formed were filtered off. Yield 10.02 g (55%). M. p. 165–166 °C. $^1$H NMR δ: 2.36 (t, 4 H, $J$ = 7.2 Hz, $CH_2CO$); 3.50 (t, 4 H, $J$ = 7.2 Hz, $CH_2N$); 6.51 (d, 2 H, $J$ = 9 Hz, 2, 6-$H_{Ar}$); 7.41 (d, 2 H, $J$ = 9 Hz, 3, 5-$H_{Ar}$). $^{13}$C NMR δ: 32.72 ($CH_2CO$); 46.52 ($CH_2N$); 76.14 (C-4); 114.28 (C-2,6); 137.29 (C-3,5); 146.61 (C-1); 173.81 (CO). MS (APCI$^+$, 20 V), *m/z* (%): 364 $[M + H]^+$ (100). Anal. calcd. for $C_{12}H_{14}INO_4$, %: C, 39.69; H, 3.89; N, 3.86. Found, %: C, 39.58; H, 3.85; N, 3.84.

**3,3'-[(2,4,6-Tribromophenyl)imino]dipropanoic acid (4).** To a solution of **1a** (23.7 g, 0.1 mol) in glacial acetic acid (20 ml), a solution of bromine (15.48 ml, 0.3 mol) in acetic acid (20 ml) was added dropwise, and the reaction mixture was stirred at room temperature for 0.5 h. Then water (50 ml) was added, and the crystals formed were filtered off. Yield 29.4 g (62%). M. p. 98–99 °C (EtOH). $^1$H NMR δ: 2.50 (t, 4 H, $J$ = 6.6 Hz, $CH_2CO$); 3.42 (t, 4 H, $J$ = 6.6 Hz, $CH_2N$); 7.78 (s, 2 H, 3, 5 $H_{Ar}$); 12.23 (s, 2 H, OH). $^{13}$C NMR δ: 34.68 ($\underline{CH_2}CO$); 43.07 ($CH_2N$); 112.94 (C-2); 116.78 (C-4); 134.51 (C-3); 144.18 (C-1); 173.20 (CO). MS (APCI$^+$, 20 V), *m/z* (%): 364 $[M + H]^+$ (100). Anal. calcd. for $C_{12}H_{12}Br_3NO_4$, %: C, 30.41; H, 2.55; N, 2.96. Found, %: C, 30.29; H, 2.29; N, 2.98.

**3,3'-[(4-Bromophenyl)imino]bis(propanoic acid hydrazide) (6).** A mixture of **2** (15.8 g, 50 mmol) and hydrazine hydrate (6.25 g, 125 mmol) in toluene (150 ml) was heated under reflux for 8 h. The liquid fractions were then evaporated on a rotary evaporator. The residue was crystallized from a mixture of 2-propanol and diethyl ether. Yield 11.3 g (66%). M. p. 165–166 °C. $^1$H NMR δ: 2.26 (t, 4 H, $J$ = 7.2 Hz, $CH_2CO$); 3.49 (t, 4 H, $J$ = 7.2 Hz, $CH_2N$); 4.20 (s, 4 H, $2NH_2$); 6.65 (d, 2 H, $J$ = 9 Hz, 2, 6-$H_{Ar}$); 7.30 (d, 2 H, $J$ = 9 Hz, 3, 5-$H_{Ar}$); 9,06 (s, 2 H, 2NH). $^{13}$C NMR δ: 32.00 ($\underline{CH_2}CO$); 47.57 ($CH_2N$); 107.37 (C-2,6); 114.53 (C-4); 132.31 (C-3,5); 146.90 (C-1); 170.52 (CO). IR ν ($cm^{-1}$): 1633–1646 (C=O); 3227–3274 ($NHNH_2$). MS (APCI$^+$, 20 V), *m/z* (%): 346 $[M + 2H]^+$ (70). Anal. calcd. for $C_{12}H_{18}BrN_5O_2$, %: C, 41.87; H, 5.27; N, 20.35. Found, %: C, 41.69; H, 5.25; N, 20.30.

