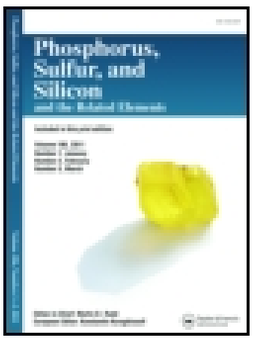


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

Facile synthesis of some new functionalized 2-selenoxopyrimidines

Ahmed M. Fouda, Mohammed A. Assiri & Tarik E. Ali

To cite this article: Ahmed M. Fouda, Mohammed A. Assiri & Tarik E. Ali (2019): Facile synthesis of some new functionalized 2-selenoxopyrimidines, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2019.1694023

To link to this article: https://doi.org/10.1080/10426507.2019.1694023

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2019.1694023

Facile synthesis of some new functionalized 2-selenoxopyrimidines

Ahmed M. Fouda, Mohammed A. Assiri, and Tarik E. Ali

Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia

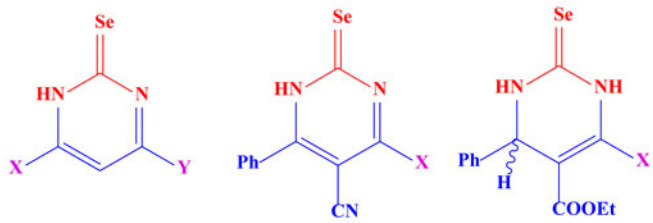
ABSTRACT

Some new functionalized 2-selenoxodihydropyrimidines **1**–**6** were synthesized in good yields *via* a simple one-pot reaction. The simple method depended on the reaction of selenourea with some nitrile active methylene compounds under basic-catalyzed conditions. Also, treatment of selenourea with each of malononitrile and ethyl cyanoacetate in the presence of benzaldehyde under the same basic reaction conditions afforded the 2-selenoxopyrimidine-5-carbonitriles **7** and **8**, respectively. Furthermore, selenourea reacted with benzaldehyde and different β-dicarbonyl compounds under *Biginelli* reaction conditions to afford the 2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **10**, **11** and **13**. Using acetylacetone as a substrate in *Biginelli* reaction yielded the unexpected 5-benzylidene-4,6-dimethyl-pyrimidine-2(5*H*)-selenone (**14**). The structures of the synthesized compounds were established on the basis of elemental analysis, IR, ^{1}H- and ^{13}C-NMR and mass spectral data.

ARTICLE HISTORY
Received 26 August 2019
Accepted 13 November 2019

KEYWORDS
Selenourea;
2-selenoxopyrimidine;
Biginelli reaction

GRAPHICAL ABSTRACT



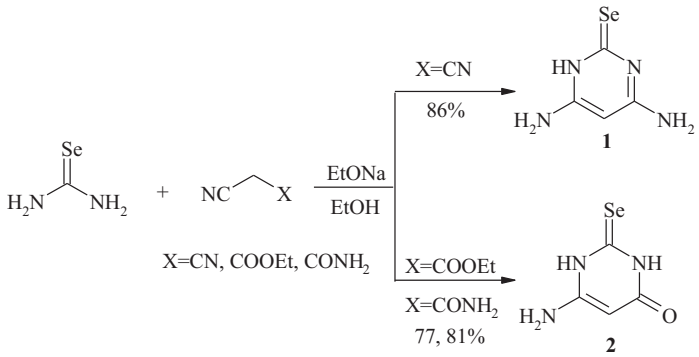
Introduction

In 1817, the selenium element was discovered. It is a red amorphous powder [1]. While some organoselenium compounds are less stable and toxic, their distinctive chemical and biological properties make the chemistry of selenium-containing heterocycles interesting [2–7]. Organoselenium compounds are well known for their antioxidant activity with the ability to mimic selenoenzyme Glutathione Peroxidase (GPx-like activity) [8, 9]. Also, these compounds are well known to inhibit cell proliferation and induce cell death in human cancer cells by apoptosis [10, 11]. In addition, some selenium compounds showed anti-inflammatory [12, 13], anticancer [14–16], neuroprotective [17] and antimelanogenesis properties [18, 19]. On the other hand, selenourea derivatives have found applications as a chalcogenizing agent [20], high potential dechloroacetylation reagent [21], and scavenger of superoxide radicals [22]. Selenoureas represent important building blocks for the synthesis of pharmacologically relevant selenium heterocycles especially 1,3-selenazoles and 1,3,4-selenadiazines [23–28]. To the best of our knowledge, selenoxopyrimidine derivatives have only been described through two reports in the literature. Klein and coworkers reported the synthesis of a single seleno-analogue of Monastrol and evaluated its ability to inhibit the Kinesin Eg5 enzyme; however, it caused a twofold decrease in the activity when compared to Monastrol [29]. In the second report, Kolb and colleagues evaluated a pyrimidinyl selenourea and its selenazolopyrimidine derivative as phosphatase inhibitors [30]. The present work was aimed to synthesize some new functionalized 2-selenoxopyrimidines by reaction of selenourea with different active methylene compounds in absolute ethanol containing sodium ethoxide as a catalyst. In addition, treatment of selenourea with benzaldehyde in the presence of different active methylene compounds under acidic or basic catalyzed reaction conditions. The obtained products will be evaluated as potential inhibitors for cancer cells.

Results and discussion

In the present work, selenourea reacted with some nitrile active methylene compounds such as malononitrile, ethyl

CONTACT Tarik E. Ali tarik_elsayed1975@yahoo.com; tismail@kku.edu.sa Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.
Supplemental data for this article can be accessed here.



