

Synthesis of novel selenocaffeine derivatives

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This article is dedicated to Professor Eder J. Lenardão, in recognition of his distinguished scientific career, inspiring contributions, and impact on synthetic organic chemistry and green chemistry

Received mm-dd-yyyy

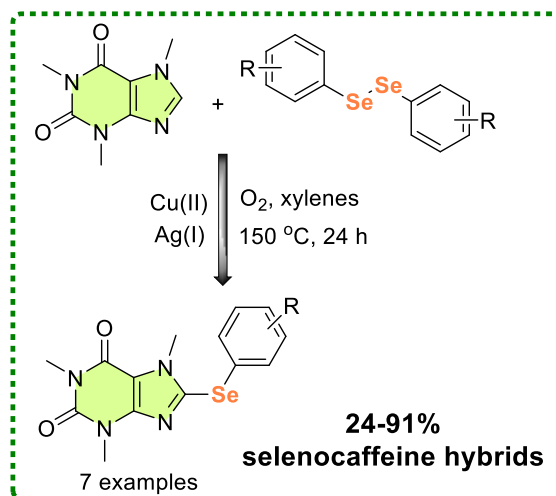
Accepted mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

We disclose a copper-catalyzed protocol for synthesizing C-8 seleno-functionalized caffeine derivatives via reaction of caffeine with diorganyl diselenides. Under the optimal conditions using Cu(OAc)₂ (20 mol%) in xylene at 150 °C for 24 h under O₂ atmosphere, the products were obtained in up to 91% yield. Various diaryl diselenides bearing electron-withdrawing and electron-donating groups were suitable substrates. The use of AgOAc (2 mol%) is non-mandatory as additive, and control experiments suggested radical involvement and the essential role of oxygen. This approach expands access to structurally diverse selenium-caffeine hybrids and minimizes the use of noble metal compared to previously reported method.



Keywords: caffeine hybrids, organoselenium compounds, C-H functionalization, copper catalysis.

Cite as

DOI: to be inserted by editorial office

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Introduction

Caffeine is one of the most widely consumed worldwide psychoactive substances, and it exhibits several pharmacological properties, including central nervous system stimulation, antioxidant activity, and neuroprotective effects.¹ Its nucleus belongs to the methylxanthine family, which consists of an imidazole ring fused to a pyrimidine-2,6-dione moiety, providing a rigid and chemically stable framework suitable for structure modifications.¹ In addition to caffeine **1**, this privileged scaffold is also found in other naturally occurring compounds, like theobromine and theophylline, which are extensively known for their diverse biological activities (Figure 1).¹

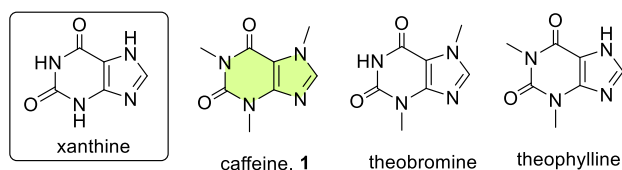


Figure 1. Xanthine and natural derivatives.

Due to its remarkable biological profile and synthetic versatility, the caffeine scaffold has attracted considerable attention as a platform for the development of novel bioactive compounds. Among the various modification strategies reported in the literature, functionalization at the C-8 position has emerged as an attractive approach to modulate the physicochemical and biological properties of caffeine.²⁻⁵

Recent studies have demonstrated that C-8 substituted caffeine derivatives display promising biological activities. For instance, compounds **A-C** are potent acetylcholinesterase (AChE) inhibitors,^{3,4} while compound **D** presents antioxidant and cytoprotective effects (Figure 2).⁵ Consequently, the development of new methodologies for the preparation of functionalized caffeine derivatives remains an active field of research in synthetic and medicinal chemistry.

