Synthesis F. Gritzenco et al. Paper

Base-Free Synthesis and Synthetic Applications of Novel 3-(Organochalcogenyl)prop-2-yn-1-yl Esters: Promising Anticancer Agents

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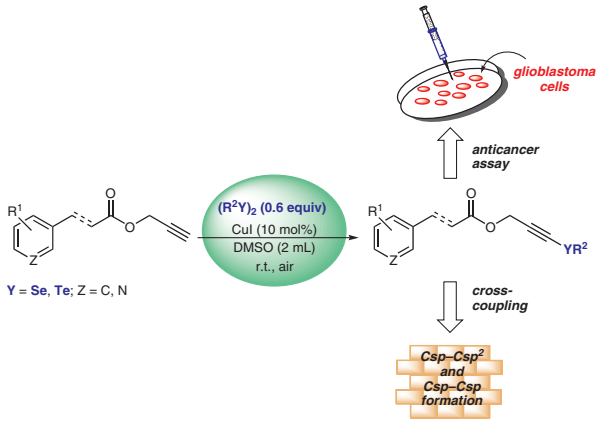

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Abstract This manuscript portrays the CuI-catalyzed Csp-chalcogen bond formation through cross-coupling reactions of propynyl esters and diorganyl dichalcogenides by using DMSO as solvent, at room temperature, under base-free and open-to-air atmosphere conditions. Generally, the reactions have proceeded very smoothly, being tolerant to a range of substituents present in both substrates, affording the novel 3-(organochalcogenyl)prop-2-yn-1-yl esters in moderate to good yields. Noteworthy, the 3-(butylselanyl)prop-2-yn-1-yl benzoate proved to be useful as synthetic precursor in palladium-catalyzed Suzuki and Sonogashira type cross-coupling reactions by replacing the carbon–chalcogen bond by new carbon–carbon bond. Moreover, the 3-(phenylselanyl)prop-2-yn-1-yl benzoate has shown promising in vitro activity against glioblastoma cancer cells.

Key words organochalcogens, copper, catalysis, cross-coupling, glioblastoma

Esters are known as a very abundant class of natural products, which are particularly responsible for the fruits and flowers scents being largely applied into the industrial and pharmacological fields.[1] More specifically, benzoates consist in a very important class of organic substances, which has found a range of applications in several research areas such as organic synthesis,[2] pharmacology,[3] and material science.[4] Both, natural and synthetic benzoate derivatives are known to compose the molecular scaffold of organic substances, which present biological and pharmacological properties as antimicrobial,[5] pesticide,[6] anti-inflammatory,[7] anesthetic,[8] and anticancer[9] activities.

On the other hand, organochalcogen-derived compounds are known to present relevant biological and pharmacological activities.[10] Indeed, organoselenium and organotellurium derivatives have become attractive synthetic targets particularly due their applications on the pharmacological field. Among their broad range of properties are included antioxidant,[11] antimicrobial,[12] anti-inflammatory,[13] antidepressive-like,[14] and anticancer[15] activities. In fact, selenium is considered an essential micronutrient for the mammalian diet being a structural component of enzymes and crucial to several metabolic pathways.[16] Besides, the introduction of an organochalcogen group into the structure of organic molecules consists in a very interesting and versatile synthetic tool, since the carbon–chalcogen bond might be easily replaced for new carbon–carbon bond through different synthetic transformations such as chalcogen/lithium exchange and transition-metal-catalyzed cross-coupling reactions.[17]

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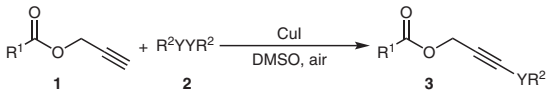
As a result of their pharmacological and synthetic applications, several studies have been focused on the development and improvement of methodologies for the preparation of this class of substances.[18] In this regard, transition-metal-catalyzed cross-coupling and atom-economic addition reactions into alkynes and alkenes are well recognized as the most important and efficient synthetic tools to promote the carbon–sulfur, carbon–selenium, and carbon–tellurium bond formation.[19] In the past years, indium, iron, and silver salts have also been efficiently applied as catalysts for the synthesis of chalcogenyl acetylenes.[20] In particular, catalytic systems based on copper salts have emerged as an alternative tool for the preparation of alkynyl chalcogenides via Csp–H activation of terminal alkynes by avoiding the use of strong bases or organometallic reagents, allying high efficiency with low cost and toxicity.[21]