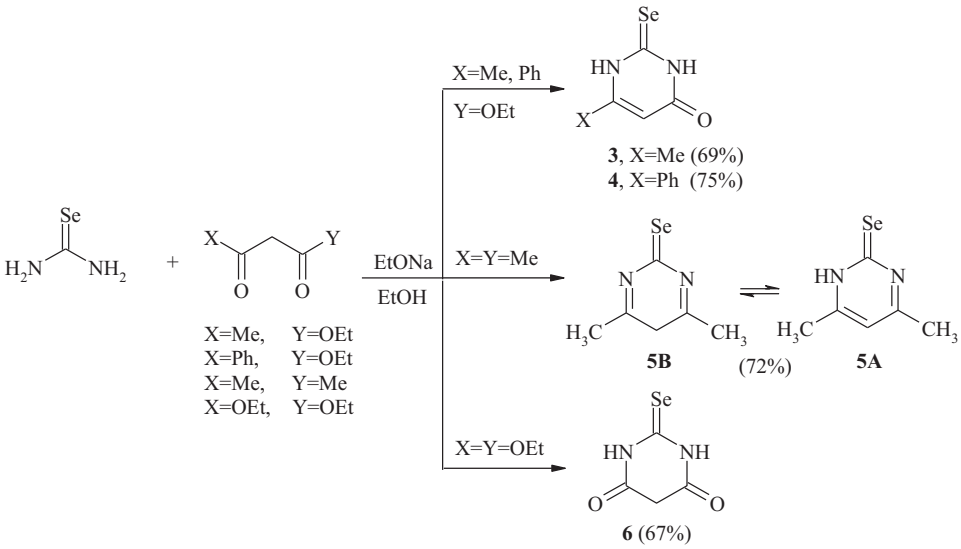
Scheme 1. Reaction of selenourea with nitrile active methylene compounds.

cyanoacetate and cyanoacetamide in the presence of ethanolic sodium ethoxide to give 4,6-diaminopyrimidine-2(1*H*)-selenone (**1**) and 6-amino-2-selenoxo-2,3-dihydropyrimidin-4(1*H*)-one (**2**), respectively (Scheme 1). Compounds **1** and **2** registered the IR absorption bands for NH_2 stretching in the range of 3430–3140 cm^{-1}, beside a carbonyl group at 1654 cm^{-1} for compound **2**. The ^{1}H-NMR spectra for these compounds exhibited characteristic signals for the protons at position 5 of pyrimidine rings in the region of δ 5.00–4.67 ppm. Their ^{13}C-NMR spectra showed the three specific carbon atoms of the pyrimidine rings in the regions of δ 74.2–78.7 (C–5), 152.7–154.7 (C–6) and 177.2–175.0 (C═Se) ppm [31], while the carbon atom of C═O in the product **2** was observed at δ 162.0 ppm.

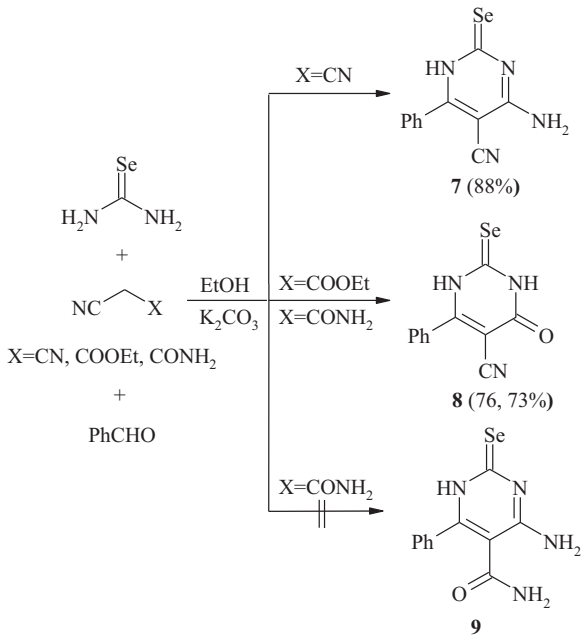
We turned our attention to study the possibility of treatment of selenourea with β-dicarbonyl compounds. Thus, reaction of selenourea with ethyl acetoacetate and ethyl benzoylacetate in the presence ethanolic sodium ethoxide led to formation of 6-methyl-2-selenoxo-2,3-dihydropyrimidin-4(1*H*)-one (**3**) and 6-phenyl-2-selenoxo-2,3-dihydropyrimidin-4(1*H*)-one (**4**), respectively, in moderate yields (Scheme 2). Similarly, 4,6-dimethyl-2-selenoxopyrimidine **5** and 2-selenoxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**6**) were isolated from reaction of selenourea with acetylacetone and diethyl malonate, respectively, under the same basic reaction conditions (Scheme 2). Compounds **3** [32] and **6** [33] were previously reported in the literature. However, compound **6** has no any reported spectral data. The suggested reaction mechanisms for the formation compounds **3**–**6** were assumed to proceed *via* cyclocondensation reactions through the nucleophilic attack of the NH_2 groups at the carbonyl groups to remove water and ethanol molecules affording the final products. The IR spectra of compounds **3**–**6** revealed the presence of absorption bands at 3115–3199 cm^{-1} which were assigned to the NH groups. Moreover, compounds **3**, **4** and **6** exhibited bands of the carbonyl groups at 1677–1655 cm^{-1}. In the meantime, the ^{1}H-NMR spectra of compounds **3**, **4** and **6** displayed singlets of the protons at position 5 at δ 5.66, 6.06 and 4.88 ppm, respectively, while the NH protons were observed in the regions δ 12.15 – 12.50 ppm. Furthermore, the ^{1}H-NMR spectrum of compound **5** confirmed its existence in two tautomeric forms **5A** and **5B** due to the presence of the protons of position 5 as two singlets at δ 6.40 (1H, form *A*) and 2.41 (2H, form *B*) ppm, beside a characteristic singlet at δ 12.47 ppm attributed to the NH proton. On the other hand, the ^{13}C-NMR spectra of compounds **3**–**6** displayed signals of the carbon atoms C–5 resonating at δ 102.6–104.1 (for compounds **3**, **4** and **5A**) and at δ 61.9–82.4 (for compounds **5B** and **6**) ppm. Moreover, compounds **3**–**6** exhibited signals of the carbon atoms of C═Se groups at δ 173.5–177.1 ppm [27].

