









# Synthesis and biological activity of 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas and their *N*-chloroacetyl derivatives

Varvara S. Evchik <sup>a</sup> , Tatiana A. Kalinina <sup>a\*</sup> , Konstantin L. Obydenov <sup>a</sup> ,  
Richard V. Asase <sup>a</sup> , Pavel A. Slepukhin <sup>ab</sup> , Tatiana V. Glukhareva <sup>a</sup> 

**a:** Institute of Chemical Engineering, Ural Federal University , Ekaterinburg 620062, Russia

**b:** Postovsky Institute of Organic Synthesis , Ural Branch of Russian Academy of Sciences, Ekaterinburg 620108, Russia

\* Corresponding author: [t.a.kalinina@urfu.ru](mailto:t.a.kalinina@urfu.ru)



## Abstract

This study presents a simple and convenient approach to the synthesis of 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas and (*Z*)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2*H*)-ylidene)-3-arylurea. The crystal structure of 3 compounds was studied, and it was shown that they possess pseudoheterocyclic system Se(1)C(5)N(1)C(6)O(2). The results of evaluating the fungicidal activity of all the obtained substances against 3 phytopathogenic fungi and the effect of 6 compounds on seed germination and development of cucumber seedlings in comparison with TDZ are presented. Compound **3b** exhibited moderate activity ( $47.21 \pm 0.43\%$ ) against *S. sclerotiorum*. Additionally, 1,2,3-selenadiazol-5-ylureas **2a** and **2d** inhibited root and stem elongation and lateral root formation in cucumber seedlings, demonstrating effects similar to those of TDZ. These findings suggest that further study of the growth-regulating properties of compounds **2a** and **2d** is warranted.

## Key findings

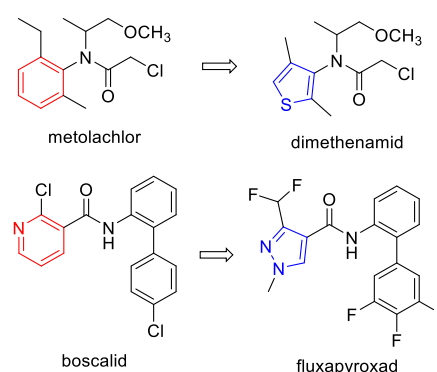
- Structural analogs of thidiazuron – 1,2,3-selenodiazolylurea derivatives were synthesized.
- Acylated derivatives of 1,2,3-selenodiazolylurea were obtained, and their molecular structures were studied using X-ray diffraction.
- Results of a study on the fungicidal activity of the compounds were obtained.
- Two compounds with a growth-regulating activity profile similar to TDZ were discovered in a cucumber seed germination experiment.

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## 1. Introduction

Isosteric substitution in the molecule of a biologically active compound is a useful tool for discovering new biologically active compounds [1]. Substitution of one or more atoms, groups, or cycles in the structure of a biologically active compound with another fragment equivalent in size, shape, and charge distribution can lead to an increase or modification of the biological activity of the compound [2]. The principle of bioisosteric ring exchange is successfully used in medicinal [3] and plant protection chemistry [4]. For example, substitution of a benzene ring with a thiophene ring in the herbicide metolachlor resulted in the production of the compound dimethenamid, which exhibits similar properties (Figure 1) [5,6]. Similarly, substitution of a pyridine

ring with a pyrazole ring in the structure of the fungicide boscalid [7] resulted in the development of the more active fungicide fluxapyroxad [8].



**Figure 1** Examples of the bioisosteric ring exchange.

## Accompanying information

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1,2,3-selenadiazoles;  
1,2,3-thiadiazoles; thidiazuron; plant growth regulators; antifungal activity; X-ray

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### Supplementary information

Supplementary materials:  READ

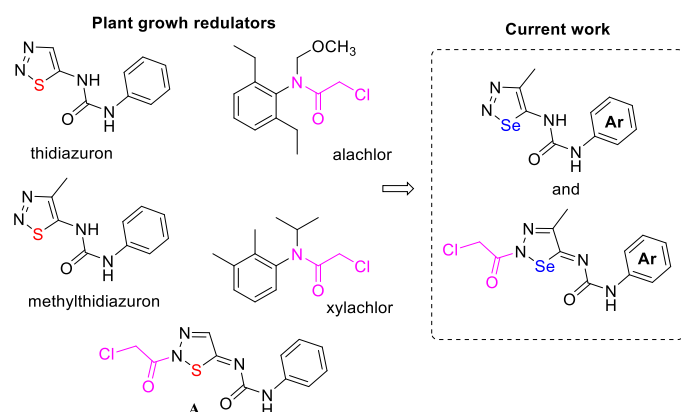
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### Sustainable Development Goals



Thiadiazole scaffold emerges as an interesting structural moiety due to the presence of different heteroatoms in its cycle and its promising therapeutic activities [9,10]. Derivatives of 1,2,3-thiadiazole exhibit various types of biological activity: antifungal [11], antibacterial [12], antiviral [13], nematocidal [14], antitumor [15]. They have found practical application as agrochemicals. For example, tiadinil [16] and methiadinil [17] are synthetic elicitors, while thidiazuron and methylthidiazuron are synthetic plant growth regulators [18]. It was shown that 1,2,3-thiadiazolyl ureas acylated at position 2 possess the ability to regulate the growth of various plant species [19]. For example, compound **A** – 1-(2-(2-chloroacetyl)-1,2,3-thiadiazol-5(2*H*)-ylidene)-3-phenylurea (Figure 2) demonstrated high defoliation activity on cotton.

Selenium can be considered the best isoster of sulfur as it is in the same group in the periodic table. These two atoms have very similar physical properties: the radius of selenium is only 12.5% bigger than that of sulfur, and their electronegativity is rather similar [20]. Over the past two decades, a number of important areas of organoselenium chemistry, including the synthesis and biological properties of selenadiazole derivatives, have been developing quite extensively [21–23]. In general, organoselenium compounds are known to exhibit various types of toxicity along with pharmacological activity [24]; however, research on the bioisosteric replacement of sulfur with selenium in biologically active compounds is very limited. The only heterocyclic drug containing a selenium atom in its structure is ebselen. Its antioxidant and anti-inflammatory properties are due to mimicking the activity of the selenoenzyme glutathione peroxidase. Ebselen protects cells from oxidative damage by catalyzing the reduction of hydroperoxides and other peroxides [25]. Sulfur contained bioisostere ebselen – ebsulfur has less antioxidant activity, and at the same time it exhibits greater inhibitory ability to trypanothione reductase (TryR) of *Trypanosoma brucei* [26]. Pedreira et al. synthesized new cardioactive compounds – *N*-acylhydrazone derivatives containing either a thienyl or a selenophenyl substituent [27]. The higher polarizability of selenium was shown to have a deshielding effect on adjacent hydrogen atoms of the compounds and affect their electron profile.



**Figure 2** Design of the target compounds.

However, the isosteric S/Se substitution did not affect the affinity or intrinsic potency of the compounds for the adenosine  $A_{2A}$  receptor ( $A_{2A}R$ ).

Substitution of selenium for the sulfur atom in the 1,2,3-thiadiazole ring may be considered as a viable approach to obtaining bioisosteres [27]. Compounds in the 1,2,3-selenadiazoles series are known to exhibit antimicrobial [28] and antitumor [29] properties. However, the biological activity of 1,2,3-selenadiazole derivatives against plants and their pathogens remains poorly studied. Specifically, 1,2,3-selenadiazol-4-ylureas demonstrated antiviral activity against the tobacco mosaic virus and were shown to induce protective properties of tobacco plants [30].

In this study, structural analogs of the plant growth regulator thidiazuron, 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas, were synthesized. To enhance the potential herbicidal properties of the resulting ureas **2a-j**, a chloroacetyl moiety was introduced into the structure, similar to compound **A** and known acetanilide herbicides such as metolachlor, alachlor, and xylachlor (Figure 2). The growth-regulating properties of the resulting 1,2,3-selenadiazol-4-yl ureas **2a-j** and their acylated derivatives **3a-j** were studied in a cucumber seed germination experiment along with their fungicidal activity against three strains of phytopathogenic fungi.