**3,3'-[(4-Iodophenyl)imino]bis(propanoic acid hydrazide) (7).** Prepared from **3** (1.81 g, 5 mmol) and hydrazine hydrate (0.75 g, 15 mmol) in toluene (50 ml) according to the synthesis procedure of **6**. Yield 1.23 g (63%). M. p. 144–145 °C. $^1$H NMR δ: 2.25 (t, 4 H, $J$ = 7.2 Hz, $CH_2CO$); 3.47 (t, 4 H, $J$ = 7.2 Hz, $CH_2N$); 4.40 (s, 4 H, $2NH_2$); 6.55 (d, 2 H, $J$ = 9 Hz, 2, 6-$H_{Ar}$); 7.43 (d, 2 H, $J$ = 9 Hz, 3, 5-$H_{Ar}$); 9.06 (s, 2 H, 2 NH). $^{13}$C NMR δ: 31.99 ($\underline{CH_2}CO$); 47.46 ($CH_2N$); 76.47 (C-4); 114.43 (C-2,6); 129.88 (C-3,5); 147.31 (C-1); 170.51 (CO). IR ν ($cm^{-1}$): 1636–1646 (C=O); 3228–3278 ($NHNH_2$). MS (APCI$^+$, 20 V), *m/z* (%): 392 $[M + H]^+$ (100). Anal. calcd. for $C_{12}H_{18}IN_5O_2$, %: C, 36.84; H, 4.64; N, 17.90. Found, %: C, 36.54; H, 4.42; N, 17.69.

**3,3'-[(2,4,6-Tribromophenyl)imino]bis(propanoic acid hydrazide) (8).** Prepared from **4** (9.48 g, 20 mmol) and hydrazine hydrate (2.5 g, 50 mmol) in toluene (100 ml) according to the synthesis procedure of **6**. Yield 8.92 g (89%). M. p. 115–116 °C. $^1$H NMR δ: 2.26 (t, 4 H, $J$ = 6.9 Hz, $CH_2CO$); 3.49 (t, 4 H, $J$ = 7.2 Hz, $CH_2N$); 4.69 (s, 4 H, $2NH_2$); 6.52, 6.55 (2 s, 1 H, $H_{Ar}$); 7.19, 7.22 (2 s, 1 H, $H_{Ar}$); 9.07 (s, 2 H, 2NH). IR ν ($cm^{-1}$): 1639 (C=O); 3275 ($NHNH_2$). MS (APCI$^+$, 20 V), *m/z* (%): 504 $[M + 2H]^+$ (60). Anal. calcd. for $C_{12}H_{16}Br_3N_5O_2$, %: C, 28.71; H, 3.21; N, 13.95. Found, %: C, 28.58; H, 3.24; N, 13.84.

**General procedure for preparation of dihydrazones 9a–d, 10a–d, 11a–d, and 12–15.** A mixture of dihydrazide **5a–d**, **6–8** (10 mmol) and appropriate aldehyde (30 mmol) in methanol (50 ml) was heated under reflux for 2 h. The reaction mixture was cooled down to 3–4 °C, the crystals formed were filtered off and washed with methanol.

**3,3'-(Phenylimino)bis{N'-[(4-bromophenyl)methylene]propanoic acid hydrazide} (9a) (isomeric mixture).** Prepared from **5a** and 4-bromobenzenecarbaldehyde. Yield 5.13 g (86%). M. p. 225–226 °C. $^1$H NMR δ: 2.82–2.95 (m, 4 H, $CH_2CO$); 3.64–3.71 (m, 4 H, $CH_2N$); 6.65 (t, 1 H, $J$ = 7.2 Hz, 4-$H_{Ar}$); 6.80 (d, 2 H, $J$ = 7.2 Hz, 2, 6-$H_{Ar}$); 7.15–7.25 (m, 2 H; 3, 5-$H_{Ar}$); 7.47–7.63 (m, 8 H, $H_{Ar'}$); 7.89, 7.91 (2 s, 1.65 H,

*s-Z*(*Z/E*), N=CH); 8.11, 8.12 (2 s, 0.35 H, *s-E*(*Z/E*), N=CH); 11.47 (s, 1.65 H, *s-Z,* NH); 11,59 (s, 0.35 H, *s-E*, NH). MS (APCI$^+$, 15 V), *m/z* (%): 600 [M + H]$^+$ (40). Anal. calcd. for $C_{26}H_{25}Br_2N_5O_2$, %: C, 52.11; H, 4.20; N, 11.69. Found, %: C, 52.28; H, 4.29; N, 11.67.