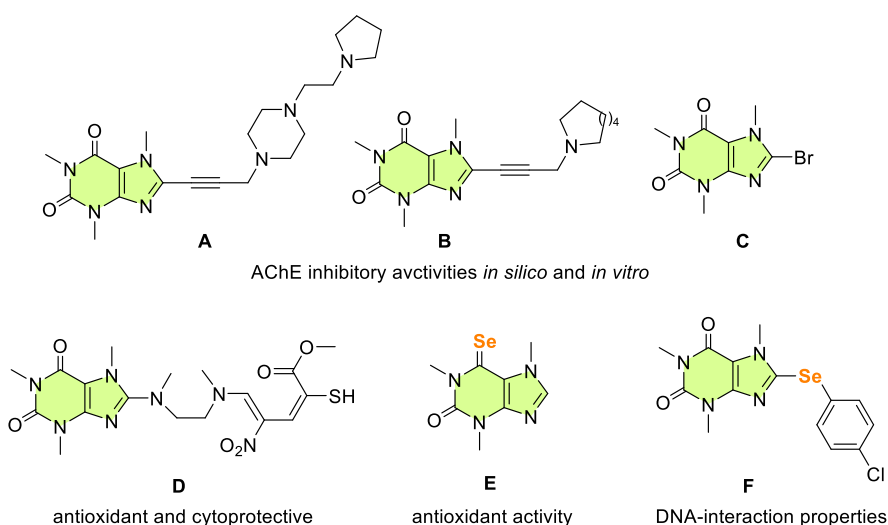


Figure 2. Bioactive C-8 substituted and Se-functionalized caffeine derivatives.

On the other hand, the importance of selenium-containing compounds is largely recognized due to their broad biological, pharmaceutical, and chemical properties.^{6,7} They have shown several relevant biological activities, such as antioxidant, antimicrobial, anti-inflammatory, neuroprotective and anticancer effects.⁸⁻¹⁰

Furthermore, selenium plays a crucial role in living organisms through its incorporation into several selenoproteins involved in redox regulation and cellular protection against oxidative stress.¹¹

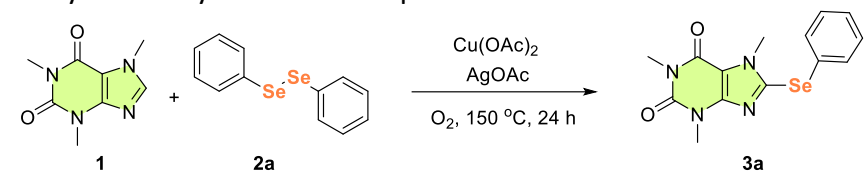
Within this framework, selenium-functionalized caffeine derivatives present an exciting opportunity as molecular hybrids. The synergistic combination of caffeine's well-documented biological activity and selenium's unique redox properties makes this a highly attractive route for bioactive compound development. This strategy was explored in the synthesis of 6-selenocaffeine **E**, which is a potent antioxidant,¹² and 8-selanyl caffeine derivative **F**, that presents a DNA-binding behavior (Figure 2).¹³

Despite the growing interest in both classes of compounds, to the best of our acknowledgement, reports concerning selenium-functionalized caffeine derivatives remain relatively scarce.^{12,13} Therefore, the development of efficient methodologies for the synthesis of selenylated caffeine derivatives continue highly desirable, providing access to structurally diverse compounds with potential applications in medicinal chemistry and related fields.

Then, we disclose herein a copper-catalyzed protocol to prepare C-8 seleno-functionalized analogues, by the reaction of caffeine with diorganyl diselenides. While this work was in progress, Brazilian colleagues published a very similar protocol to prepare a series of compounds analogous to those we describe here.¹³