The chemical modification of the pyrimidine ring can lead to strengthening or changing the pharmacological properties by adding bioactive moiety or group [34]. Thus, in this paper, we extended selenourea to react with some nitrile active methylene compounds in the presence of benzaldehyde. Thus, 4-amino-6-phenyl-2-selenoxo-1,2-dihydropyrimidine-5-carbonitrile (**7**) and 4-oxo-6-phenyl-2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**8**) were synthesized for the first time in a one pot reaction from selenourea, benzaldehyde and active methylene compounds (namely, malononitrile, ethyl cyanoacetate or cyanoacetamide) *via* a base-catalyzed reaction conditions (Scheme 3). The structures of the compounds **7** and **8** were identified by NMR analysis, IR and mass spectra. Their IR spectra confirmed the presence of the nitrile groups at 2187 and 2240 cm^{-1}, respectively. The ^{1}H-NMR spectra of compounds **7** and **8** showed singlets in range δ 9.98 – 13.28 ppm due to the NH protons, besides a singlet at δ 6.12 ppm was observed in compound **7** which could be attributed to the protons of the NH_2 group. In addition, their ^{13}C-NMR spectra exhibited signals of the carbon atoms of the C≡N and C═Se groups at δ 119.9 – 115.1 and 174.5 – 176.7 ppm, respectively, while the carbon atom of C═O group in compound **8** was observed at δ 161.4 ppm. All the spectral data of the product **8** confirmed exclusion of the other proposed structure **9** [35, 36]. The computational studies of the products **8** and **9** are still under investigation. Aiding by the calculated frequencies and chemical shifts, the observed infrared bands and NMR resonances will confidently assign why the product **8** was achieved. In addition, the proposed mechanism for both reaction pathways will be theoretically studied based on the calculated electronic structure for reaction intermediates and thermodynamic parameters for the involved steps.

As one of the most important multicomponent reactions (MCRs), *Biginelli* reaction provided an easy and effective process to prepare 3,4-dihydropyrimidin-2(1*H*)-ones [37]. As reported, the acid catalyst played a key role in *Biginelli* reaction to performing the reaction of aromatic aldehydes



Scheme 2. Reaction of selenourea with β-dicarbonyl compounds.



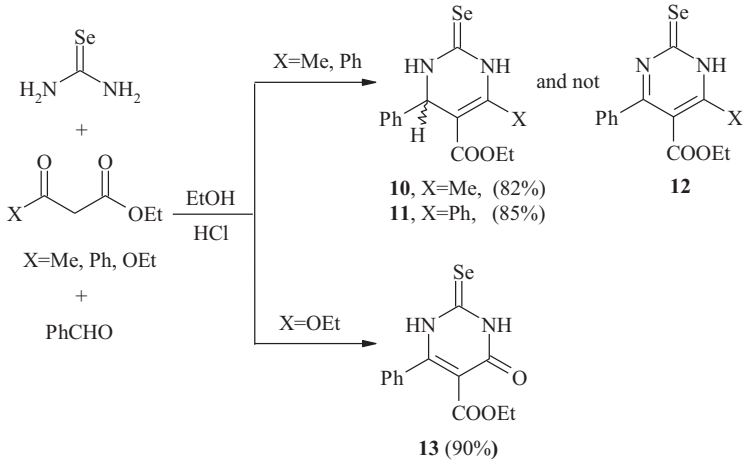
Scheme 3. Reaction of selenourea with benzaldehyde and nitrile active methylene compounds.

and β-dicarbonyl compounds with urea and thiourea [38]. The synthesis of 3,4-dihydropyrimidin-2(1*H*)-selenones by *Biginelli* reaction, was rarely mentioned in the literature [29, 39]. Thus, we studied the possibility of using selenourea in *Biginelli* reaction with benzaldehyde and β-dicarbonyl compounds (including ethyl acetoacetate, ethyl benzoylacetate, diethyl malonate and acetylacetone) under acidic catalyzed reaction conditions (Schemes 4 and 5).

By using ethyl acetoacetate and ethyl benzoylacetate as substrates in *Biginelli* reaction, to react with benzaldehyde and selenourea in absolute ethanol containing drops of concentrated HCl, the 2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **10** and **11**, respectively, were isolated and not the 2-selenoxo-1,2-dihydropyrimidine-5-carboxylates **12** (Scheme 4). On the contrary, using diethyl malonate afforded the 4-oxo-2-selenoxo-1,2,3,4-tetrahydropyrimidine -5-carboxylate **13** (Scheme 4). Although the product **10** was known in the literature [40], it was synthesized by reaction of ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro- pyrimidine-5-carboxylate with methyl iodide and NaSeH. This known method needed more than 15 h to give the product [40]. The structure of compounds **10** and **11** was obtained from their ^{1}H-NMR, ^{13}C-NMR and mass spectra. In the ^{1}H-NMR spectra, besides the signals due to the ester groups, three singlets appeared at regions δ 5.15–5.26, 9.62–9.73 and 10.30–10.45 ppm which could be attributed to the $C_4-H_{pyrimidine}$ and two types of NH protons, respectively. The ^{13}C-NMR spectra of **10** and **11** showed signals at δ 165.6–165.3 ppm which corresponded to the carbonyls of ester groups, as well as signals at δ 54.5 and 174.7–174.9 ppm due to the $C-4_{pyrimidine}$ and C═Se atoms [27].

Interestingly, using acetylacetone to react with benzaldehyde and selenourea under the acidic-catalyzed conditions, the unexpected 5-benzylidene-4,6-dimethylpyrimidine-2(5*H*)-selenone (**14**) was isolated and not the desired compound **15** (Scheme 5). The structure of **14** was in agreement with elemental analysis and spectral data. Its IR spectrum confirmed the absence of any intense absorption bands due to carbonyl group. Its ^{1}H-NMR spectrum exhibited two signals due to methyl protons at δ 1.89 and 2.09 ppm, multiplet signals at δ 7.30–7.49 ppm owing to the aromatic protons, beside a singlet due to $CH_{exocyclic}$ at δ 7.77 ppm. Additionally, its ^{13}C-NMR spectrum showed the presence of two methyl carbons at δ 20.4 and 21.9 ppm and $CH_{exocyclic}$ at δ 138.3 ppm, as well as C − 4, C − 6 and C═Se of pyrimidine ring at δ 150.3, 152.1 and 179.4 ppm, respectively. Its mass spectrum revealed the molecular ion peak at *m*/*z* 275 (M^+, 15%).

The synthesized 2-selenoxopyrimidines **1**–**14** could have promising applications in drug discovery as potential inhibitors for cancer cells. This aspect is currently under study in our laboratory and will be reported in due course.



Scheme 4. Reaction of selenourea with benzaldehyde and β-dicarbonyl compounds.