## 2. Experimental

### 2.1. Synthesis of target compounds

Melting points were determined using a Stuart SMP 3 apparatus (Staffordshire, ST15 OSA, UK). The progress of the reactions and the purity of the compounds were monitored by TLC on TLC Silica gel 60 F245 aluminum sheets (Merck KGaA) in an EtOAc-hexane system (1:2 or 1:1). Spectral data were obtained in the Laboratory of Complex Research and Expert Evaluation of Organic Materials, Center for Collective Use of the Ural Federal University, <https://ckp.urfu.ru>.  $^1H$  and  $^{13}C$  NMR spectra were recorded with a Bruker Avance II (Karlsruhe, Germany) spectrometer (400 MHz for  $^1H$ , 100 MHz for  $^{13}C$ ) and Bruker Avance NEO (Karlsruhe, Germany) spectrometer (150 MHz for  $^{13}C$ ). The NMR spectra of all the compounds are demonstrated in the Supplementary materials. Mass spectra were recorded with a Shimadzu GCMS-QP 2010 "Ultra" (Kyoto, Japan) in electron ionization (EI) mode (electron energy 70 eV). The Fourier transform infrared (FT-IR) spectra were obtained using a Bruker Alpha (ATR, ZnSe) spectrometer (Ettlingen, Germany). Elemental analyses were performed with a Perkin-Elmer 2400 Series II CHNS/O analyzer (Shelton, CT USA).

#### 2.1.1. General procedure for preparation of 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas (**2a-j**)

4-Methyl-1,2,3-selenadiazole-5-carbonyl azide **1** was synthesized according to the published method [31]. 4-Methyl-1,2,3-selenadiazole-5-carbonyl azide **1** (0.324 g, 1.5 mmol) was dissolved in 5 mL of dry 1,4-dioxane, and 1 mmol of

aniline derivatives was added. The reaction mixture was refluxed for 4–5 h. The precipitate was filtered off, washed with dry 1,4-dioxane, and dried.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-phenylurea**

**(2a).** Yield 0.316 g (75%), yellow powder, mp 236–237 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3272, 3144, 2883, 1687 (C=O), 1621, 1600, 1558, 1498, 1443, 1311, 1288, 1247, 1214, 1081, 1046, 1034.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.09 (1H, s, NH), 9.03 (1H, s, NH), 7.47 (2H, d,  $J = 7.7$ , CH Ar), 7.28 (2H, t,  $J = 7.9$ , CH Ar), 7.01 (1H, t,  $J = 7.4$ , CH Ar), 2.69 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 151.7 (C=O); 149.8 (C Het); 141.7 (C Het); 138.3 (C Ar); 129.0 (CH Ar); 123.1 (CH Ar); 118.6 (CH Ar); 12.3 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 282 [ $\text{M}$ ] $^+$  (9), 254 [ $\text{M}-\text{N}_2$ ] $^+$  (1), 120 (6), 119 (11), 93 (100), 92 (16), 77 (30), 65 (12). Found, %: C 42.84, H 3.42, N 19.79.  $\text{C}_{10}\text{H}_{10}\text{N}_4\text{OSe}$ . Calculated, %: C 42.72, H 3.58, N 19.93.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(o-tolyl)urea**

**(2b).** Yield 0.337 g (76%), beige powder, mp 210–211 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3298, 3225, 3037, 2844, 1684 (C=O), 1587, 1538, 1497, 1453, 1334, 1289, 1276, 1247, 1212, 1186, 1117, 1042.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.42 (1H, s, NH), 8.44 (1H, s, NH), 7.84 (1H, d,  $J = 7.8$ , CH Ar), 7.15 (2H, dd,  $J = 7.4$ ,  $J = 7.2$ , CH Ar), 6.98 (1H, t,  $J = 7.4$ , CH Ar), 2.71 (3H, s,  $\text{CH}_3$ ), 2.30 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 152.0 (C=O), 150.0 (C Het), 141.5 (C Het), 136.2 (C Ar), 130.4 (CH Ar), 128.2 (C Ar), 126.4 (CH Ar), 123.9 (CH Ar), 121.4 (CH Ar), 17.8 ( $\text{CH}_3$ ), 12.4 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 296 [ $\text{M}$ ] $^+$  (9), 294 (5), 268 [ $\text{M}-\text{N}_2$ ] $^+$  (3), 135 (11), 134 (13), 133 (15), 132 (9), 108 (13), 107 (100), 106 (36), 104 (15), 91 (36), 78 (10), 77 (15), 65 (18). Found, %: C 44.65, H 4.19, N 19.21.  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{OSe}$ . Calculated, %: C 44.76, H 4.10, N 18.98.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(m-tolyl)urea**

**(2c).** Yield 0.354 g (80%), beige powder, mp 226–227 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3124, 3060, 2891, 1686 (C=O), 1619, 1595, 1551, 1515, 1485, 1445, 1346, 1294, 1262, 1226, 1041.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.13 (1H, s, NH), 8.99 (1H, s, NH), 7.34 (1H, s, CH Ar), 7.22–7.13 (2H, m, CH Ar), 6.82 (1H, d,  $J = 7.2$ , CH Ar), 2.68 (3H, s,  $\text{CH}_3$ ), 2.34 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 151.7 (C=O), 149.8 (C Het), 141.6 (C Het), 138.4 (C Ar), 138.2 (C Ar), 128.9 (CH Ar), 123.8 (CH Ar), 119.0 (CH Ar), 115.7 (CH Ar), 21.1 ( $\text{CH}_3$ ), 12.3 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 296 [ $\text{M}$ ] $^+$  (9), 268 [ $\text{M}-\text{N}_2$ ] $^+$  (2), 134 (10), 133 (13), 132 (8), 108 (11), 107 (100), 106 (25), 104 (8), 91 (26), 77 (12), 65 (14). Found, %: C 44.82, H 4.24, N 18.79.  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{OSe}$ . Calculated, %: C 44.76, H 4.10, N 18.98.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(p-tolyl)urea**

**(2d).** Yield 0.297 g (67 %), light yellow powder, mp 247–248 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3272, 3134, 2860, 1685 (C=O), 1613, 1551, 1515, 1316, 1283, 1243, 1203, 1120, 1042.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.14 (1H, s, NH), 9.00 (1H, s, NH), 7.35 (2H, d,  $J = 8.4$ , CH Ar), 7.07 (2H, d,  $J = 8.2$ , CH Ar), 2.69 (3H, s,  $\text{CH}_3$ ), 2.30 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 151.6

(C=O), 149.8 (C Het), 141.4 (C Het), 135.7 (C Ar), 132.0 (C Ar), 129.3 (CH Ar), 118.6 (CH Ar), 20.2 ( $\text{CH}_3$ ), 12.2 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 296 [ $\text{M}$ ] $^+$  (9), 268 [ $\text{M}-\text{N}_2$ ] $^+$  (2), 133 (13), 108 (11), 107 (100), 106 (44), 104 (8), 91 (16), 79 (8), 77 (14), 65 (11). Found, %: C 44.68, H 4.15, N 18.57.  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{OSe}$ . Calculated, %: C 44.76, H 4.10, N 18.98.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(2,6-dimethylphenyl)urea (2e).**

Yield 0.357 g (77 %), beige powder, mp 200–201 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3262, 3117, 2856, 1684 (C=O), 1602, 1533, 1474, 1442, 1386, 1339, 1265, 1232, 1162, 1120, 1098, 1082, 1055, 1036.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.32 (1H, s, NH), 8.19 (1H, s, NH), 7.10–7.04 (3H, br. s, CH Ar), 2.71 (3H, s,  $\text{CH}_3$ ), 2.21 (6H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 152.5 (C Ar), 150.6 (C Het), 141.3 (C Het), 135.4 (CH Ar), 134.4 (C Ar), 127.9 (CH Ar), 126.7 (C Ar), 18.1 ( $\text{CH}_3$ ), 12.4 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 310 [ $\text{M}$ ] $^+$  (13), 308 (6), 282 [ $\text{M}-\text{N}_2$ ] $^+$  (10), 148 (14), 147 (12), 135 (26), 133 (15), 132 (14), 131 (8), 122 (9), 121 (100), 120 (24), 119 (10), 118 (10), 108 (11), 106 (23), 105 (46), 104 (9), 103 (14), 91 (18), 79 (20), 77 (30), 65 (7). Found, %: C 46.52, H 4.37, N 18.43.  $\text{C}_{12}\text{H}_{14}\text{N}_4\text{OSe}$ . Calculated, %: C 46.61, H 4.56, N 18.12.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(4-methoxyphenyl)urea (2f).**

Yield 0.313 g (67 %), beige powder, mp 222–223 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3271, 3126, 2891, 1678 (C=O), 1621, 1552, 1506, 1437, 1385, 1319, 1287, 1238, 1215, 1185, 1169, 1035.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.05 (1H, s, NH), 8.86 (1H, s, NH), 7.37 (2H, d,  $J = 9.0$ , CH Ar), 6.83 (2H, d,  $J = 9.0$ , CH Ar), 3.76 (3H, s,  $\text{CH}_3$ ), 2.68 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 155.3 (C Ar), 151.8 (C=O), 150.0 (C Het), 141.5 (C Het), 131.2 (C Het), 120.5 (CH Ar), 114.2 (CH Ar), 55.2 ( $\text{OCH}_3$ ), 12.3 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 312 [ $\text{M}$ ] $^+$  (10), 310 (5), 284 [ $\text{M}-\text{N}_2$ ] $^+$  (3), 149 (19), 135 (12), 134 (24), 124 (8), 123 (100), 122 (44), 108 (71), 107 (10), 106 (18), 95 (15), 92 (9), 80 (12), 79 (6), 78 (12), 77 (9), 65 (6). Found, %: C 42.59, H 3.92, N 17.89.  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_2\text{Se}$ . Calculated, %: C 42.45, H 3.89, N 18.00.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(3-chloro-4-methylphenyl)urea (2g).**