Results and Discussion

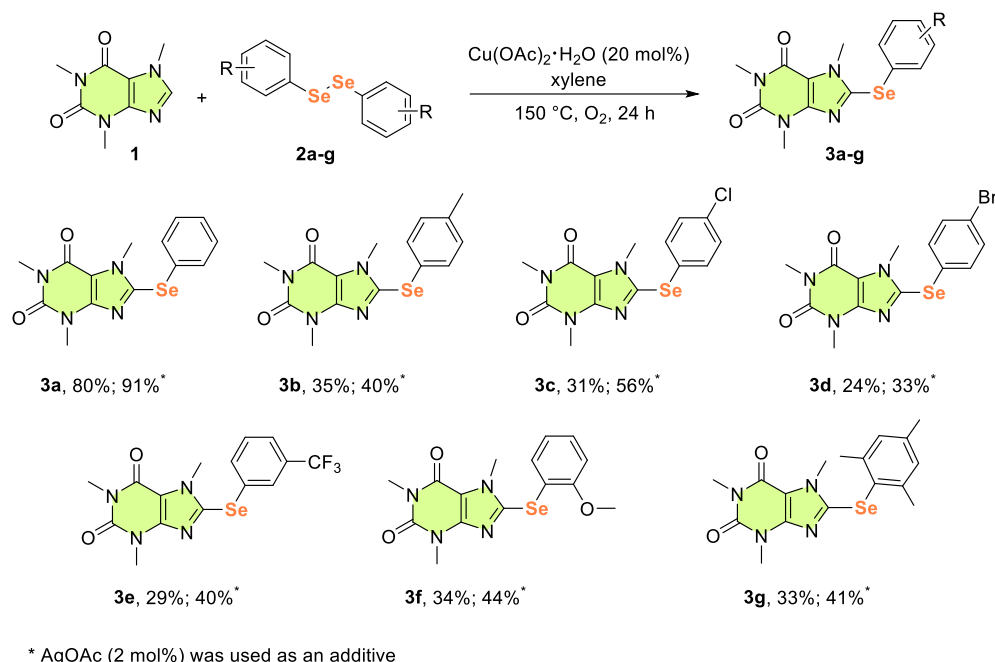
Inspired by the work from Luo, Zhu, and coworkers,¹⁴ who described the synthesis of C-8 thio-substituted caffeine derivatives using disulfides, we used as standard starting materials caffeine **1** (0.25 mmol) and diphenyl diselenide **2a** (0.15 mmol), that were reacted in the presence of 20 mol% of Cu(OAc)₂•H₂O and 2 mol% of AgOAc, in xylene as solvent. After stirring at 150 °C for 24 h under oxygen atmosphere (balloon), the desired product **3a** was formed in an excellent yield of 91% (Table 1, entry 1). In the sequence, different solvents were investigated in substitution to xylene, such as DMF, DMSO, γ -valerolactone (GVL), dimethyl carbonate (DMC), and glycerol. With DMF, DMSO, and GVL was possible to observe only traces of the product, while with DMC and glycerol the reaction didn't occur (Table 1, entries 2-6). Next, a shorter time reaction (16 h) was tested, and the product was achieved in 55% yield (Table 1, entry 7). When the reaction was performed under air atmosphere (open flask), or using AgNO₃ as additive instead of AgOAc, **3a** was obtained in only 60% yield (Table 1, entries 8 and 9). We observed that the use of an additive is not mandatory to produce **3a**, once it could be obtained in 80% yield by using just the copper catalyst (Table 1, entry 10). Thus, due to this good result, we continued the optimization study without using additive. Copper(I) and copper(II) chlorides were tested instead of Cu(OAc)₂ and no product was formed in these cases, with the starting materials being recovered (Table 1, entries 11 and 12). The effect of temperature was also investigated, and no reaction was observed at lower temperature (100 °C) (Table 1, entry 13). The stoichiometric ratio between caffeine **1** and diselenide **2a** was changed by using 1 equiv. of **2a** (instead of 1.2 equiv.) and an excess of **1** (1.2 equiv.), and the desired product **3a** was formed in 47% and 60% yield, respectively (Table 1, entries 14 and 15). Different sources of selenium were used instead of diselenide **2a**, such as benzeneseleninic acid (BSA) and phenylselenenyl bromide (PhSeBr). With BSA, product **3a** was obtained in 66% yield, while no consume of caffeine **1** was observed using PhSeBr (Table 1, entries 16 and 17). A pronounced decrease in yields was noted when the amount of Cu(OAc)₂•H₂O was reduced to 15, 10, and 5 mol%, while no reaction occurs in its absence (Table 1, entries 18-21).