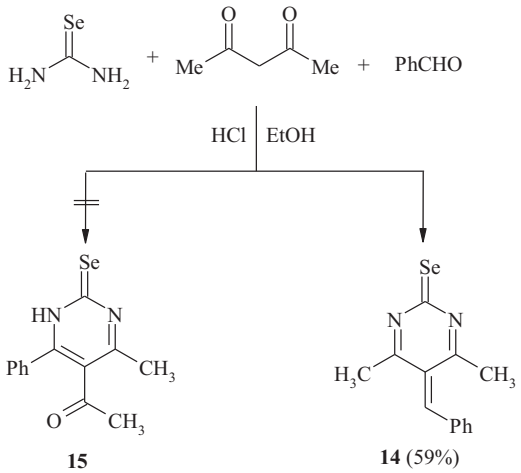
Experimental

The melting points were determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectra were measured on FT-IR (Nicolet IS10) spectrophotometer using KBr disks and Perkin-Elmer 293 spectrophotometer using KBr disks. ^{1}H- and ^{13}C-NMR spectra were measured on Gemini-300BB spectrometer (400 and 100 MHz), using DMSO-d_6 as a solvent and TMS (δ) as an internal standard. Mass spectra were recorded on a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 ev and direct probe controller inlet part to single quadropole mass analyzer in (Thermo Scientific GCMS). Elemental microanalysis was performed on Perkin-Elmer 2400II at the Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for products **1** – **14** (Figures S1–S24).

General procedure for reaction of selenourea with appropriate nitrile active methylene or β-dicarbonyl compounds: Synthesis of the products 1-6

A mixture of selenourea (2.5 mmol, 0.31 g) and appropriate nitrile active methylene (including malononitrile, ethyl cyanoacetate and cyanoacetamide) or β-dicarbonyl compounds (including ethyl acetoacetate, ethyl benzoylacetate, acetylacetone and diethyl malonate) (2.5 mmol) in ethanolic sodium ethoxide solution (0.1 g of Na in 20 mL of absolute EtOH) was heated under reflux for 4–10 h. The reaction mixtures were cooled, poured into ice and acidified with diluted hydrochloric acid (10%). The resulting precipitates **1**–**6** were filtered off, washed with water several times and crystallized from EtOH.

4,6-Diaminopyrimidine-2(1H)-selenone (**1**): white solid; yield 86%; mp >300 °C. IR (KBr, cm^{-1}): 3418, 3333, 3281, 3140 (2 NH_2), 3108 (NH), 1622 (C=N), 1572 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 5.00 (s, 1H, $C_5-H_{pyrimidine}$), 6.53 (br, 4H, 2 NH_2), 10.92 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 74.3 (C – 5), 152.7 (C – 6), 155.6 (C – 4), 177.8 (C – 2). MS (*m/z*, I %): 189 (M^+, 6%). Anal. Calcd for $C_4H_6N_4Se$ (189.08): C, 25.41; H, 3.20; N, 29.63. Found: C, 25.12; H, 2.96; N, 29.32.



Scheme 5. Reaction of selenourea with benzaldehyde and acetylacetone.

6-Amino-2-selenoxo-2,3-dihydropyrimidin-4(1H)-one (**2**): white solid; yield 77% and 81%; mp >300 °C. IR (KBr, cm^{-1}): 3430, 3324 (NH_2), 3220 (br, 2 NH), 1654 (C=O), 1628 (C=N), 1552 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 4.67 (s, 1H, $C_5-H_{pyrimidine}$), 6.34 (br, 2H, NH_2), 11.48 (s, 1H, NH), 11.59 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 78.7 (C – 5), 154.7 (C – 6), 162.0 (C – 4), 175.0 (C – 2). MS (*m/z*, I %): 190 (M^+, 16%). Anal. Calcd for $C_4H_5N_3OSe$ (190.06): C, 25.28; H, 2.65; N, 22.11. Found: C, 25.06; H, 2.46; N, 21.93.

6-Methyl-2-selenoxo-2,3-dihydropyrimidin-4(1H)-one (**3**): white solid; yield 69%; mp 288 – 290 °C (Lit. [32] mp >250 °C). IR (KBr, cm^{-1}): 3115 (br, 2 NH), 2934, 2884 ($C-H_{aliph}$), 1671 (C=O), 1632 (C=N), 1560 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 2.04 (s, 3H, CH_3), 5.66 (s, 1H, $C_5-H_{pyrimidine}$), 12.21 (s, 1H, NH), 12.26 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 18.5 (CH_3), 104.1 (C – 5), 153.5 (C – 6), 161.4 (C – 4), 176.3 (C – 2). MS (*m/z*, I %): 189 (M^+, 30%). Anal. Calcd for $C_5H_6N_2OSe$ (189.08): C, 31.76; H, 3.20; N, 14.82. Found: C, 31.50; H, 3.01; N, 14.59.

6-Phenyl-2-selenoxo-2,3-dihydropyrimidin-4(1H)-one (**4**): yellow solid; yield 75%; mp 252 – 254 °C. IR (KBr, cm^{-1}): 3199 (br, 2 NH), 3096 (C–H_{arom}), 2934 (C–H_{aliph}), 1667 (C=O), 1620 (C=N), 1548 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 6.06 (s, 1H, C_5–$H_{pyrimidine}$), 7.45–7.55 (m, 3H, Ph–H), 7.67–7.69 (m, 2H, Ph–H), 12.44 (s, 1H, NH), 12.50 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 103.5 (C – 5), 127.9 (C – 2`,6`$_{phenyl}$), 129.1 (C – 3`,5`$_{phenyl}$), 131.4 (C – 4`$_{phenyl}$), 131.6 (C – 1`$_{phenyl}$), 153.6 (C – 6), 161.4 (C – 4), 177.1 (C – 2). MS (*m/z*, I %): 251 (M^+, 4%). Anal. Calcd for $C_{10}H_8N_2OSe$ (251.15): C, 47.82; H, 3.21; N, 11.15. Found: C, 47.59; H, 3.02; N, 10.94.

4,6-Dimethylpyrimidine-2(5H)-selenone (**5A**) ***and 4,6-dimethylpyrimidine-2(1H)-selenone*** (**5B**): yellow solid; yield 72%; mp 168 – 170 °C. IR (KBr, cm^{-1}): 3138 (br, NH), 2880 (C–H_{aliph}), 1628 (C=N), 1596 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 2.11 (s, 6H, 2 CH_3 form *B*), 2.27–2.34 (m, 6H, 2 CH_3 form *A*), 2.41 (s, 2H, CH_2 form *B*), 6.40 (s, 1H, C_5–$H_{pyrimidine}$ form *A*), 12.47 (s, 1H, NH form *A*). ^{13}C-NMR (δ ppm, DMSO-d_6): 18.5 (CH_3, form *A*), 23.8 (CH_3, form *B*), 61.9 (CH_2, form *B*), 102.6 (C – 5, form *A*), 148.1 (C – 6, form *A*), 152.3 (C – 4, form *A*), 159.5 (C – 4,6, form *B*), 171.3 (C – 2, form *A*), 173.5 (C – 2, form *B*). MS (*m/z*, I %): 187 (M^+, 4%). Anal. Calcd for $C_6H_8N_2Se$ (187.10): C, 38.52; H, 4.31; N, 14.97. Found: C, 38.14; H, 4.09; N, 14.74.