Yield 0.445 g (90 %), pale yellow powder, mp 235–236 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3187, 3071, 2909, 1684 (C=O), 1607, 1544, 1463, 1445, 1396, 1342, 1302, 1278, 1245, 1216, 1153, 1053, 1014.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.35 (1H, s, NH), 9.28 (1H, s, NH), (1H, s, CH Ar), 7.69–7.29 (2H, m, CH Ar), 2.67 (3H, s,  $\text{CH}_3$ ), 2.27 (3H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 151.7 (C=O), 149.8 (C Het), 141.9 (C Het), 137.4 (C Ar), 133.3 (C Ar), 131.4 (CH Ar), 129.8 (C Ar), 118.5 (CH Ar), 117.4 (CH Ar), 18.8 ( $\text{CH}_3$ ), 12.3 ( $\text{CH}_3$ ). EI-MS  $m/z$  (%): 332 [ $\text{M}+2$ ] $^+$  (6), 330 [ $\text{M}$ ] $^+$  (13), 328 (6), 302 [ $\text{M}-\text{N}_2$ ] $^+$  (2), 190 (9), 169 (8), 167 (25), 166 (8), 143 (32), 142 (15), 141 (100), 140 (24), 134 (9), 133 (10), 132 (62), 107 (8), 106 (19), 105 (6), 89 (12), 78 (8), 77 (25), 76 (8), 63 (6). Found, %: C 39.73, H 3.49, N 17.11.  $\text{C}_{11}\text{H}_{11}\text{ClN}_4\text{OSe}$ . Calculated, %: C 40.08, H 3.36, N 17.00.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(4-chlorophenyl)urea (2h).** Yield 0.379 g (80 %), pale yellow powder, mp 255–256 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3265, 3077, 2863, 1697 (C=O), 1621, 1598, 1559, 1489, 1401, 1389, 1351, 1311, 1280, 1247, 1210, 1117, 1085, 1042, 1011.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.36 (1H, s, NH), 9.35 (1H, s, NH), 7.53 (2H, d,  $J$  = 8.2, CH Ar), 7.38 (2H, d,  $J$  = 8.2, CH Ar), 2.67 (3H, s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (151 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 151.8 (C=O), 149.8 (C Het), 142.0 (C Het), 137.3 (C Ar), 128.9 (CH Ar), 126.8 (C Ar), 120.2 (CH Ar), 12.3 (CH<sub>3</sub>). EI-MS  $m/z$  (%): 318 [ $\text{M}+2$ ]<sup>+</sup> (3), 316 [ $\text{M}$ ]<sup>+</sup> (7), 288 [ $\text{M}-\text{N}_2$ ]<sup>+</sup> (1), 190 (8), 153 (16), 134 (10), 129 (30), 128 (13), 127 (100), 126 (19), 125 (15), 111 (10), 99 (12), 90 (17), 75 (15), 64 (7), 63 (14). Found, %: C 38.24, H 2.96, N 17.64. C<sub>10</sub>H<sub>9</sub>ClN<sub>4</sub>OSe. Calculated, %: C 38.05, H 2.87, N 17.75.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(4-bromophenyl)urea (2i).** Yield 0.443 g (82 %), beige powder, mp 244–245 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3266, 3076, 2883, 1698 (C=O), 1620, 1591, 1557, 1488, 1391, 1311, 1285, 1246, 1210, 1073, 1043.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.27 (1H, s, NH), 9.30 (1H, s, NH), 7.43 (4H, dd,  $J$  = 8.7, 8.8, CH Ar), 2.69 (3H, s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (151 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 151.7 (C=O), 149.7 (C Het), 141.9 (C Het), 137.7 (C Ar), 131.8 (CH Ar), 120.6 (CH Ar), 114.7 (C Ar), 12.3 (CH<sub>3</sub>). EI-MS  $m/z$  (%): 362 [ $\text{M}+2$ ]<sup>+</sup> (14), 360 [ $\text{M}$ ]<sup>+</sup> (19), 358 (8), 332 [ $\text{M}-\text{N}_2$ ]<sup>+</sup> (2), 199 (35), 197 (36), 190 (18), 188 (10), 173 (83), 172 (22), 171 (100), 169 (14), 163 (13), 157 (9), 155 (8), 135 (10), 134 (24), 133 (10), 132 (14), 131 (9), 119 (8), 108 (9), 107 (16), 106 (9), 105 (9), 93 (11), 92 (16), 91 (42), 90 (74), 82 (8), 76 (23), 75 (22), 74 (8), 65 (11), 64 (28), 63 (52), 62 (17). Found, %: C 33.48, H 2.34, N 15.68. C<sub>10</sub>H<sub>9</sub>BrN<sub>4</sub>OSe. Calculated, %: C 33.36, H 2.52, N 15.56.

**1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-(4-fluorophenyl)urea (2j).** Yield 0.395 g (88%), beige powder, mp 247–248 °C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3274, 3124, 2821, 1696 (C=O), 1655, 1624, 1576, 1557, 1510, 1456, 1441, 1412, 1386, 1349, 1310, 1288, 1253, 1219, 1159, 1104, 1045, 1013.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.34 (1H, s, NH), 9.25 (1H, s, NH), 7.50 (2H, dd,  $J$  = 8.5, 4.8, CH Ar), 7.18 (2H, t,  $J$  = 8.7, CH Ar), 2.67 (3H, s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (151 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 158.1 (d,  $J$  = 239.8, C Ar), 151.9 (C=O), 149.9 (C Het), 141.8 (C Het), 134.6 (C Ar), 120.6 (d,  $J$  = 7.8, CH Ar), 115.6 (d,  $J$  = 22.4, CH Ar), 12.3 (CH<sub>3</sub>). EI-MS  $m/z$  (%): 300 [ $\text{M}$ ]<sup>+</sup> (10), 298 (5), 272 [ $\text{M}-\text{N}_2$ ]<sup>+</sup> (1), 137 (20), 111 (100), 110 (20), 109 (15), 95 (12), 83 (14), 82 (10), 75 (7), 69 (6). Found, %: C 40.28, H 3.15, N 18.62. C<sub>10</sub>H<sub>9</sub>FN<sub>4</sub>OSe. Calculated, %: C 40.15, H 3.03, N 18.73.

### 2.1.2. General procedure for preparation of (Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-arylureas (3a-j)

1-(4-Methyl-1,2,3-selenadiazol-5-yl)-3-arylurea **2** (1 mmol) was dissolved in DMF and cooled in an ice bath, after which 10 mmol of chloroacetyl chloride was added. The reaction