Table 1. Optimization study for the synthesis of compound **3a**.^a


#	2a (equiv.)	Cu(OAc) ₂ (mol%)	AgOAc (mol%)	solvent	Yield (%) ^b
1	1.2	20	2	xylene	91
2	1.2	20	2	DMF	traces
3	1.2	20	2	DMSO	traces
4	1.2	20	2	GVL	traces
5	1.2	20	2	DMC	NR
6	1.2	20	2	glycerol	NR
7 ^c	1.2	20	2	xylene	55
8 ^d	1.2	20	2	xylene	60
9 ^e	1.2	20	2	xylene	60
10	1.2	20	-	xylene	80
11 ^f	1.2	20	-	xylene	NR
12 ^g	1.2	20	-	xylene	NR
13 ^h	1.2	20	-	xylene	NR
14 ⁱ	1.0	20	-	xylene	47
15 ^j	0.8	20	-	xylene	60
16 ^k	1.2	20	-	xylene	66
17 ^l	1.2	20	-	xylene	NR
18	1.2	15	-	xylene	33
19	1.2	10	-	xylene	24
20	1.2	5	-	xylene	17
21	1.2	-	-	xylene	NR

^a Reaction conditions: Caffeine **1** (0.25 mmol), PhSeSePh **2a** (0.15 mmol), catalyst (Cu(OAc)₂, mol %), additive (AgOAc, 2 mol%), solvent (2.0 mL), 150 °C, O₂ atmosphere (balloon). ^b Yield obtained after purification by column chromatography using a mixture of hexanes/ethyl acetate (80:20). ^c Reaction time of 16 h. ^d Open-air. ^e AgNO₃ was used as additive. ^f CuCl₂ was used as catalyst. ^g CuCl was used as catalyst. ^h Reaction temperature 100 °C. ⁱ Reaction with 1 equiv. of **2a**. ^j Reaction with 1.2 equiv. of caffeine **1**. ^k Reaction with benzeneseleninic acid. ^l Reaction with phenyl selenium bromide. NR = no reaction.

Under the optimized conditions, set out in the lines 1 and 10 of Table 1, we performed a reaction scope study, to investigate the generality of the developed method. As depicted in Scheme 1, caffeine **1** was employed in the reaction with different diaryl diselenides, bearing electron-withdrawing and electron-donating groups **2b-g**. Firstly, the reactions were performed in the absence of AgOAc, starting by bis(*p*-tolyl)diselenide **2b** (R = 4-CH₃), affording the expected 8-seleno-substituted caffeine **3b** in 35% yield. Halogenated diaryl diselenides **2c** (R = 4-Cl) and **2d** (R = 4-Br) furnished the respective products **3c** and **3d** in 31% and 24%. Product **3e** (R = 3-CF₃), bearing the strong electron-withdrawing trifluoromethyl group at the *meta*-position, was achieved in 29% yield. A slightly higher yield was obtained starting from bis(*o*-anisoyl)diselenide, affording the respective compound **3f** in 34% yield. The protocol was suitable also when sterically hindered dimesityl diselenide **2g** was used, and product **3g** was reached in 33% yield (Scheme 1).



Scheme 1. Scope of the reaction.

Products **3a-g** were synthesized also following the reaction conditions set out in the line 1 of Table 1, using 2 mol% of the additive AgOAc, affording slightly higher yields in all cases (Scheme 1).

Regrettably, no reaction was observed starting from *p*-fluorophenyl, *p*-anisoyl-, 1-naphthyl, 2-thienyl, and 2-naphthyl derived diselenides (**2h-l**), and the respective products **3h-l** were not formed under both the tested conditions (with or without additive). Similarly, dibutyl diselenide **2m** and diphenyl ditelluride **2n** were not suitable substrates for the reaction, and the respective caffeine-derivatives **3m** and **3n** could not be obtained (Figure 3).