2-Selenoxodihydropyrimidine-4,6(1H,5H)-dione (**6**): white solid; yield 67%; mp 203 – 205 (dec.) °C (Lit. [33] mp 195–210 °C). IR (KBr, cm^{-1}): 3164 (br, 2 NH), 2977, (C–H_{aliph}), 1655 (C=O). ^{1}H-NMR (δ ppm, DMSO-d_6): 4.88 (s, 2H, CH_2), 12.15 (s, 2H, 2 NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 82.4 (C – 5), 162.5 (C – 4,6), 175.5 (C – 2). MS (*m/z*, I %): 191 (M^+, 22%). Anal. Calcd for $C_4H_4N_2O_2Se$ (191.05): C, 25.15; H, 2.11; N, 14.66. Found: C, 24.83; H, 2.02; N, 14.39.

General procedure for reaction of selenourea with appropriate nitrile active methylene compounds and benzaldehyde: Synthesis of the products 7 and 8

A mixture of selenourea (2.5 mmol, 0.31 g), benzaldehyde (2.5 mmol, 0.24 mL), and appropriate nitrile active methylene (including malononitrile, ethyl cyanoacetate and cyanoacetamide) (2.5 mmol) in absolute ethanol (20 mL) containing anhydrous potassium carbonate (0.3 mL), was heated under reflux for 4–9 h. The reaction mixtures were cooled. The resulting precipitates were filtered off, washed with ethanol several times and crystallized from EtOH.

4-Amino-6-phenyl-2-selenoxo-1,2-dihydropyrimidine-5-carbonitrile (**7**): pale yellow solid; yield 88%; mp 218 – 219 °C. IR (KBr, cm^{-1}): 3423, 3329 (NH_2), 3215 (br, NH), 3027 (C–H_{arom}), 2187 (C≡N), 1663 (C=N), 1583 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 6.12 (s, 2H, NH_2), 7.12–7.39 (m, 5H, Ph–H), 9.98 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 89.9 (C – 5), 119.9 (C≡N), 126.6 (C – 2`,6`$_{phenyl}$), 128.3 (C – 4`$_{phenyl}$), 129.1 (C – 3`,5`$_{phenyl}$), 130.7 (C – 1`$_{phenyl}$), 143.7 (C – 6), 149.2 (C – 4), 174.5 (C – 2). MS (*m/z*, I %): 275 (M^+, 8%). Anal. Calcd for $C_{11}H_8N_4Se$ (275.17): C, 48.01; H, 2.93; N, 20.36. Found: C, 47.83; H, 2.72; N, 20.11.

4-Oxo-6-phenyl-2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**8**): pale yellow solid; yield 76% and 73%; mp 296 – 297 °C. IR (KBr, cm^{-1}): 3182 (br, 2 NH), 3070 (C–H_{arom}), 2240 (C≡N), 1695 (C=O), 1666 (C=N), 1573 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 7.42–7.66 (m, 5H, Ph–H), 13.14 (s, 1H, NH), 13.28 (brs, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 91.2 (C – 5), 115.1 (C≡N), 127.1 (C – 4`$_{phenyl}$), 128.9 (C – 2`,6`$_{phenyl}$), 129.2 (C – 3`,5`$_{phenyl}$), 132.6 (C – 1`$_{phenyl}$), 158.9 (C – 6), 161.4 (C – 4), 176.7 (C – 2). MS (*m/z*, I %): 276 (M^+, 28%). Anal. Calcd for $C_{11}H_7N_3OSe$ (276.16): C, 47.84; H, 2.55; N, 15.22. Found: C, 47.59; H, 2.37; N, 14.98.

General procedure for reaction of selenourea with appropriate β-dicarbonyl compounds and benzaldehyde (Biginelli reaction): synthesis of the products 10, 11, 13 and 14

A mixture of selenourea (2.5 mmol, 0.31 g), benzaldehyde (2.5 mmol, 0.24 mL), and appropriate β-dicarbonyl compounds (including ethyl acetoacetate, ethyl benzoylacetate, diethyl malonate and acetylacetone) (2.5 mmol) in absolute ethanol (20 mL) containing concentrated HCl (0.5 mL), was heated under reflux for 3–6 h. The reaction mixtures were cooled. The resulting precipitates **10**–**14** were filtered off, washed with ethanol several times and crystallized from EtOH.

Ethyl 6-methyl-4-phenyl-2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**10**): white solid; yield 82%; mp 204 – 206 °C (Lit. [40] mp 196-198 °C). IR (KBr, cm^{-1}): 3329, 3174 (2 NH), 3106 (C–H_{arom}), 2980 (C–H_{aliph}), 1671 (C=O), 1575 (C=C), 1028 (O–C). ^{1}H-NMR (δ ppm, DMSO-d_6): 1.08 (t, 3H, *J*=6.8 Hz, CH_3), 2.27 (s, 3H, CH_3), 3.99 (q, 2H, *J*=6.8 Hz, CH_2), 5.15 (s, 1H, C_4–$H_{pyrimidine}$), 7.19–7.35 (m, 5H, Ph–H), 9.62 (s, 1H, NH), 10.30 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 14.4 (CH_3), 17.6 (CH_3), 54.5 (C – 4), 60.0 (CH_2O), 101.1 (C – 5), 126.8 (C – 2`,6`$_{phenyl}$), 128.1 (C – 4`$_{phenyl}$), 128.9 (C – 3`,5`$_{phenyl}$), 143.9 (C – 1`$_{phenyl}$), 145.4 (C – 6), 165.6 (C=O), 174.7 (C – 2). MS (*m/z*, I %): 323 (M^+, 14%). Anal. Calcd for $C_{14}H_{16}N_2O_2Se$ (323.26): C, 52.02; H, 4.99; N, 8.67. Found: C, 51.83; H, 4.72; N, 8.41.