**3,3'-[(4-Methylphenyl)imino]bis{N'-[(4-bromophenyl) methylene]propanoic acid hydrazide} (9b) (isomeric mixture).** Prepared from **5b** and 4-bromobenzenecarbaldehyde. Yield 4.90 g (80%). M. p. 209–210 °C. $^1$H NMR δ: 2.19, 2.20 (2 s, 3 H, *s-Z* / *s-E*, $CH_3$); 2.81–2.90 (m, 4 H, $CH_2CO$); 3.59–3.69 (m, 4 H, $CH_2N$); 6.56–6.98 (m, 4 H, $H_{Ar}$); 7.41–7.73 (m, 8 H, $H_{Ar'}$); 7.87, 7.90 (2 s, 1.65 H, *s-Z*(*Z/E*), N=CH); 8.11, 8.12 (2 s, 0.35 H, *s-E*(*Z/E*), N=CH); 11.48 (s, 1.65 H, *s-Z*(*Z/E*), NH); 11.61 (s, 0.35 H, *s-E*(*Z/E*), NH). MS (APCI$^+$, 20 V), *m/z* (%): 614 [M + H]$^+$ (100). Anal. calcd. for $C_{27}H_{27}Br_2N_5O_2$, %: C, 52.87; H, 4.44; N, 11.42. Found, %: C, 52.58; H, 4.39; N, 11.41.

**3,3'-[(4-Methoxyphenyl)imino]bis{N'-[(4-bromophenyl)methylene]propanoic acid hydrazide} (9c) (isomeric mixture).** Prepared from **5c** and 4-bromobenzenecarbaldehyde. Yield 4.15 g (66%). M. p. 212–213 °C. $^1$H NMR δ: 2.43–2.49 (m, 1 H, *s-Z*, $CH_2CO$); 2.85–2.89 (m, 3 H, *s-E*, $CH_2CO$); 3.55–3.62 (m, 4 H, $CH_2N$); 3.68 (s, 3 H, $CH_3O$); 6.75–6.84 (m, 4 H, $H_{Ar}$); 7.49–7.59 (m, 8 H, $H_{Ar'}$); 7.94, 7.96 (2 s, 1.35 H, *s-Z*(*Z/E*), N=CH); 8.11 (s, 0.65 H, *s-E*(*Z/E*), N=CH); 11.45 (s, 1.35 H, *s-Z*, NH); 11.49, 11.51 (2 s, 0.65 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 630 [M + H]$^+$ (90). Anal. calcd. for $C_{27}H_{27}Br_2N_5O_3$, %: C, 51.53; H, 4.32; N, 11.13. Found, %: C, 51.30; H, 4.39; N, 11.09.

**3,3'-[(4-Ethoxyphenyl)imino]bis{N'-[(4-bromophenyl) methylene]propanoic acid hydrazide} (9d) (isomeric mixture).** Prepared from **5d** and 4-bromobenzenecarbaldehyde. Yield 4.90 g (88%). M. p 142–143 °C. $^1$H NMR δ: 1.29 (t, 3 H, *J* = 6.9 Hz, $\underline{CH_3}CH_2O$); 2.42–2.47 (m, 1 H, *s-Z*, $CH_2CO$); 2.82–2.86 (m, 3 H, *s-E*, $CH_2CO$); 3.54–3.63 (m, 4 H, $CH_2N$); 3.91 (q, 2 H, *J* = 6.9 Hz, $CH_3\underline{CH_2}O$); 6.75–6.82 (m, 4 H, $H_{Ar}$); 7.45–7.81 (m, 8 H, $H_{Ar'}$); 7.92, 7.94 (2 s, 1.5 H, *s-Z*(*Z/E*), N=CH); 8.10, 8.12 (2 s, 0.5 H, *s-E*(*Z/E*), N=CH); 11.41 (s, 1.5 H, *s-Z*, NH), 11.47 (s, 0.5 H, *s-E*, NH). MS (APCI$^+$, 15 V), *m/z* (%): 644 [M + H]$^+$ (70). Anal. calcd. for $C_{28}H_{29}Br_2N_5O_3$, %: C, 52.27; H, 4.54; N, 10.89. Found, %: C, 51.97; H, 4.39; N, 10.73.