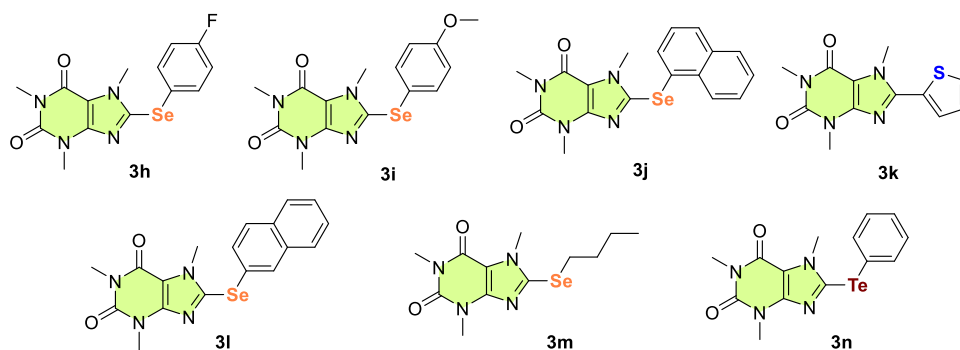
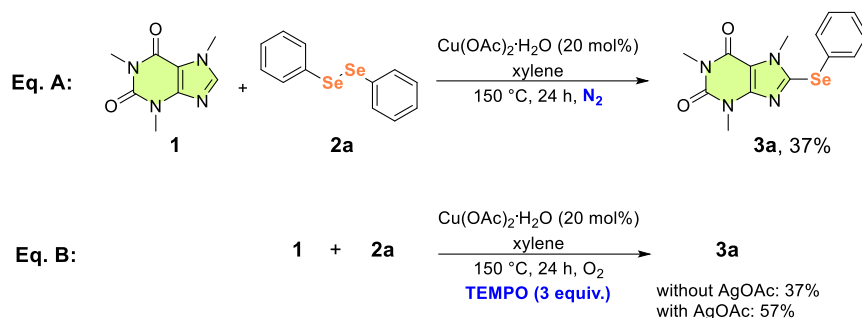


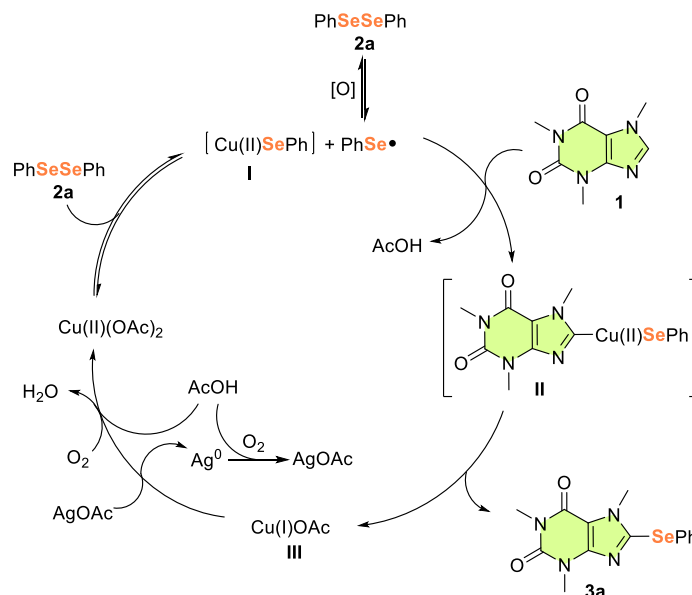
Figure 3. Unsuccessful examples.

To collect insights to propose a mechanism for the reaction, some control experiments involving caffeine **1** and diphenyl diselenide **2a** were conducted, as depicted in Scheme 3. First, the reaction was performed under nitrogen atmosphere, affording the desired product **3a** in 37% yield, demonstrating the pivotal role of molecular oxygen in the reaction (Scheme 2, Eq. A). When a radical scavenger was added to the standard reaction conditions, the compound **3a** was formed in 37% (without additive) and 57% (with additive) (Scheme 2, Eq. B). The decrease in yield suggests that radical species could be involved in the reaction pathway.



Scheme 2. Control experiments.

Thus, based on the results of the control experiments and on the literature,^{13,14} a plausible mechanism was proposed (Scheme 3). Firstly, the interaction between the copper(II) species and diphenyl diselenide **2a** generates the intermediate **I** and radical PhSe•. Radical selenide is oxidized in the reaction medium to diselenide **2a**, while **I** is inserted to C-8, releasing AcOH and forming the intermediate **II**. After a reductive elimination in **II**, product **3a** and copper(I) species **III** are formed. Species **III** can be oxidized by both molecular O₂ and AgOAc (when present) to regenerate the catalyst for a new cycle.



Scheme 3. Proposed reaction mechanism.