mixture was stirred under cooling for 10 min. The precipitate was filtered off, washed with distilled water, and dried.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-phenylurea (3a).** Yield 0.272 g (76 %), beige powder, mp 201 °C (decomp.). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3341 (NH), 1685 (C=O), 1613, 1594 (C=O), 1548 (C=N), 1499, 1442, 1398, 1378, 1343, 1332, 1314, 1244, 1212, 1183, 1046, 1032.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 11.29 (1H, s, NH), 7.73 (2H, d,  $J$  = 7.6, CH Ar), 7.38 (2H, t,  $J$  = 7.9, CH Ar), 7.14 (1H, t,  $J$  = 7.4, CH Ar), 5.00 (2H, s, CH<sub>2</sub>), 2.57 (3H, s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 172.4 (C-5 Het), 166.6 (C=O), 162.3 (C=O), 150.7 (C-4 Het), 138.1 (C Ar), 128.7 (CH Ar), 124.0 (CH Ar), 119.1 (CH Ar), 41.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>). EI-MS  $m/z$  (%): 360 [ $\text{M}+2$ ]<sup>+</sup> (19), 358 [ $\text{M}$ ]<sup>+</sup> (45), 356 (22), 355 (8), 268(24), 266 [ $\text{M}-\text{C}_6\text{H}_5\text{NH}$ ]<sup>+</sup> (53), 264 (24), 262 (9), 192 (15), 190 (82), 188 (41), 187 (15), 186 (16), 120 (25), 119 (11), 107 (9), 93 (37), 92 (41), 91 (14), 79 (9), 78 (9), 77 (100), 65 (20). Found, %: C 40.41, H 3.15, N 15.54. C<sub>12</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub>Se. Calculated, %: C 40.30, H 3.10, N 15.67.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(o-tolyl)urea (3b).** Yield 0.257 g (69 %), pale yellow powder, mp 151 °C (decomp.). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3403 (NH), 1695 (C=O), 1651, 1620, 1585 (C=O), 1538 (C=N), 1495, 1455, 1429, 1404, 1380, 1340, 1322, 1308, 1216, 1187, 1163, 1118, 1051, 1034, 1008.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 10.61 (1H, s, NH), 7.42 (1H, d,  $J$  = 7.7, CH Ar), 7.28–7.16 (3H, m, CH Ar), 4.98 (2H, s, CH<sub>2</sub>), 2.58 (3H, s, CH<sub>3</sub>), 2.25 (3H, s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 172.9 (C-5 Het), 166.8 (C=O), 163.5 (C=O), 150.6 (C-4 Het), 135.6 (C Ar), 132.4 (C Ar), 130.5 (CH Ar), 126.3 (CH Ar), 126.2 (CH Ar), 125.1 (CH Ar), 42.3 (CH<sub>2</sub>), 17.8 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>). EI-MS  $m/z$  (%): 374 [ $\text{M}+2$ ]<sup>+</sup> (17), 372 [ $\text{M}$ ]<sup>+</sup> (39), 370 (19), 268 (20), 266 [ $\text{M}-\text{CH}_3\text{C}_6\text{H}_4\text{NH}$ ]<sup>+</sup> (48), 264 (23), 192 (17), 190 (95), 188 (46), 187 (19), 186 (20), 134 (35), 133 (16), 132 (12), 107 (36), 106 (48), 105 (19), 104 (18), 91 (100), 90 (12), 79 (21), 78 (18), 77 (62), 65 (36). Found, %: C 42.42, H 3.68, N 14.92. C<sub>13</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>2</sub>Se. Calculated, %: C 42.01, H 3.53, N 15.07.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(m-tolyl)urea (3c).** Yield 0.290 g (78 %), bright yellow powder, mp 228 °C (decomp.). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3358 (NH), 1683 (C=O), 1613, 1589 (C=O), 1547 (C=N), 1501, 1446, 1429, 1394, 1379, 1337, 1326, 1313, 1297, 1263, 1224, 1209, 1175, 1038, 1017.  $^1\text{H}$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, ( $J$ , Hz): 11.21 (1H, s, NH), 7.56 (1H, s, CH Ar), 7.51 (1H, d,  $J$  = 8.3, CH Ar), 7.25 (1H, t,  $J$  = 7.8, CH Ar), 6.95 (1H, d,  $J$  = 7.5, CH Ar), 4.97 (2H, s, CH<sub>2</sub>), 2.55 (3H, s, CH<sub>3</sub>), 2.31 (3H, s, CH<sub>3</sub>).  $^{13}\text{C}$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 172.4 (C-5 Het), 166.9 (C=O), 162.4 (C=O), 150.8 (C-4 Het), 138.3 (C Ar), 138.2 (C Ar), 128.8 (CH Ar), 124.9 (CH Ar), 119.6 (CH Ar), 116.4 (CH Ar), 42.3 (CH<sub>2</sub>), 21.2 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>). EI-MS  $m/z$  (%): 374 [ $\text{M}+2$ ]<sup>+</sup> (19), 372 [ $\text{M}$ ]<sup>+</sup> (42), 370 (21), 268 (21), 266 [ $\text{M}-\text{CH}_3\text{C}_6\text{H}_4\text{NH}$ ]<sup>+</sup> (48), 264 (22), 192 (18), 190 (100), 188 (50),

187 (20), 186 (21), 183 (12), 134 (32), 133 (20), 132 (14), 107 (49), 106 (44), 104 (14), 91 (97), 79 (77), 78 (17), 77 (66), 65 (38). Found, %: C 42.19, H 3.66, N 14.95.  $C_{13}H_{13}ClN_4O_2Se$ . Calculated, %: C 42.01, H 3.53, N 15.07.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(p-tolyl)urea (3d).** Yield 0.342 g (92 %), dark yellow powder, mp 241 °C (decomp.). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3343 (NH), 1682 (C=O), 1613, 1599 (C=O), 1542 (C=N), 1513, 1494, 1458, 1426, 1411, 1394, 1378, 1342, 1318, 1298, 1212, 1187, 1172, 1036, 1020, 1010.  $^1H$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, (*J*, Hz): 11.21 (1H, s, NH), 7.61 (2H, d, *J* = 8.4, CH Ar), 7.18 (2H, d, *J* = 8.4, CH Ar), 4.99 (2H, s, CH<sub>2</sub>), 2.56 (3H, s, CH<sub>3</sub>), 2.28 (3H, s, CH<sub>3</sub>).  $^{13}C$  NMR spectrum (151 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 172.2 (C-5 Het), 166.9 (C=O), 162.3 (C=O), 150.8 (C-4 Het), 135.8 (C Ar), 133.3 (C Ar), 129.4 (CH Ar), 119.1 (CH Ar), 42.4 (CH<sub>2</sub>), 20.5 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>). EI-MS *m/z* (%): 374 [M+2]<sup>+</sup> (20), 372 [M]<sup>+</sup> (47), 370 (23), 268 (19), 266 [M-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>NH]<sup>+</sup> (44), 264 (21), 192 (18), 190 (100), 188 (49), 187 (19), 186 (21), 183 (16), 134 (25), 133 (29), 132 (18), 107 (52), 106 (82), 105 (16), 104 (14), 91 (53), 79 (33), 78 (19), 77 (67), 65 (31). Found, %: C 42.13, H 3.39, N 14.98.  $C_{13}H_{13}ClN_4O_2Se$ . Calculated, %: C 42.01, H 3.53, N 15.07.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(2,6-dimethylphenyl)urea (3e).** Yield 0.351 g (91 %), bright yellow powder, mp 197 °C (decomp.). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3376 (NH), 1695 (C=O), 1606, 1584 (C=O), 1554 (C=N), 1538, 1447, 1407, 1375, 1335, 1308, 1271, 1246, 1222, 1204, 1171, 1097, 1037, 1006.  $^1H$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, (*J*, Hz): 10.54 (1H, s, NH), 7.13–7.11 (3H, m, CH Ar), 4.97 (2H, s, CH<sub>2</sub>), 2.58 (3H, s, CH<sub>3</sub>), 2.16 (6H, s, CH<sub>3</sub>).  $^{13}C$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 173.1 (C-5 Het), 166.9 (C=O), 163.5 (C=O), 150.6 (C-4 Het), 135.0 (CH Ar), 134.4 (C Ar), 128.0 (CH Ar), 127.2 (C Ar), 42.4 (CH<sub>2</sub>), 18.0 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>). EI-MS *m/z* (%): 388 [M+2]<sup>+</sup> (18), 386 [M]<sup>+</sup> (41), 284 (21), 268 (24), 266 [M-(CH<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH]<sup>+</sup> (53), 264 (25), 192 (18), 190 (100), 188 (49), 187 (23), 186 (21), 147 (26), 146 (13), 121 (20), 120 (29), 119 (15), 118 (14), 106 (12), 105 (53), 104 (16), 103 (20), 91 (22), 79 (37), 78 (16), 77 (69), 76 (15), 65 (9). Found, %: C 43.41, H 3.84, N 14.71.  $C_{14}H_{15}ClN_4O_2Se$ . Calculated, %: C 43.60, H 3.92, N 14.53.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(p-methoxyphenyl)urea (3f).** Yield 0.260 g (67 %), orange powder, mp 231 °C (decomp.). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3334 (NH), 1680 (C=O), 1597 (C=O), 1547 (C=N), 1512, 1494, 1465, 1416, 1396, 1378, 1341, 1316, 1304, 1268, 1239, 1214, 1171, 1030, 1008.  $^1H$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, (*J*, Hz): 11.16 (1H, s, NH), 7.64 (2H, d, *J* = 9.1, CH Ar), 6.96 (2H, d, *J* = 9.1, CH Ar), 4.98 (2H, s, CH<sub>2</sub>), 3.75 (3H, s, OCH<sub>3</sub>), 2.56 (3H, s, CH<sub>3</sub>).  $^{13}C$  NMR spectrum (100 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 171.9 (C-5 Het), 166.8 (C=O), 162.1 (C=O), 156.0 (C Ar), 150.8 (C-4 Het), 131.3 (C Ar), 120.7 (CH Ar), 114.1 (CH Ar), 55.2 (OCH<sub>3</sub>), 42.3 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>). EI-MS *m/z* (%): 390 [M+2]<sup>+</sup> (13), 388 [M]<sup>+</sup> (28), 386 (14), 268 (8), 266 [M-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>NH]<sup>+</sup>