Ethyl 4,6-diphenyl-2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**11**): white solid; yield 85%; mp 183 – 185 °C. IR (KBr, cm^{-1}): 3173 (br, 2 NH), 2980 (C–H_{aliph}), 1698 (C=O), 1571 (C=C), 1029 (O–C). ^{1}H-NMR (δ ppm, DMSO-d_6): 0.71 (t, 3H, *J*=7.2 Hz, CH_3), 3.72 (q, 2H, *J*=7.2 Hz, CH_2), 5.26 (s, 1H, C_4–$H_{pyrimidine}$), 7.27–7.42 (m, 10H, Ph–H), 9.73 (s, 1H, NH), 10.45 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 13.8 (CH_3), 54.5 (C – 4), 59.9 (CH_2O), 102.2 (C – 5), 126.8 (C – 2`,6`$_{phenyl}$), 128.1 (C – 2``,6``$_{phenyl}$), 128.2 (C – 4`$_{phenyl}$), 129.0 (C – 3`,5`$_{phenyl}$), 129.1 (C – 3``,5``$_{phenyl}$), 129.5 (C – 4``$_{phenyl}$), 134.4 (C – 1``$_{phenyl}$), 143.4 (C – 1`$_{phenyl}$), 146.3 (C – 6), 165.3 (C=O), 174.9 (C – 2). MS (*m/z*, I %): 385 (M^+, 9%). Anal. Calcd for $C_{19}H_{18}N_2O_2Se$ (385.33): C, 59.23; H, 4.71; N, 7.27. Found: C, 58.97; H, 4.52; N, 6.95.

Ethyl 4-oxo-6-phenyl-2-selenoxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**13**): white solid; yield 90%; mp

250 – 252 °C. IR (KBr, cm^{-1}): 3478, 3191 (br, 2 NH), 3080 (C–H_{arom}), 2878 (C–H_{aliph}), 1719 (C=O), 1690 (C=O), 1615 (C=C), 1033 (O-C). ^{1}H-NMR (δ ppm, DMSO-d_6): 1.03 (t, 3H, J=7.2 Hz, CH_3), 3.42 (q, 2H, J=7.2 Hz, CH_2), 7.33–7.91 (m, 5H, Ph–H), 10.00 (s, 1H, NH), 11.89 (s, 1H, NH). ^{13}C-NMR (δ ppm, DMSO-d_6): 18.9 (CH_3), 56.5 (CH_2O), 102.7 (C – 5), 129.6 (C – 2`,6`$_{phenyl}$), 129.4 (C – 4`$_{phenyl}$), 129.9 (C – 3`,5`$_{phenyl}$), 130.2 (C – 1`$_{phenyl}$), 151.3 (C – 6), 165.1 (C – 4), 171.0 (C=O), 176.4 (C – 2). MS (*m/z*, I %): 323 (M^+, 14%). Anal. Calcd for $C_{13}H_{12}N_2O_3Se$ (323.21): C, 48.31; H, 3.74; N, 8.67. Found: C, 48.06; H, 3.48; N, 8.46.

5-Benzylidene-4,6-dimethylpyrimidine-2(5H)-selenone (**14**): orange solid; yield 59%; mp 220 – 222 °C. IR (KBr, cm^{-1}): 3030 (C–H_{arom}), 2950 (C–H_{aliph}), 1605 (C=N), 11560 (C=C). ^{1}H-NMR (δ ppm, DMSO-d_6): 1.89 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 7.30 (d, 2H, Ph–H), 7.45–7.49 (m, 3H, Ph–H), 7.77 (s, 1H, $CH_{exocyclic}$). ^{13}C-NMR (δ ppm, DMSO-d_6): 20.4 (CH_3), 21.9 (CH_3), 112.2 (C – 5), 127.1 (C – 4`$_{phenyl}$), 128.5 (C – 2`,6`$_{phenyl}$), 129.9 (C – 3`,5`$_{phenyl}$), 131.9 (C – 1`$_{phenyl}$), 138.3 ($CH_{exocyclic}$), 150.3 (C – 4), 152.1 (C – 6), 179.4 (C – 2). MS (*m/z*, I %): 275 (M^+, 15%). Anal. Calcd for $C_{13}H_{12}N_2Se$ (275.21): C, 56.74; H, 4.39; N, 10.18. Found: C, 56.51; H, 4.13; N, 9.93.

Conclusion

In summary, we have suggested facile synthesis of some new 2-selenoxopyrimidines. The methods include reaction of selenourea with each different active methylene compounds. Addition of benzaldehyde to the previous components under basic and acidic catalyzed conditions gave some novel functionalized 2-selenoxopyrimidine-5-carbonitriles and 2-selenoxopyrimidine-5-carboxylates in moderate to good yields.

Funding

The authors extend their appreciation to the deanship of scientific research at King Khalid University for funding this work through general research project under grant number (R.G.P/142/40).

ORCID

Tarik E. Ali http://orcid.org/0000-0002-7992-3478

References

[1] Garud, D. R.; Koketsu, M.; Ishihara, H. Isoselenocyanates: A Powerful Tool for the Synthesis of Selenium-Containing Heterocycles. *Molecules* **2007**, *12*, 504–535. DOI: 10.3390/12030504.

[2] Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982–1995*; Elsevier Science: Oxford, **1996**; Vol. 1–11.

[3] Wirth, T. *Organoselenium Chemistry: Modern Development in Organic Synthesis, Selenocarbonyls*; Springer: Berlin, **2000**; pp 178–193.

[4] Pfeiffer, W. D.; Romberg, H.; Kelzhanova, N.; Saginayev, A. T.; Villinger, A.; Langer, P. Synthesis and Reactions of 1,3,4-Selenadiazines. *Heterocycles* **2014**, *8*, 1397–1431. DOI: 10.3987/COM-13-S(S)109.

[5] Bodtke, A.; Kandt, M.; Pfeiffer, W. D.; Langer, P. Synthesis of 4-Aryl-2-Imino-2H-Selenazolines by a Reaction of α α-(Selenocyanato)Acetophenones with Anilines. *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 209–217. DOI: 10.1080/10426500600892685.

[6] Below, H.; Pfeiffer, W. D.; Geisler, K.; Lalk, M.; Langer, P. 1,3-Selenazole. *Eur. J. Org. Chem.* **2005**, *2005*, 3637–3639. DOI: 10.1002/ejoc.200500456.