Conclusions

In this work, a protocol to prepare C-8 selenylated caffeine derivatives was developed, using Cu(OAc)₂ as catalyst in the presence or not of AgOAc as additive. Compared to previously described, close-related work, this protocol minimizes or eliminates the use of noble metal silver as additive. Additionally, four unprecedented derivatives were prepared, expanding the possibilities to explore the pharmacological properties of caffeine-selenium hybrids.

Experimental Section

General. The reactions were monitored by TLC carried out on pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV₂₅₄ by using UV light as visualization agent and the mixture of 5% vanillin in 10% H₂SO₄ under heating conditions as developing agent. Merck silica gel (particle size 63-200 µm) was used to flash chromatography, and PTLC Glass Plates L × W 20 cm × 20 cm, silica gel 60 F₂₅₄, 1 mm, was used in the preparative thin layer chromatography. Hydrogen nuclear magnetic resonance spectra (¹H NMR) were obtained at 400 MHz on a Bruker Ascend 400 spectrometer. The spectra were recorded in CDCl₃ solutions. The chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Hydrogen coupling patterns are described as broad signal (br), singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of doublet of doublets (ddd) and multiplet (m). Coupling constants (*J*) are reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (¹³C NMR) were obtained at 100 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to the solvent peak of CDCl₃. Selenium-77 nuclear magnetic resonance spectra (⁷⁷Se NMR) were obtained at 76 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to diphenyl diselenide as the external reference. The HRMS analysis was performed in a Bruker micrOTOF-QII spectrometer equipped with an APCI source operating in positive mode. The samples were solubilized in acetonitrile and analyzed by direct infusion at a constant flow rate of 180 µL/min. The acquisition parameters were capillary: 4000 V, end plate offset: -500 V, nebulizer: 1.5 bar, dry gas: 1.5 L min⁻¹, and dry heater: 180 °C. The collision cell energy was set to 5.0 eV. The mass-to-charge ratio (*m/z*) data were processed and analyzed using Bruker Daltonics software: Compass Data Analysis and Isotope Pattern. Melting point (m.p.) values were measured in a Marte PFD III instrument.

General procedure for the synthesis of the products 3a-g. In a Schlenk tube were added caffeine **1** (0.25 mmol), diaryl diselenide **2a-g** (0.15 mmol), Cu(OAc)₂•H₂O (20 mol%), AgOAc (2 mol%; when used) and xylene (2.0 mL). The resulting mixture was stirred at 150 °C, under oxygen atmosphere (balloon) for 24 hours. After this time, the reaction was received in NH₄Cl saturated aqueous solution, extracted with ethyl acetate (3x10 mL), dried over MgSO₄, and concentrated under vacuum. Then, the crude was purified by column chromatography in a mixture of hexanes/ethyl acetate (80:20) as the eluent.

1,3,7-Trimethyl-8-(phenylselanyl)-3,7-dihydro-1H-purine-2,6-dione (3a).¹³ Yield: 0.070 g; 0.08 g (80%; 91%); white solid; m.p.: 153 – 156 °C (Lit.:¹³ 165 °C). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.50-7.47 (m, 2H), 7.32-7.29 (m, 3H), 3.92 (s, 3H), 3.58 (s, 3H), 3.39 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.83, 151.41, 148.54, 142.60, 132.56, 129.78, 128.46, 127.25, 109.91, 34.15, 29.84, 27.95. ⁷⁷Se (76 MHz) δ (ppm) 331.43.

1,3,7-Trimethyl-8-(p-tolylselanyl)-3,7-dihydro-1H-purine-2,6-dione (3b).¹³ Yield: 0.032 g; 0.036 g (36%; 40%); pale white solid; m.p.: 123 – 133 °C (Lit.:¹³ 148 °C). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.40 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 3.90 (s, 3H), 3.57 (s, 3H), 3.39 (s, 3H), 2.34 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.81, 151.43, 148.51, 143.15, 138.84, 133.08, 130.56, 123.24, 109.82, 34.10, 29.84, 27.93, 21.11. ⁷⁷Se (76 MHz) δ (ppm) 326.68.