(18), 199 (14), 192 (12), 190 (68), 188 (34), 187 (18), 186 (15), 150 (12), 149 (100), 148 (20), 134 (22), 123 (26), 122 (79), 121 (24), 108 (17), 107 (11), 106 (13), 95 (17), 92 (9), 79 (15), 78 (12), 77 (38), 76 (11). Found, %: C 40.41, H 3.25, N 14.62.  $C_{13}H_{13}ClN_4O_3Se$ . Calculated, %: C 40.28, H 3.38, N 14.45.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(3-chloro-4-methylphenyl)urea (3g).** Yield 0.378 g (93 %), dark yellow powder, mp 230 °C (decomp.). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3349 (NH), 1688 (C=O), 1615, 1596 (C=O), 1536 (C=N), 1494, 1461, 1441, 1389, 1378, 1338, 1327, 1315, 1301, 1280, 1244, 1227, 1208, 1174, 1054, 1041, 1018.  $^1H$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, (*J*, Hz): 11.36 (1H, s, NH), 7.83 (1H, d, *J* = 1.9, CH Ar), 7.57 (1H, dd, *J* = 8.4, *J* = 1.9, CH Ar), 7.34 (1H, d, *J* = 8.4, CH Ar), 4.99 (2H, s, CH<sub>2</sub>), 2.56 (3H, s, CH<sub>3</sub>), 2.29 (3H, s, CH<sub>3</sub>).  $^{13}C$  NMR spectrum (151 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 172.8 (C-5 Het), 166.8 (C=O), 162.3 (C=O), 150.9 (C-4 Het), 137.5 (C Ar), 133.3 (C Ar), 131.4 (CH Ar), 130.8 (C Ar), 118.8 (CH Ar), 117.7 (CH Ar), 42.4 (CH<sub>2</sub>), 19.0 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>). EI-MS *m/z* (%): 410 [M+4]<sup>+</sup> (5), 408 [M+2]<sup>+</sup> (18), 406 [M]<sup>+</sup> (27), 404 (13), 268 (24), 266 [M-CH<sub>3</sub>ClC<sub>6</sub>H<sub>3</sub>NH]<sup>+</sup> (53), 264 (26), 192 (18), 190 (100), 188 (49), 187 (20), 186 (21), 167 (11), 142 (19), 141 (54), 140 (54), 134 (12), 133 (13), 132 (39), 125 (22), 107 (12), 106 (14), 105 (11), 104 (22), 90 (11), 89 (33), 79 (17), 78 (15), 77 (88), 76 (14). Found, %: C 38.61, H 3.04, N 13.69.  $C_{13}H_{12}Cl_2N_4O_2Se$ . Calculated, %: C 38.45, H 2.98, N 13.80.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(4-chlorophenyl)urea (3h).** Yield 0.345 g (88 %), dark orange powder, mp 225 °C (decomp.). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3341 (NH), 1680 (C=O), 1609, 1594 (C=O), 1539 (C=N), 1488, 1404, 1390, 1377, 1341, 1325, 1311, 1289, 1241, 1212, 1182, 1093, 1072, 1033, 1013.  $^1H$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, (*J*, Hz): 11.43 (1H, s, NH), 7.76 (2H, d, *J* = 8.8, CH Ar), 7.45 (2H, d, *J* = 8.8, CH Ar), 5.00 (2H, s, CH<sub>2</sub>), 2.57 (3H, s, CH<sub>3</sub>).  $^{13}C$  NMR spectrum (151 MHz, DMSO- $d_6$ ),  $\delta$ , ppm: 172.9 (C-5 Het), 166.9 (C=O), 162.5 (C=O), 150.9 (C-4 Het), 137.3 (C Ar), 129.0 (CH Ar), 127.8 (C Ar), 120.7 (CH Ar), 42.4 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>). EI-MS *m/z* (%): 396 [M+4]<sup>+</sup> (5), 394 [M+2]<sup>+</sup> (20), 392 [M]<sup>+</sup> (30), 390 (14), 268 (27), 266 [M-ClC<sub>6</sub>H<sub>4</sub>NH]<sup>+</sup> (61), 264 (29), 263 (10), 262 (11), 192 (18), 190 (100), 189 (11), 188 (49), 187 (20), 186 (20), 153 (17), 128 (19), 127 (28), 126 (51), 125 (20), 111 (24), 99 (20), 90 (14), 79 (14), 77 (42), 76 (13), 75 (22), 63 (12). Found, %: C 36.87, H 2.71, N 14.14.  $C_{12}H_{10}Cl_2N_4O_2Se$ . Calculated, %: C 36.76, H 2.57, N 14.29.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(4-bromophenyl)urea (3i).** Yield 0.305 g (70 %), dark yellow powder, mp 238 °C (decomp.). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3339 (NH), 1680 (C=O), 1605, 1587 (C=O), 1538 (C=N), 1486, 1404, 1390, 1377, 1340, 1326, 1310, 1288, 1239, 1221, 1210, 1182, 1075, 1032, 1010.  $^1H$  NMR spectrum (400 MHz, DMSO- $d_6$ ),  $\delta$ , ppm, (*J*, Hz): 11.43 (1H, s, NH), 7.70 (2H, d, *J* = 8.8, CH Ar), 7.57 (2H, d, *J* = 8.8, CH Ar), 5.01 (2H, s, CH<sub>2</sub>), 2.57 (3H, s, CH<sub>3</sub>).  $^{13}C$  NMR spectrum

(151 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 172.9 (C-5 Het), 166.9 (C=O), 162.4 (C=O), 150.9 (C-4 Het), 137.8 (C Ar), 131.9 (CH Ar), 121.0 (CH Ar), 115.9 (C Ar), 42.4 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>). EI-MS *m/z* (%): 440 [M+4]<sup>+</sup> (9), 438 [M+2]<sup>+</sup> (26), 436 [M]<sup>+</sup> (28), 434 (12), 268 (31), 266 [M-BrC<sub>6</sub>H<sub>4</sub>NH]<sup>+</sup> (73), 265 (11), 264 (35), 263 (12), 262 (13), 192 (18), 190 (100), 189 (12), 188 (50), 187 (21), 186 (21), 172 (21), 171 (15), 170 (22), 157 (14), 155 (14), 134 (11), 107 (12), 91 (28), 90 (22), 79 (14), 77 (44), 76 (25), 75 (18), 63 (16). Found, %: C 33.22, H 2.12, N 12.91. C<sub>12</sub>H<sub>10</sub>BrClN<sub>4</sub>O<sub>2</sub>Se. Calculated, %: C 33.02, H 2.31, N 12.83.

**(Z)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2H)-ylidene)-3-(4-fluorophenyl)urea (3j).** Yield 0.297 g (79 %), dark yellow powder, mp 239 °C (decomp.). IR spectrum,  $\nu$ , cm<sup>-1</sup>:  $\nu$ , cm<sup>-1</sup>: 3341 (NH), 1682 (C=O), 1610, 1599 (C=O), 1549 (C=N), 1498, 1409, 1396, 1375, 1339, 1324, 1311, 1245, 1212, 1160, 1106, 1032, 1014. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm, (*J*, Hz): 11.33 (1H, s, NH), 7.76–7.72 (2H, m, CH Ar), 7.23 (2H, t, *J* = 8.9, CH Ar), 4.99 (2H, s, CH<sub>2</sub>), 2.56 (3H, s, CH<sub>3</sub>). <sup>13</sup>C NMR spectrum (151 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 172.4 (C-5 Het), 166.6 (C=O), 162.3 (C=O), 158.5 (d, *J* = 241.3, C Ar), 150.7 (C-4 Het), 134.5 (d, *J* = 1.5, C Ar), 120.9 (d, *J* = 7.9, C Ar), 115.3 (d, *J* = 22.5, C Ar), 41.8 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>). EI-MS *m/z* (%): 378 [M+2]<sup>+</sup> (16), 376 [M]<sup>+</sup> (32), 268 (23), 266 [M-FC<sub>6</sub>H<sub>4</sub>NH]<sup>+</sup> (54), 264 (26), 190 (100), 188 (47), 111 (29), 110 (77), 109 (22), 95 (32), 83 (34), 77 (35), 49 (29). C<sub>12</sub>H<sub>10</sub>ClFN<sub>4</sub>O<sub>2</sub>Se. Calculated, %: C 38.37, H 2.68, N 14.91.

## 2.2. X-ray diffraction study

Crystals of compounds **3b,c,f** suitable for X-ray diffraction (XRD) analysis were grown by slow evaporation of a solution of the corresponding compound in dimethyl sulfoxide (DMSO) at room temperature. The XRD experiment was performed on an automated X-ray diffractometer «Xcalibur 3» with CCD detector using the standard procedure. An empirical absorption correction was applied. The structure was solved by method of the intrinsic phases in ShelXT program [32] and refined by ShelXL [33] employing full-matrix least-squared method for non-hydrogen atoms. The hydrogen atoms of C-H bonds were placed in the calculated positions; the protons of NH groups were localized along the peaks of the spatial electron density and refined independently in the isotropic approximation. The solution and refinement of the structures were accomplished with Olex program package [34]. Detailed parameters are shown in Table S1 (Supplementary materials). The XRD data were deposited in the Cambridge Structural Database. This data can be requested free of charge via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).