**3,3'-(Phenylimino)bis{N'-[(2-chlorophenyl)methylene]propanoic acid hydrazide} (10a) (isomeric mixture).** Prepared from **5a** and 2-chlorobenzenecarbaldehyde. Yield 4.75 g (82%). M. p. 197–198 °C. $^1$H NMR δ: 2.53–2.57 (m, 1 H, $CH_2CO$); 2.91–2.96 (m, 3 H, $CH_2CO$); 3.64–3.71 (m, 4 H, $CH_2N$); 6.65 (t, 1 H, *J* = 7.2 Hz, 4-$H_{Ar}$); 6.80 (d, 2 H, *J* = 7.2 Hz, 2, 6-$H_{Ar}$); 7.15–7.22 (m, 2 H, 3, 5-$H_{Ar}$); 7.30–7.86 (m, 8 H, $H_{Ar'}$); 8.37, 8.39 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.53, 8.55 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.60 (s, 1.3 H, *s-Z*, NH); 11.70 (s, 0.7 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 512 [M + 2H]$^+$ (100). Anal. calcd. for $C_{26}H_{25}Cl_2N_5O_2$, %: C, 61.18; H, 4.94; N, 13.72. Found, %: C, 60.95; H, 4.85; N, 13.58.

**3,3'-[(4-Methylphenyl)imino]bis{N'-[(2-chlorophenyl) methylene]propanoic acid hydrazide} (10b) (isomeric mixture).** Prepared from **5b** and 2-chlorobenzenecarbaldehyde. Yield 6.22 g (60%). M. p. 228–229 °C. $^1$H NMR δ: 2.17 (s, 0.2 H, $CH_3$); 2.19 (s, 2.8 H, $CH_3$); 2.47–2.51 (m, 1 H, $CH_2CO$); 2.88–2.93 (m, 3 H, $CH_2CO$); 3.63–3.67 (m, 4 H, $CH_2N$); 6.71 (d, 2 H, *J* = 8.4 Hz, 2, 6-$H_{Ar}$); 6.96–7.05 (m, 2 H, 3, 5-$H_{Ar}$); 7.29–7.52 (m, 8 H, $H_{Ar'}$); 8.36, 8.39 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.52, 8.54 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.58 (s, 1.3 H, *s-Z*, NH); 11.69 (s, 0.7 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 526 [M + 2H] (90). Anal. calcd. for $C_{27}H_{27}Cl_2N_5O_2$, %: C, 61.84; H, 5.19; N, 13.35. Found, %: C, 61.40; H, 4.95; N, 13.29.

**3,3'-[(4-Methoxyphenyl)imino]bis{N'-[(2-chlorophenyl)methylene]propanoic acid hydrazide} (10c) (isomeric mixture).** Prepared from **5c** and 2-chlorobenzenecarbaldehyde. Yield 3.92 g (73%). M. p. 187–188 °C. $^1$H NMR δ: 2.40–2.51 (m, 1 H, *s-Z*, $CH_2CO$); 2.85–2.92 (m, 3 H, *s-E*, $CH_2CO$); 3.53–3.62 (m, 4 H, $CH_2N$); 3.67 (s, 3 H, $CH_3O$); 6.72–6.84 (m, 4 H, $H_{Ar}$); 7.49–7.61 (m, 8 H, $H_{Ar'}$); 7.89, 7.91 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.10, 8.12 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.40 (s, 1.35 H, *s-Z*, NH); 11.49 (s, 0.65 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 542 [M + 2H]$^+$ (100). Anal. calcd. for $C_{27}H_{27}Cl_2N_5O_3$, %: C, 60.00; H, 5.04; N, 12.96. Found, %: C, 59.68; H, 5.10; N, 12.76.