[7] Geisler, K.; Künzler, A.; Below, H.; Bulka, E.; Pfeiffer, W. D.; Langer, P. Synthesis and Reactivity of 2-Acyl-1,3-Selenazoles. *Synthesis* **2004**, 97–105. DOI: 10.1055/s-2003-44348.

[8] Bhabak, K. P.; Mugesh, G. Functional Mimics of Glutathione Peroxidase: Bioinspired Synthetic Antioxidants. *Acc. Chem. Res.* **2010**, *43*, 1408–1419. DOI: 10.1021/ar100059g.

[9] Alberto, E. E.; Do Nascimento, V.; Braga, A. L. Catalytic Application of Selenium and Tellurium Compounds as Glutathione Peroxidase Enzyme Mimetics. *J. Braz. Chem. Soc.* **2010**, *21*, 2032–2041. DOI: 10.1590/S0103-50532010001100004.

[10] Sinha, R.; El-Bayoumy, K. Apoptosis is a Critical Cellular Event in Cancer Chemoprevention and Chemotherapy by Selenium Compounds. *Curr. Cancer Drug Targets* **2004**, *4*, 13–28. DOI: 10.2174/1568009043481614.

[11] Rikiishi, H. Apoptotic Cellular Events for Selenium Compounds Involved in Cancer Prevention. *J. Bioenerg. Biomembr.* **2007**, *39*, 91–98. DOI: 10.1007/s10863-006-9065-7.

[12] Nam, K. N.; Koketsu, M.; Lee, E. H. 5-Chloroacetyl-2-Amino-1,3-Selenazoles Attenuate Microglial Inflammatory Responses through NF-κB Inhibition. *Eur. J. Pharmacol.* **2008**, *589*, 53–57. DOI: 10.1016/j.ejphar.2008.03.034.

[13] Choi, S. Y.; Jo, Y. O.; Koketsu, M.; Ishihara, H.; Kim, S. H.; Kim, S. Y. Inhibitory Effects of 2-(4-Chlorophenyl)-1,3-Selenazol-4-One on Lipopolysaccharide-Induced Nitric Oxide Production in RAW 264.7 Cells. *J. Korean Soc. Appl. Biol.* Chem**.** **2009**, *52*, 371–374. DOI: 10.3839/jksabc.2009.066.

[14] El-Bayoumy, K.; Sinha, R. Mechanisms of Mammary Cancer Chemoprevention by Organoselenium Compounds. *Mutat. Res.* **2004**, *551*, 181–197. DOI: 10.1016/j.mrfmmm.2004.02.023.

[15] Block, E.; Bird, S.; Tyson, J. F.; Uden, P. C.; Zhang, X.; Denoyer, E. The Search for Anticarcinogenic Organoselenium Compounds from Natural Sources. *Phosphorus Sulfur Silicon Relat. Elem.* **1998**, *136*, 1–10. DOI: 10.1080/10426509808545931.

[16] Ahn, H. J.; Koketsu, M.; Yang, E. M.; Kim, Y. M.; Ishihara, H.; Yang, H. O. 2-(4-Methylphenyl)-1,3-Selenazol-4-One Induces Apoptosis by Different Mechanisms in SKOV3 and HL 60 Cells. *J. Cell. Biochem.* **2006**, *99*, 807–815. DOI: 10.1002/jcb.20973.

[17] Nishina, A.; Sekiguchi, A.; Fukumoto, R.; Koketsu, M.; Furukawa, S. Selenazoles (Selenium Compounds) Facilitate Survival of Cultured Rat Pheochromocytoma PC12 Cells after Serum-Deprivation and Stimulate Their Neuronal Differentiation via Activation of Akt and Mitogen-Activated Protein Kinase, Respectively. *Biochem. Biophys. Res. Commun.* **2007**, *352*, 360–365. DOI: 10.1016/j.bbrc.2006.11.025.

[18] Koketsu, M.; Choi, S. Y.; Ishihara, H.; Lim, B. O.; Kim, H.; Kim, S. Y. Inhibitory Effects of 1,3-Selenazol-4-One Derivatives on Mushroom Tyrosinase. *Chem. Pharm. Bull.* **2002**, *50*, 1594–1596. DOI: 10.1248/cpb.50.1594.

[19] Lee, E. H.; Lim, Y. J.; Ha, S. K.; Kang, T. H.; Koketsu, M.; Kang, C. H.; Kim, S. Y.; Park, J. H. Inhibitory Effects of 5-Chloroacetyl-2-Piperidino-1,3-Selenazole, a Novel Selenium-Containing Compound, on Skin Melanin Biosynthesis. *J. Pharm. Pharmacol.* **2010**, *62*, 352–359. DOI: 10.1211/jpp.62.03.0010.

[20] Tulenin, S. S.; Markov, V. F.; Maskaeva, L. N.; Kuznetsov, M. V. Deposition Conditions, Composition, and Structure of Chemically Deposited In_2Se_3 Films. *Russ. J. Inorg. Chem.* **2016**, *61*, 488–495. DOI: 10.1134/S0036023616040227.

[21] Sogabe, S.; Ando, H.; Koketsu, M.; Ishihara, H. A Novel Dechloroacetylation Reagent: 1-Seleonocarbamoylpiperidine.

Tetrahedron Lett. **2006**, *47*, 6603–6606. DOI: 10.1016/j.tetlet.2006.07.009.

[22] Takahashi, H.; Nishina, A.; Fukumoto, R. H.; Kimura, H.; Koketsu, M.; Ishihara, H. Selenoureas and Thioureas Are Effective Superoxide Radical Scavengers in Vitro. *Life Sci.* **2005**, *76*, 2185–2192. DOI: 10.1016/j.lfs.2004.08.037.

[23] Olsen, J. I.; Plata, G. B.; Padrón, J. M.; López, Ó.; Bols, M.; Fernández-Bolaños, J. G. Selenoureido-Iminosugars: A New Family of Multitarget Drugs. *Eur. J. Med. Chem.* **2016**, *123*, 155–160. DOI: 10.1016/j.ejmech.2016.07.021.