## 2.3. Study of fungicidal activity

The *in vitro* fungicidal activity of compounds **2a–j** and **3a–j** against *Botrytis cinerea* Pers. MFG 60449, *Phytophthora infestans* (Mont.) de Bary, and *Sclerotinia sclerotiorum* was tested according to the reported method at a concentration

of 0.5 mg/mL [35]. *P. infestans* was isolated at Nankai University (Tianjin, China). *B. cinerea* and *S. sclerotiorum* were purchased from the Russian Collection of Agricultural Microorganisms (St. Petersburg, Russia).

The percentage of fungus growth inhibition was determined by the formula:

$$I (\%) = [(C - T)/(C - 4 \text{ mm})] \cdot 100, \quad (1)$$

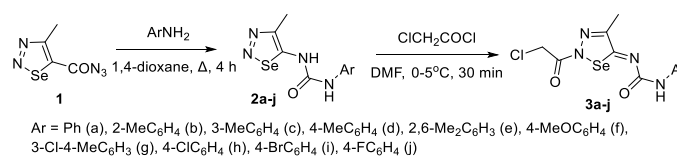
where *I* (%) is the degree of inhibition of mycelial growth, *T* (mm) is the mean value of the diameter of the colonies in the presence of a given concentration of each compound, and *C* (mm) is the mean diameter of the colonies in the absence of the compound under the same conditions. The mycelial cake inoculation on the PDA was in a diameter of 4 mm. All the experiments were carried out in triplicate, and the standard deviation was calculated.

## 2.4. Study of plant growth regulation

The growth-regulating properties of compounds **2a,d,g** and **3a,d,g** were studied on cucumber seeds of the Izyashchnye variety (Russia) at a concentration of 5 mg/L. The synthetic growth regulator thidiazuron (TDZ) was selected as reference substance. To each Petri dish containing 2 layers of filter paper, 7 mL of an aqueous solution of the test compound at the required concentration, containing 0.1% DMSO, was added. The control Petri dishes contained 7 mL of water. Ten seeds were placed on the filter paper in each Petri dish. For each compound at all the concentrations the experiment was run three times. The Petri dishes were placed in the Binder growth chamber at a temperature of 25 °C, 50% humidity, and a 16-hour photoperiod. The measurements were taken for parameters including stem length and width, root length and width, sprout length, cotyledon length and width, and number of lateral roots on the 5th and 7th day. The averages for all experimental treatments are presented in Tables S2 (Supplementary materials). The experimental results were analyzed using STATISTICA 8.0 software package. Descriptive statistics were used: mean, standard deviation (SD), standard error of the mean, and coefficient of variation (CV).

## 3. Results and Discussion

Compounds **2a–j** was obtained by reacting 4-methyl-1,2,3-selenadiazole-5-carbonyl azide **1** and corresponding aniline derivatives in 1,4-dioxane according to the previously published procedure (Scheme 1) [36]. Further acylation with chloroacetyl chloride in dimethylformamide at 0–5 °C afforded products **3a–j** in 67–93% yields.



**Scheme 1** Synthesis of compounds **2a–j** and **3a–j**.

Acylation of ureas **2** occurs at the nitrogen atom at position 2 of the 1,2,3-selenadiazole ring. The structures of the products **3** were confirmed by their spectral data. The carbon atom signals in the  $^{13}\text{C}$  NMR spectra were resolved using two-dimensional HSQC and HMBC spectra.

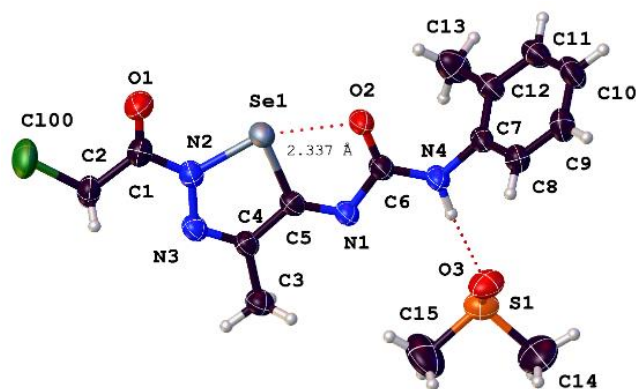
When comparing the  $^1\text{H}$  NMR spectra of compounds **3** with those of the starting compounds **2**, the appearance of signals from the protons of the methylene group and the disappearance of the signal from the proton of one of the amino groups can be observed. Also, when comparing the  $^{13}\text{C}$  NMR spectra of compounds **3** and ureas **2**, the appearance of a signal from the carbon of the methylene group in the region of 41.81–42.38 ppm as well as a signal from the carbon of the carbonyl group of the chloroacetyl fragment in the region of 166.60–166.94 ppm can be observed. Additionally, there is a shift in the signal of the carbon atom at the 5-position of the ring from the region of 149.73–150.56 ppm to the region of 172.2–173.1 ppm and a shift in the signal of the carbon atom of the urea fragment from the region of 151.65–152.02 ppm to the region of 162.07–163.51 ppm.

It is known that acylation of 1,2,3-thiadiazolyl ureas occurs at the nitrogen atom in position 2 of the thiadiazole ring, as previously described using acetyl chloride and chloroacetic anhydride [19]. For 1,2,3-selenadiazoles, the acylation reaction of ethyl 1,2,3-selenadiazole-4-carboxylates by aroyl chlorides was reported [37].

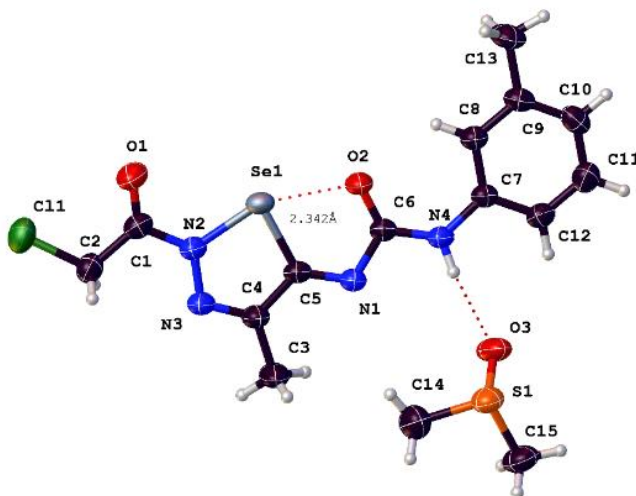
We identified only one published 2-substituted-2,5-dihydro-1,2,3-selenadiazole derivative **I**, whose structure was confirmed by X-ray structural analysis [38] (Figure 6). This compound is ethyl 2-(4-methylbenzoyl)-5-((4-methylbenzoyl)imino)-2,5-dihydro-1,2,3-selenadiazole-4-carboxylate. We grew single crystals of three 2-acyl-selenodiazoles **3b,c,f**, suitable for X-ray structural analysis, and their structures were confirmed by X-ray crystallography (Figures 3–5).

Compounds **3b,c,f** crystallize in the triclinic space group P-1. In all structures **3b,c,f**, the chloroacetyl fragment is bonded to the nitrogen atom at position 2 of the Se(1)N(2)N(3)C(4)C(5) cycle. In these crystal structures, the lengths of the N(2)–N(3) (1.350–1.353 Å) and C(4)–C(5) (1.451–1.459 Å) bonds are greater than the similar bonds in 2-unsubstituted selenadiazoles: 1.26–1.27 Å [39–43] and 1.36–1.37 Å [39–43], respectively. Conversely, N(3)–C(4) bonds in **3b,c,f** (1.288–1.304 Å) are shorter than those in 2-unsubstituted selenadiazoles (1.38–1.39 Å) [39–43].

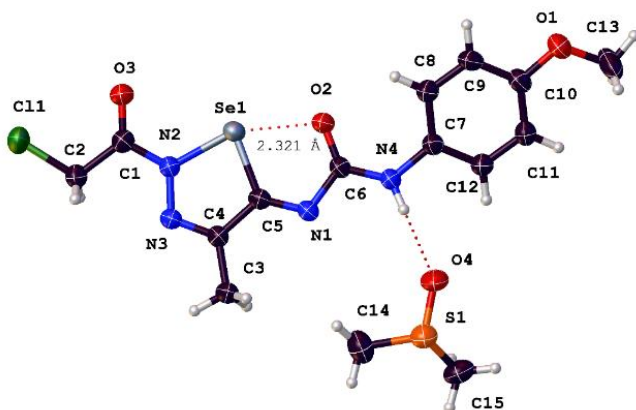
In all crystal structures, the distance ( $d$ ) between the Se(1) and O(2) atoms is less than the sum of their van der Waals radii ( $\Sigma = r(\text{Se})_{\text{vdw}} + r(\text{O})_{\text{vdw}} = 1.90 \text{ \AA} + 1.52 \text{ \AA} = 3.42 \text{ \AA}$ ) (Figure 6). The difference between the sum of the van der Waals radii of Se and O atoms and their interatomic distance ( $r(\text{Se})_{\text{vdw}} + r(\text{O})_{\text{vdw}} - d_{\text{Se,O}}$ ) characterizes the approach of atoms compared to their equilibrium arrangement in crystal structures and was more than 1 Å in the crystal of the previously described 2-unsubstituted selenadiazoles **I** [38].