**3,3'-[(4-Ethoxyphenyl)imino]bis{N'-[(2-chlorophenyl) methylene]propanoic acid hydrazide} (10d) (isomeric mixture).** Prepared from **5d** and 2-chlorobenzenecarbaldehyde. Yield 4.75 g (86%). M. p. 191–192 °C. $^1$H NMR δ: 1.29 (t, 3 H, *J* = 6.9 Hz, $\underline{CH_3}CH_2O$); 2.21–2.45 (m, 1 H, *s-Z*, $CH_2CO$); 2.67–2.79 (m, 3 H, *s-E*, $CH_2CO$); 3.42–3.52 (m, 4 H, $CH_2N$); 3.91 (q, 2 H, *J* = 6.9 Hz, $CH_3\underline{CH_2}O$); 6.68–6.83 (m, 4 H, $H_{Ar}$); 7.35–7.61 (m, 8 H, $H_{Ar'}$); 7.87, 7.89 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.11, 8.13 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.40 (s, 1.35 H, *s-Z*, NH); 11.49 (s, 0.65 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 556 [M + 2H]$^+$ (100). Anal. calcd. for $C_{28}H_{29}Cl_2N_5O_3$, %: C, 60.65; H, 5.27; N, 12.63. Found, %: C, 60.58; H, 5.24; N, 12.59.

**3,3'-(Phenylimino)bis{N'-[(4-chlorophenyl)methylene]propanoic acid hydrazide} (11a) (isomeric mixture).** Prepared from **5a** and 4-chlorobenzenecarbaldehyde. Yield 4.95 g (97%). M. p. 202–203 °C. $^1$H NMR δ: 2.88–2.94 (m, 4 H, $CH_2CO$); 3.63–3.70 (m, 4 H, $CH_2N$); 6.65 (t, 1 H, *J* = 7.2 Hz, 4-$H_{Ar}$); 6.79 (d, 2 H, *J* = 7.2 Hz, 2, 6-$H_{Ar}$); 7.17–7.23 (m, 2 H, 3, 5-$H_{Ar}$); 7.41–7.72 (m, 8 H, $H_{Ar'}$); 7.97, 7.99 (2 s, 1.65 H, *s-Z*, N=CH); 8.13, 8.15 (2 s, 0.35 H, *s-E*, N=CH); 11.45 (s, 1.65 H, *s-Z*, NH); 11.53 (s, 0.35 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 512 [M + 2H]$^+$ (60). Anal. calcd. for $C_{26}H_{25}Cl_2N_5O_2$, %: C, 61.18; H, 4.94; N, 13.72. Found, %: C, 60.84; H, 4.71; N, 13.55.

**3,3'-[(4-Methylphenyl)imino]bis{N'-[(4-chlorophenyl) methylene]propanoic acid hydrazide} (11b) (isomeric mixture).** Prepared from **5b** and 4-chlorobenzenecarbaldehyde. Yield 5.1 g (97%). M. p. 200–201 °C. $^1$H NMR δ: 2.17 (s, 0.2 H, $CH_3$); 2.19 (s, 2.8 H, $CH_3$); 2.47–2.51 (m, 1 H, $CH_2CO$); 2.88–2.93 (m, 3 H, $CH_2CO$); 3.63–3.67 (m, 4 H, $CH_2N$); 6.71 (d, 2 H, *J* = 8.4 Hz, 2, 6-$H_{Ar}$); 6.96–7.05 (m, 2 H; 3, 5-$H_{Ar}$); 7.29–7.52 (m, 8 H, $H_{Ar'}$); 8.36, 8.39 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.52, 8.54 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.58 (s, 1.3 H, *s-Z*, NH); 11.69 (s, 0.7 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 526 [M + 2H]$^+$ (50). Anal. calcd. for $C_{27}H_{27}Cl_2N_5O_2$, %: C, 61.84; H, 5.19; N, 13.35. Found, %: C, 61.58; H, 5.04; N, 13.05.