8-((4-Chlorophenyl)selanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3c).¹³ Yield: 0.030 g; 0.054 g (31%; 56%); white solid; m.p.: 161 – 175 °C (Lit.:¹³ not listed). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.45 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 3.94 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.79, 148.56, 142.16, 134.99, 134.07, 129.93, 125.16, 109.95, 34.11, 29.83, 27.95. ⁷⁷Se (76 MHz) δ (ppm) 329.42.

8-((4-Bromophenyl)selanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3d). Yield: 0.026 g; 0.036 g (24%; 33%); pale white solid; m.p.: 134-136. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.45 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 3.94 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.83, 151.42, 148.59, 142.05, 134.24, 132.91, 125.95, 123.08, 110.01, 34.16, 29.88, 28.00. ⁷⁷Se (76 MHz) δ (ppm) 328.38 HRMS (APCI-QTOF) *m/z*: [M + H]⁺ Calcd for C₁₄H₁₃BrN₄O₂Se: 428.9457, found: 428.9453.

1,3,7-Trimethyl-8-((3-(trifluoromethyl)phenyl)selanyl)-3,7-dihydro-1H-purine-2,6-dione (3e). Yield: 0.030 g; 0.042 g (29%; 40%); white solid; m.p.: 162 – 177 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.86 (s, 1H), 7.68 (d, *J* = 4 Hz, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.45 (t, *J* = 8 Hz, 1H), 3.97 (s, 3H), 3.56 (s, 3H), 3.40 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.82, 151.38, 148.63, 141.63, 135.73, 132.02 (d, *J* = 32 Hz), 130.04, 129.30 (q, *J* = 4 Hz), 128.24, 125.33 (q, *J* = 4 Hz), 123.35 (q, *J* = 271 Hz) 110.06, 34.13, 29.80, 27.98. ⁷⁷Se (76 MHz) δ (ppm) 338.25. ⁷⁷Se (76 MHz) δ (ppm) 338.25 HRMS (APCI-QTOF) *m/z*: [M + H]⁺ Calcd for C₁₅H₁₃F₃N₄O₂Se: 419.0229, found: 419.0212.

8-((2-Methoxyphenyl)selanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3f). Yield: 0.032 g; 0.042 g (34%; 44%); pale brown solid; m.p.: 150 – 160 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.28-7.24 (m, 1H), 6.94-6.82 (m, 3H), 3.96 (s, 3H), 3.89 (s, 3H), 3.60 (s, 3H), 3.42 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 156.61, 154.87, 151.43, 148.70, 141.45, 130.52, 129.00, 122.09, 117.91, 110.99, 110.07, 56.01, 34.23, 29.87, 27.97. ⁷⁷Se (76 MHz) δ (ppm) 338.25. ⁷⁷Se (76 MHz) δ (ppm) 272.38 HRMS (APCI-QTOF) *m/z*: [M + H]⁺ Calcd for C₁₅H₁₆N₄O₃Se: 381.0461, found: 381.0458.

8-(Mesitylselanyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (3g). Yield: 0.032 g; 0.040 g (33%; 41%); pale brown solid; m.p.: 190 – 210 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 6.97 (s, 2H), 3.78 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H), 2.45 (s, 6H), 2.29 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ (ppm) 154.65, 151.47, 148.70, 144.93, 142.70, 139.79, 129.28, 124.41, 109.31, 33.45, 29.78, 27.84, 24.24, 20.96. ⁷⁷Se (76 MHz) δ (ppm) 338.25. ⁷⁷Se (76 MHz) δ (ppm) 246.98 HRMS (APCI-QTOF) *m/z*: [M + H]⁺ Calcd for C₁₇H₂₀N₄O₂Se: 393.0825, found: 393.0819.

Acknowledgements

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. FAPERGS (grant numbers 23/2551-0000800-9 and 25/2551-0002914-7), CNPq (grant number 403217/2023-7 and 422645/2021-4) and FINEP are acknowledged for financial support. CNPq is also acknowledged for fellowships to E.J.L. and M.S.S.. Prof. Thiago Barcellos, from Universidade de Caxias do Sul (Brazil) is acknowledged for providing HRMS analysis.

Supplementary Material

Supplementary Files contained all the data obtained in this work.