**Figure 3** The molecular structure of compound **3b**, showing the atom numbering scheme for the non-H atoms. Displacement ellipsoids are drawn at the 50% probability level. The non-covalent interactions are indicated by a dashed line.



**Figure 4** The molecular structure of compound **3c**, showing the atom numbering scheme for the non-H atoms. Displacement ellipsoids are drawn at the 50% probability level. The non-covalent interactions are indicated by a dashed line.



**Figure 5** The molecular structure of compound **3f**, showing the atom numbering scheme for the non-H atoms. Displacement ellipsoids are drawn at the 50% probability level. The non-covalent interactions are indicated by a dashed line.

Such atom proximity can only be explained by the emergence of an additional stabilizing interaction between these atoms. Previously, the overlap of  $n_{\text{O}}-\sigma_{\text{Se}}^*$  orbitals was proposed as a mechanism for such interaction [44].

To quantify the degree of interaction between atoms, the covalence ratio factor ( $\chi$ ) is widely used [45,46], which is defined by the following expression:

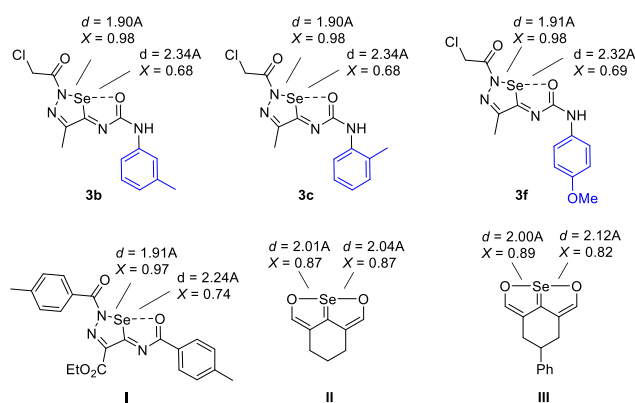
$$\chi = \frac{(R_X + R_Y) - d_{XY}}{(R_X + R_Y) - (r_X + r_Y)} \quad (2)$$

where  $R_X$  and  $R_Y$  are the van der Waals radii of atoms X and Y, respectively;  $r_X$  and  $r_Y$  are the covalent radii of atoms X and Y, respectively;  $d_{XY}$  is the experimentally determined distance between X and Y atoms.

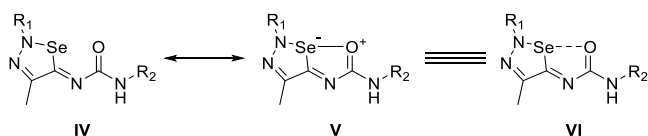
At  $R(N) = 1.55 \text{ \AA}$ ,  $R(O) = 1.52 \text{ \AA}$ ,  $R(\text{Se}) = 1.90 \text{ \AA}$  [47],  $r(N) = 0.70 \text{ \AA}$ ,  $r(O) = 0.66 \text{ \AA}$ ,  $r(\text{Se}) = 1.17 \text{ \AA}$  [48], the values of  $\chi(\text{Se},\text{O})$  calculated for **3b,c,f** are 0.68, 0.68, 0.69, respectively. These calculated values of  $\chi$  are by 0.05–0.06 lower compared to the similar value for compound **I** (Figure 6) and by 0.13–0.21 lower than those in 6,7-dihydro-5H-2,3-dioxo-2 $\lambda^4$ -selenacyclopenta[hi]indenes **II–III** [49,50].

Also, in compounds **3b,c,f**, planarity of the Se(1)C(5)N(1)C(6)O(2) fragment is observed, which favors the overlap of the  $n_o$  and  $\sigma^*_{\text{se}}$  orbitals. RMSD of Se(1)C(5)N(1)C(6)O(2) fragment for **3b,c,f** are 0.007  $\text{\AA}$ , 0.006  $\text{\AA}$  and 0.003  $\text{\AA}$ , respectively. Taking into account the abovementioned factors, the presence of a stabilizing interaction between the Se(1) and O(2) atoms and the planarity of the Se(1)C(5)N(1)C(6)O(2) fragment, it can be stated that structures **3b,c,f** have a pseudoheterocyclic system Se(1)C(5)N(1)C(6)O(2) (Scheme 2) that can be represented by superpositions of the resonance structures **IV** and **V**, which is equivalent to structure **VI** (Scheme 2).

Considering the fact that the 1,2,3-selenadiazole ring can open upon cleavage of the Se(1)-N(2) bond, we also calculated the  $\chi$  for this bond for structures **3b,c,f**. In this case, the  $\chi$  value was 0.98, indicating the covalent nature of the Se(1)-N(2) bond.



**Figure 6** Key bond lengths and  $\chi$  values in titular and previously reported heterocycles containing a selenium atom.



**Scheme 2** Possible resonance structures for compounds **3**.

All the three crystal structures of compounds **3b,c,f** contain a molecule of co-crystallized dimethyl sulfoxide, with which an intermolecular N(4)H(4)...O hydrogen bond is formed. Geometrical parameters of intermolecular hydrogen bonds are presented in Table 1.

Since it is known that replacing sulfur with selenium can lead to an increase in toxicity, in particular in the antimicrobial properties [51] of substances, a promising direction is the study of the fungicidal activity of 1,2,3-selenadiazoles derivatives. The fungicidal activity of obtained compounds **2a–j** and **3a–j** was studied against 2 strains of phytopathogenic fungi *B. cinerea*, *S. sclerotiorum* and 1 oomycete *P. infestans*. The bioassay results of fungicidal activity for the studied compounds are presented in Table 2.

Most of the obtained compounds did not effectively inhibit fungal mycelial growth at a concentration of 50  $\mu\text{g/mL}$ .

**Table 1** Geometrical parameters of intermolecular hydrogen bonds with the DMSO molecule in **3b,c,f**.

Compound	N4-H4, $\text{\AA}$	H4...O, $\text{\AA}$	N4...O, $\text{\AA}$	N4-H4...O, $^\circ$
<b>3b</b>	0.93	1.87	2.797	171
<b>3c</b>	0.86	2.04	2.899	172
<b>3f</b>	0.89	2.00	2.856	162

**Table 2** Results of antifungal activity study *in vitro* for compounds **2a–j** and **3a–j** at a concentration of 50  $\mu\text{g/mL}$ .\*

Compound	Degree of inhibition of mycelial growth (I $\pm$ SD%) calculated by formula (1)		
	<i>B. cinerea</i>	<i>P. infestans</i>	<i>S. sclerotiorum</i>
<b>2a</b>	0	1.50 $\pm$ 0.31	4.06 $\pm$ 0.19
<b>2b</b>	0	4.41 $\pm$ 1.08	14.30 $\pm$ 0.63
<b>2c</b>	0	7.67 $\pm$ 0.47	5.14 $\pm$ 1.35
<b>2d</b>	0	0	0
<b>2e</b>	18.22 $\pm$ 1.65	16.74 $\pm$ 1.86	13.17 $\pm$ 3.08
<b>2f</b>	0	0.79 $\pm$ 0.52	10.27 $\pm$ 3.10
<b>2g</b>	0	1.66 $\pm$ 0.15	0.27 $\pm$ 0.05
<b>2h</b>	0	9.52 $\pm$ 0.31	21.02 $\pm$ 1.17
<b>2i</b>	0	2.55 $\pm$ 1.17	6.73 $\pm$ 1.36
<b>2j</b>	0	0	1.39 $\pm$ 0.80
<b>3a</b>	0	3.17 $\pm$ 0.23	6.81 $\pm$ 0.94
<b>3b</b>	11.60 $\pm$ 1.71	26.71 $\pm$ 1.40	<b>47.21 <math>\pm</math> 0.43</b>
<b>3c</b>	0	6.74 $\pm$ 0.86	13.15 $\pm$ 2.78
<b>3d</b>	0	4.79 $\pm$ 0.72	2.38 $\pm$ 0.71
<b>3e</b>	16.78 $\pm$ 0.49	10.29 $\pm$ 0.62	5.71 $\pm$ 0.46
<b>3f</b>	0	9.90 $\pm$ 0.75	8.00 $\pm$ 2.34
<b>3g</b>	0	0.82 $\pm$ 0.07	1.36 $\pm$ 0.27
<b>3h</b>	0	2.97 $\pm$ 0.27	0
<b>3i</b>	0	7.67 $\pm$ 0.61	10.77 $\pm$ 2.76
<b>3j</b>	0	1.30 $\pm$ 0.33	6.75 $\pm$ 0.93
<b>BC</b>	95.20 $\pm$ 1.34	23.10 $\pm$ 2.11	100 $\pm$ 0
<b>CZ</b>	100 $\pm$ 0	0	98.28 $\pm$ 0.65

\* BC - commercial fungicide boscalid, CZ - commercial fungicide carbendazim, SD - standard deviation, I = 100 - active compound, I = 0 - not active compound.