[24] Romero-Hernandez, L. L.; Merino-Montiel, P.; Montiel-Smith, S.; Meza-Reyes, S.; Vega-Báez, J. L.; Abasolo, I.; Schwartz, S.; López, O.; Fernández-Bolaños, J. G. Diosgenin-Based Thio(Seleno)Ureas and Triazolyl Glycoconjugates as Hybrid Drugs. Antioxidant and Antiproliferative Profile. *Eur. J. Med. Chem.* **2015**, *99*, 67–81. DOI: 10.1016/j.ejmech.2015.05.018.

[25] Merino-Montiel, P.; Maza, S.; Martos, S.; López, Ó.; Maya, I.; Fernández-Bolaños, J. G. Synthesis and Antioxidant Activity of O-Alkyl Selenocarbamates, Selenoureas and Selenohydantoins. *Eur. J. Pharm. Sci.* **2013**, *48*, 582–592. DOI: 10.1016/j.ejps.2012.12.016.

[26] Ibáñez, E.; Plano, D.; Font, M.; Calvo, A.; Prior, C.; Palop, J. A.; Sanmartín, C. Synthesis and Antiproliferative Activity of Novel Symmetrical Alkylthio- and Alkylseleno-Imidocarbamates. *Eur. J. Med. Chem.* **2011**, *46*, 265–274. 2010.11.013. DOI: 10.1016/j.ejmech.

[27] Pfeiffer, W. D.; Ahlers, K. D.; Falodun, A.; Villinger, A.; Langer, P. Synthesis and Spectroscopic Characterization of Arylated Selenoureas. *Phosphorus Sulfur Silicon Relat. Elem.* **2014**, *189*, 324–332. DOI: 10.1080/10426507.2013.820729.

[28] Geisler, K.; Pfeiffer, W. D.; Künzler, A.; Below, H.; Bulka, E.; Langer, P. Synthesis of 1,3-Selenazoles and Bis(Selenazoles) from Primary Selenocarboxylic Amides and Selenourea. *Synthesis* **2004**, 875–884. DOI: 10.1055/s-2004-822312.

[29] Klein, E.; De Bonis, S.; Thiede, B.; Skoufias, D.; Kozielski, F.; Lebeau, L. New Chemical Tools for Investigating Human Mitotic Kinesin Eg5. *Bioorg. Med. Chem.* **2007**, *15*, 6474–6488. DOI: 10.1016/j.bmc.2007.06.016.

[30] Kolb, S.; Mondesert, O.; Goddard, M. L.; Jullien, D.; Villoutreix, B. O.; Ducommun, B.; Garbay, C.; Braud, E. Development of Novel Thiazolopyrimidines as CDC25B Phosphatase Inhibitors. *Chem. Med. Chem.* **2009**, *4*, 633–648. DOI: 10.1002/cmdc.200800415.

[31] Schneider, M.; Gil, M. J.; Reliquet, A.; Meslin, J. C.; Levillain, J.; Vazeux, M.; Jury, D.; Mieloszynski, J. L.; Paquer, D. Correlations Des DéPlacements Chimiques En Rmn ^{13}C De Composés Carbonyles, Thiocarbonyles Et Selenocarbonyles. *Phosphorus Sulfur Silicon Relat. Elem.* **1998**, *134*, 295–305. DOI: 10.1080/10426509808545470.

[32] Antoniadis, C. D.; Hadjikakou, S. K.; Hadjiliadis, N.; Papakyriakou, A.; Baril, M.; Butler, I. S. Synthesis and Structures of Se Analogues of the Antithyroid Drug 6-*n*-Propyl-2-Thiouracil and Its Alkyl Derivatives: Formation of Dimeric Se–Se Compounds and Deselenation Reactions of Charge-Transfer Adducts of Diiodine. *Chem. Eur. J.* **2006**, *12*, 6888–6897. DOI: 10.1002/chem.200501455.

[33] Mautner, H. G.; Clayton, E. M. 2-Selenobarbiturates. Studies of Some Analogous Oxygen, Sulfur and Selenium Compounds. *J. Am. Chem. Soc.* **1959**, *81*, 6270–6273. DOI: 10.1021/ja01532a037.

[34] Diao, P. C.; Lin, W. Y.; Jian, X. E.; Li, Y. H.; You, W. W.; Zhao, P. L. Discovery of Novel Pyrimidine-Based Benzothiazole Derivatives as Potent Cyclin-Dependent Kinase 2 Inhibitors with Anticancer Activity. *Eur. J. Med. Chem.* **2019**, *179*, 196–207. DOI: 10.1016/j.ejmech.2019.06.055.

[35] Baryshnikov, G. V.; Minaeva, V. A.; Minaev, B. F.; Sun, V. H.; Grigoras, M. Analysis of the Electronic, IR, and ^{1}H-NMR Spectra of Conjugated Oligomers Based on 4,4'-Triphenylamine Vinylene. *Opt. Spectrosc.* **2016**, *121*, 348–356. DOI: 10.1134/S0030400X16090046.

[36] Karaush, N. N.; Minaeva, V. A.; Baryshnikov, G. V.; Minaev, B. F.; Ågren, H. Identification of Tautomeric Intermediates of a Novel Thiazolylazonaphthol Dye-A Density Functional Theory Study. *Spectrochim. Acta Part A* **2018**, *203*, 324–332. DOI: 10.1016/j.saa.2018.05.096.

[37] Panda, S. S.; Khanna, P.; Khanna, L. *Biginelli Reaction: A Green Perspective*. *Curr. Org. Chem.* **2012**, *16*, 507–520. DOI: 10.2174/138527212799499859.

[38] Nagarajaiah, H.; Mukhopadhyay, A.; Moorthy, J. N. Biginelli Reaction: An Overview. *Tetrahedron Lett.* **2016**, *57*, 5135–5149. DOI: 10.1016/j.tetlet.2016.09.047.

[39] Chen, P.; Tu, M. Synthesis of 2-Selenoxo DHPMs by Biginelli Reaction with $Hf(OTf)_4$ as Catalyst. *Tetrahedron Lett.* **2018**, *59*, 987–990. DOI: 10.1016/j.tetlet.2018.01.070.

[40] Barbosa, F. A. R.; Siminski, T.; Canto, R. F. S.; Almeida, G. M.; Mota, N. S. R. S.; Ourique, F.; Pedrosa, R. C.; Braga, A. L. Novel Pyrimidinic Selenourea Induces DNA Damage, Cell Arrest and Apoptosis in Human Breast Carcinoma. *Eur. J. Med. Chem.* **2018**, *155*, 503–515. DOI: 10.1016/j.ejmech.2018.06.026.