**3,3'-[(4-Methoxyphenyl)imino]bis{N'-[(4-chlorophenyl) methylene]propanoic acid hydrazide} (11c) (isomeric mixture).** Prepared from **5c** and 4-chlorobezenecarbaldehyde. Yield 4.43 g (82%). M. p. 199–200 °C. $^1$H NMR δ: 2.41–2.48 (m, 1 H, *s-Z*, $CH_2CO$); 2.82–2.88 (m, 3 H, *s-E*, $CH_2CO$); 3.51–3.61 (m, 4 H, $CH_2N$); 3.67 (s, 3 H, $CH_3O$); 6.73–6.82 (m, 4 H, $H_{Ar}$); 7.38–7.69 (m, 8 H, $H_{Ar'}$); 7.95, 7.96 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.12, 8.13 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.40 (s, 1.35 H, *s-Z*, NH); 11.48 (s, 0.65 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 542 $[M + 2H]^+$ (100). Anal. calcd. for $C_{27}H_{27}Cl_2N_5O_3$, %: C, 60.00; H, 5.04; N, 12.96. Found, %: C, 60.06; H, 5.16; N, 12.89.

**3,3'-[(4-Ethoxyphenyl)imino]bis{N'-[(4-chlorophenyl) methylene]propanoic acid hydrazide} (11d) (isomeric mixture).** Prepared from **5d** and 4-chlorobezenecarbaldehyde. Yield 4.2 g (76%). M. p. 183–184 °C. $^1$H NMR δ: 1.29 (t, 3 H, *J* = 6.9 Hz, $\underline{CH_3}CH_2O$); 2.41–2.48 (m, 1 H, *s-Z*, $CH_2CO$); 2.82–2.88 (m, 3 H, *s-E*, $CH_2CO$); 3.52–3.65 (m, 4 H, $CH_2N$); 3.91 (q, 2 H, *J* = 6.9 Hz, $CH_3\underline{CH_2}O$); 6.73–6.82 (m, 4 H, $H_{Ar}$); 7.38–7.70 (m, 8 H, $H_{Ar'}$); 7.91, 7.93 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.10, 8.12 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.41 (s, 1.35 H, *s-Z*, NH); 11.49 (s, 0.65 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 556 $[M + 2H]^+$ (100). Anal. calcd. for $C_{28}H_{29}Cl_2N_5O_3$, %: C, 60.76; H, 5.24; N, 12.66. Found, %: C, 60.39; H, 5.24; N, 12.70.

**3,3'-[(2,4,6-Tribromophenyl)imino]bis{N'-[(4-bromophenyl)methylene]propanoic acid hydrazide} (12) (isomeric mixture).** Prepared from **8** and *p*-bromobenzaldehyde. Yield 1.15 g (69%). M. p. 228–229 °C (from DMF and water mixture). $^1$H NMR δ: 2.79–2.94 (m, 2 H, s-*Z,* $CH_2CO$); 3.33–3.51 (m, 2 H, *s-E,* $CH_2CO$); 3.60–3.69 (m, 4 H, $CH_2N$); 6.72–6.79 (m, 2 H, $H_{Ar}$); 7.49–7.59 (m, 8 H, $H_{Ar'}$); 7.99; 8.03 (2 s, 1 H, *s-Z*(*Z/E*), N=CH); 8.13 (s, 1 H, *s-E*, N=CH); 11.47 (s, 1 H, *s-Z,* NH); 11.50, 11.56 (2 s, 1 H, *s-E,* NH). MS (APCI$^+$, 20 V), *m/z* (%): 838 $[M + 2H]^+$ (30). Anal. calcd. for $C_{26}H_{22}Br_5N_5O_2$, %: C, 37.35; H, 2.65; N, 8.38. Found, %: C, 37.26; H, 2.39; N, 8.37.

**3,3'-[(2,4,6-Tribromophenyl)imino]bis{N'-[(2-chlorophenyl)methylene]propanoic acid hydrazide} (13) (isomeric mixture).** Prepared from **8** and 2-chlorobenzaldehyde. Yield 3.44 (46%). M. p. 156–157 °C (from DMF and water mixture). $^1$H NMR δ: 2.91 (t, 4 H, *J* = 6.6 Hz, $CH_2CO$); 3.60–3.72 (m, 4 H, $CH_2N$); 6.71–6.77 (m, 2 H, $H_{Ar}$); 7.25–7.64 (m, 8 H, $H_{Ar'}$); 8.16, 8.19 (2 s, 1.3 H, *s-Z*(*Z/E*), N=CH); 8.52, 8.54 (2 s, 0.7 H, *s-E*(*Z/E*), N=CH); 11.60 (s, 1.3 H, *s-Z*, NH); 11.68 (s, 0.7 H, *s-E*, NH). MS (APCI$^+$, 20 V), *m/z* (%): 749 $[M + 2H]^+$ (70). Anal. calcd. for $C_{26}H_{22}Br_3Cl_2N_5O_2$, %: C, 41.80; H, 2.97; N, 9.37. Found, %: C, 41.63; H, 2.85; N, 9.36.