The degree of inhibition of mycelial growth ranged from 0 to 47%. All the tested compounds except **2e**, **3b**, and **3e** did not inhibit the radial growth of *B. cinerea*. Compound **3b**, containing a 2-methylphenyl substituent and a chloroacetyl moiety, exhibited the highest activity against two phytopathogens: *P. infestans* ( $I = 26.71 \pm 1.40\%$ ) and *S. sclerotiorum* ( $I = 47.21 \pm 0.43\%$ ).

In most cases, the introduction of a chloroacetyl moiety into the heteroring of 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas slightly increased fungicidal activity against *P. infestans* and *S. sclerotiorum*, especially for compound **3b**.

For the initial evaluation of growth-regulating properties, three 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas **2a,d,g** and their acylated derivatives **3a,d,g** were selected. The synthetic growth regulator thidiazuron (TDZ) was used as a reference compound.

The values of the seedling morphometric parameters (Table S1) are presented in the Supplementary materials. Comparative graphs of the seedling morphometric parameters, including stem length and thickness, root length and thickness, total seedling length, and the number of lateral roots, are shown in Figure 7.

All the tested compounds inhibited seedling development (Figure 7, Table S2 (Supplementary materials)). Stem and root lengths on days 5 and 7 were shorter in cucumber seedlings of the treated samples than in those of the control samples.

The greatest differences in the linear dimensions of the seedling stem compared to the seedlings of the control line were observed in lines **2a**, **2d** and **TDZ** on day 5, as well as on day 7 in lines **2a**, **TDZ**. Thus, the smallest value of the seedling stem length on day 5 was observed in line **2a** ( $5.44 \pm 1.58$  mm), while the control measured  $8.49 \pm 1.89$  mm. On day 7, the smallest stem length was observed in line **TDZ** ( $7.67 \pm 2.85$  mm),  $13.15 \pm 2.10$  mm in the control. The greatest difference in the sizes of the main root of the seedlings compared to the control on days 5 and 7 of the experiment were also found in lines **2a**, **2d** and **TDZ**. The lowest root size was recorded on day 5 in line **2a** (approximately 5 times lower than the control), and on day 7 in line **TDZ** (approximately 7 times lower). Seedling length in all lines of the studied compounds was shorter than in the control samples, with the smallest seedling size observed in lines **2a**, **2d**, and **TDZ**.



**Figure 7** Effects of compound treatments on seedling morphometric parameters. The error bars represent the standard error (SE) of the mean. Statistical significance was determined by t-tests comparing each treatment with the water control. ns – not significant; \* –  $p < 0.05$ ; \*\* –  $p < 0.01$ ; \*\*\* –  $p < 0.001$ .

The greatest stem width was observed in seedlings of lines **2a**, **2d**, and **TDZ**. On day 5 of the experiment, stem width in line **TDZ** was nearly twice that of the control. The largest diameter of the primary root was noted in lines **2a**, **3d**, and **TDZ**, while the smallest diameter was observed on day 5 in lines **2d** and **3g**, and on day 7 in the **control**, **3a**, and **3g**.

Among all cucumber seedling traits, the number of lateral roots showed the greatest variability, ranging from 0% (**TDZ**) to 90.03% (**2a**) on day 5, which decreased by day 7 becoming, from 0% (**TDZ**) to 54.39% (control). In general, lateral roots did not develop in the **TDZ** line seedlings; in lines **2a** and **2d**, the number of lateral roots was significantly lower ( $3.63 \pm 3.26$  and  $5.80 \pm 3.76$  on day 5,  $7.69 \pm 3.34$  and  $8.00 \pm 2.76$  on day 7, respectively) compared to the seedlings treated with water ( $12.50 \pm 4.98$  on day 5 and  $18.00 \pm 8.79$  on day 7).

Thus, compounds **2a** and **2d** exhibit effects similar to **TDZ** on cucumber seedling development: they shorten and thicken the roots and stems and reduce the number of lateral roots. However, at the studied concentration of 5 mg/L, the effects of compounds **2a** and **2d** are less pronounced than those of the commercial plant growth regulator thidiazuron.

## 4. Limitations

In this work, we present the first data on the antifungal and plant growth-regulating activity of 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas and (*Z*)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2*H*)-ylidene)-3-arylurea derivatives. To obtain potential fungicidal compounds, it is necessary to expand the range of acylating agents, as acylation leads to increased fungicidal activity. In this study, only chloroacetyl chloride was used as the acylating agent.

To develop the structures of potential plant growth regulators based on 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylurea derivatives, further studies of their mechanism of biological action and the identification of biological targets are necessary. Further *in vivo* biological studies of compounds **2a** and **2d** are also needed to assess their effects on different plants at different growth stages, as well as their toxicity to humans, animals and beneficial microorganisms.

## 5. Conclusions

The 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas structurally related to the synthetic plant growth regulator thidiazuron were synthesized and characterized. It was demonstrated that their acylation reaction with chloroacetyl chloride occurs at the nitrogen atom in position 2 of the 1,2,3-selenadiazole ring. The fungicidal activity of 1-(4-methyl-1,2,3-selenadiazol-5-yl)-3-arylureas and (*Z*)-1-(2-(2-chloroacetyl)-4-methyl-1,2,3-selenadiazol-5(2*H*)-ylidene)-3-arylureas against three phytopathogenic fungi was studied. Compound **3b** has shown to exhibit moderate activity

( $47.21 \pm 0.43\%$ ) against *S. sclerotiorum*. The plant growth-regulating activity of the six compounds obtained was evaluated at a concentration of 5 mg/L in the cucumber seed germination assay. Two 1,2,3-selenadiazol-5-ylureas **2a** and **2d** showed a biological effect profile similar to that of thidiazuron in the seed germination experiment. 1,2,3-Selenadiazol-5-ylureas **2a** and **2d**, like thidiazuron, inhibited root and stem elongation as well as lateral root formation in seedlings. Stem and root thickening was observed, particularly for **TDZ** and **2a**. These results suggest that compounds **2a** and **2d** warrant further investigation for their growth-regulating properties.

## Supplementary materials

This article contains supplementary materials with <sup>1</sup>H and <sup>13</sup>C NMR spectra, and the table with morphometric parameters of cucumber seedlings on 5<sup>th</sup> and 7<sup>th</sup> days of experiment. The supplementary materials are available on the corresponding online page.

## Data availability statement

The data that supports the findings of this study are available in the supplementary materials of this article.

## Acknowledgments

None.

## Author contributions

Conceptualization: T.A.K., T.V.G.  
 Data curation: T.A.K., T.V.G.  
 Formal Analysis: T.A.K., K.L.O., T.V.G.  
 Funding acquisition: T.A.K.  
 Investigation: V.S.E., T.A.K., P.A.S.  
 Methodology: T.V.G.  
 Project administration: T.A.K.  
 Resources: T.A.K., T.V.G.  
 Supervision: T.V.G.  
 Validation: T.A.K., R.V.A., T.V.G.  
 Visualization: K.L.O., R.V.A.  
 Writing – original draft: V.S.E., T.A.K., K.L.O.  
 Writing – review & editing: T.V.G.

## Conflict of interest

The authors declare no conflict of interest.

## Additional information

Author IDs:

Tatiana A. Kalinina, Scopus ID [54684032600](https://orcid.org/0000-0002-5468-4032);  
 Konstantin L. Obydenov, Scopus ID [54684683000](https://orcid.org/0000-0002-5468-4683000);  
 Richard V. Asase, Scopus ID [57463260000](https://orcid.org/0000-0002-5746-3260000);  
 Pavel A. Slepukhin, Scopus ID [6506482417](https://orcid.org/0000-0002-6506-482417);  
 Tatiana V. Glukhareva, Scopus ID [6602582999](https://orcid.org/0000-0002-6602-582999).

Websites:

Ural Federal University, <https://urfu.ru/en>.  
 Postovsky Institute of Organic Synthesis, <https://iosuran.ru/>.

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