References

1. Liu, X.; Xu, S. *Hereditas* **2026**, *163*, 36.
<https://doi.org/10.1186/s41065-026-00648-z>
2. Jasiewicz, B.; Sierakowska, A.; Jankowski, W.; Hoffmann, M.; Piorońska, W.; Górnicka, A.; Mrówczyńska, L. *Free Rad. Res.* **2018**, *52*, 724–773.
<https://doi.org/10.1080/10715762.2018.1467561>
3. Reshetnikov, D. V.; Ivanov, I. D.; Baev, D. S.; Rybalova, T. V.; Mozhaitsev, E. S.; Patrushev, S. S.; Vavilin, V. A.; Tolstikova, T. G.; Shult, E. E. *Molecules* **2022**, *27*, 8787.

<https://doi.org/10.3390/molecules27248787>

4. Furlani, G. M.; Silva, J. G.; Dutra, L. L.; Leite, J. P. V.; Martins, F. T.; Demuner, A. J.; Varejão, E. V. V.; Santos, M. H. J. *Braz. Chem. Soc.* **2026**, 37, e-20260066.

<https://doi.org/10.21577/0103-5053.20260066>

5. Sierakowska, A.; Jasiewicz, B.; Piosik, L.; Mrówczyńska, L. *Sci. Rep.* **2023**, 13, 1785.

<https://doi.org/10.1038/s41598-022-27205-8>

6. Lippolis, V.; Santi, C.; Lenardão, E. J.; Braga, A. L. (eds.). *Chalcogen Chemistry: Fundamentals and Applications*. Croydon, UK: The Royal Society of Chemistry. 2023.

<https://doi.org/10.1039/9781839167386>

7. Lenardão, E. J.; Santi, C.; Sancineto, L. *New Frontiers in Organoselenium Compounds*. Cham: Springer International Publishing, 2018.

<https://doi.org/10.1007/978-3-319-92405-2>

8. Jain, V. K.; Priyadarsini, K. I. (eds.). *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*. London: The Royal Society of Chemistry, 2018.

<https://doi.org/10.1039/9781788011907>

9. Gallo-Rodriguez, C.; Rodriguez, J. B. *ChemMedChem* **2024**, 19, e202400063.

<https://doi.org/10.1002/cmdc.202400063>

10. Friberg, L. I. M.; Kavanagh, A.; Amado, M.; Lowe, G.; Zuegg, J.; Paula, M. N.; Onawole, A.; Floyd, H. E. E.; Kravchenko, A. N.; Guan, D.; Elliott, A. G.; Kuchar, J.; Mohr, F.; Luzina, O.; Salakhutdinov, N.; Volcho, K.; Farrukh, H. S. U. B.; Kalsoom, U.; Saleem, R. S. Z.; Blanchfield, J.; Blaskovich, M. A. T.; Hansford, K. A. *RSC Med. Chem.* **2025**, 16, 3213–3228.

<https://doi.org/10.1039/d4md00677a>

11. Zhang, Y.; Roh, Y. J.; Han, S.-J.; Park, I.; Lee, H. M.; Ok, Y. S.; Lee, B. C.; Lee, S.-R. *Antioxidants*, **2020**, 9, 383.

<https://doi.org/10.3390/antiox9050383>

12. Martins, I. L.; Miranda, J. P.; Oliveira, N. G.; Fernandes, A. S.; Gonçalves, S.; Antunes, A. M. M. *Molecules* **2013**, 18, 5251–5264.

<https://doi.org/10.3390/molecules18055251>

13. Holthausen, C.; Carlos, I. B. R.; Gomes, S. Q.; Granja, I. J. A.; Silva, S. S.; Silva, A. C.; Junca, E.; Zimmermann, M. V. G.; Raitz, I.; Federico, L. B.; Braga, A. L.; Rafique, J.; Saba, S.; Frizon, T. E. A. *Org. Biomol. Chem.* **2026**, 24, 5846–5848.

<https://doi.org/10.1039/d6ob00464d>

14. He, Z.; Luo, F.; Li, Y.; Zhu, G. *Tetrahedron Lett.* **2013**, 54, 5907–5910.

<http://dx.doi.org/10.1016/j.tetlet.2013.08.097>

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