**3,3'-[(2,4,6-Tribromophenyl)imino]bis{N'-[(4-chlorophenyl)methylene]propanoic acid hydrazide} (14) (isomeric mixture).** Prepared from **8** and 4-chlorobenzaldehyde. Yield 4.33 g (58%). M. p. 211–212 °C (from DMF and water mixture). $^1$H NMR δ: 2.85–2.94 (m, 4 H, $CH_2CO$); 3.59–3.72 (m, 4 H, $CH_2N$); 6.70–6.75 (m, 2 H, $H_{Ar}$); 7.27–7.72 (m, 8 H, $H_{Ar'}$); 8.13, 8.14 (2 s, 1 H, *s-Z*, N=CH); 8.74 (s, 1 H, *s-E*(*Z/E*), N=CH); 11.47 (s, 1.3 H, *s-Z,* NH); 11.51 (s, 0.7 H, *s-E,* NH). MS (APCI$^+$, 20 V), *m/z* (%): 749 $[M + 2H]^+$ (80). Anal. calcd. for $C_{26}H_{22}Br_3Cl_2N_5O_2$, %: C, 41.80; H, 2.97; N, 9.37. Found, %: C, 41.75; H, 2.69; N, 9.35.

**3,3-[(2,4,6-Tribromophenyl)imino]bis{N'-[(2-hydroxy-5-nitrophenyl)methylene]propa-noic acid hydrazide} (15) (isomeric mixture).** Prepared from **8** and 2-hydroxy-5-nitrobenzenecarbaldehyde. Yield 7.35 g (92%). M. p. 237–238 °C (from DMF and water mixture). $^1$H NMR δ: 2.88–2.95 (m, 2 H, *s-Z*, $CH_2CO$); 3.31–3.41 (m, 2 H, *s-E*, $CH_2CO$); 3.64–3.74 (m, 4 H, $CH_2N$); 6.72–6.79 (m, 2 H, $H_{Ar}$); 6.97–7.36 (m, 6 H, $H_{Ar'}$); 8.71, 8.72 (2 s, 1 H, *s-Z*, N=CH); 9.10 (s, 1 H, *s-E*, N=CH); 11.49, 11.52 (2 s, 1 H, *s-Z*, NH); 11.84 (s, 1 H, *s-E*, NH). MS (APCI$^+$, 15 V), *m/z* (%): 802 $[M + 2H]^+$ (40). Anal. calcd. for $C_{26}H_{22}Br_3N_7O_8$, %: C, 39.02; H, 2.77; N, 12.25. Found, %: C, 38.98; H, 2.75; N, 12.19.

## CONCLUSIONS

Bromination or iodination reactions of 3,3'-(phenylimino) dipropanoic acid resulted in the formation of 3,3'-[(4-bromo-, 2,4,6–tribromo- and 4-iodophenyl)imino]dipropanoic acids which were transformed to the corresponding dihydrazides on treatment with hydrazine. The condensation reaction of hydrazides with aldehydes provided hydrazones. The results of the primary screening of biological activity of the synthesized compounds have revealed that compounds containing a bromine atom are more active in a wider range of concentrations than analogous compounds containing chlorine or iodine atoms or no halogen atom.

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## 3,3'-(ARILIMINO)DIPROPANO RŪGŠČIŲ HALOGENINTŲ DARINIŲ SINTEZĖ IR BIOLOGINIS AKTYVUMAS

*S a n t r a u k a*

Atliktos 3,3'-(fenilimino)dipropano rūgšties halogeninimo reakcijos. Iš jų produktų susintetinti dihidrazidai bei dihidrazonai, kurių sudėtyje yra halogeno atomų. Atlikti susintetintų junginių augalų augimą reguliuojančio poveikio tyrimai.