Despite the number of studies related to the achievement of alkynyl chalcogenide derivatives, there is no report regarding the synthesis of organochalcogen-containing propynyl benzoates. Notably, the preparation of this kind of compounds is very interesting since it allows exploring the combination of well-known properties of benzoate derivatives with that of the organochalcogens. According to the above mentioned, herein we describe an atom-economic approach for the synthesis of 3-(organochalcogenyl)prop-2-yn-1-yl benzoates **3** through CuI-catalyzed cross-coupling reactions of propynyl esters **1** and diorganyl dichalcogenides **2**, under mild and base-free reaction conditions (Scheme 1). In addition to the synthetic studies, to our knowledge, this is the first time that an alkynyl selenide have demonstrated potential anticancer activity against a GBM cell line.



R^1 = aryl, 3-pyridyl, styryl; R^2 = aryl, alkyl; Y = Se, Te

Scheme 1 CuI-catalyzed cross-coupling reactions

In order to evaluate the most appropriate reaction condition, the prop-2-yn-1-yl benzoate (**1a**) and diphenyl diselenide (**2a**) were selected as standard substrates (Table 1). Several parameters were evaluated, which include stoichiometry of substrates, base, solvent, amount and type of the copper catalyst, temperature, and reaction atmosphere. Initially, the desired 3-(phenylselanyl)prop-2-yn-1-yl benzoate (**3a**) was obtained in 69% yield by treating **1a** with **2a** (0.5 equiv) in DMSO as a solvent in the presence of CuI (10 mol%) under open-to-air atmosphere, at room temperature (Table 1, entry 1). Nonetheless, by employing only a small excess of **2a** a significant improvement in the reaction yield was achieved and the product **3a** was synthesized in very high yield (entry 2). Superior amount of diphenyl diselenide did not improve the reaction efficiency (entry 3). These results have revealed an important characteristic of the methodology, which is the atom-economic process since both 'PhSe' moieties of diphenyl diselenide (**2a**) were consumed during the formation of desired product. Next, we evaluated the influence of the catalyst on the reaction media (entries 4–10). By reducing the amount of the copper salt from 10 to 5 mol% just a brief decrease in the reaction yield was observed (entry 4). Similarly, a decrease in the reaction yield was observed by increasing the amount of CuI to 15 mol% (entry 5). Next, a screening of the copper salts was realized, employing either copper(I) (CuCl, CuBr) or copper(II) ($CuBr_2$, CuO, CuO_{nano}) species (entries 6–10). However, no catalytic activity has been observed by using these copper sources. In fact, the high catalytic activity of the CuI for this transformation was confirmed once the desired product was obtained in 88% yield by using only 10 mol% of this catalyst (entry 2). To verify the influence of the reaction atmosphere we have carried out an experiment under argon, which furnished the product **3a** in lower yield (entry 11). This result might indicate that the air plays an important role for the catalytic system, most probably by assisting the oxidative steps (see proposed mechanism).

The catalytic system showed to be highly dependent to the use of DMSO as solvent since different protic and aprotic solvents such as DCM, MeCN, EtOH, 1,4-dioxane, and THF did not afford the desired product (Table 1, entries 12–16). In this sense, a lower catalytic activity was observed when DMF was employed as solvent leading to the product in 42% yield (entry 17). The well-known coordinative and oxidative properties of DMSO[22] as well as the better solubility of the catalyst might explain the higher efficiency of this solvent when compared with others.

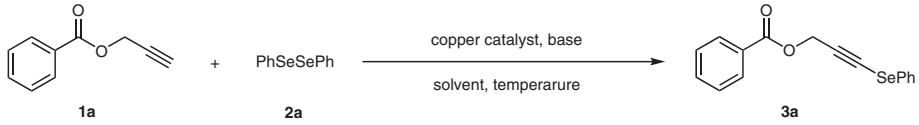
Regarding the reaction temperature, no improvement in the yield value of **3a** was observed by increasing the temperature from 25 °C to 50 and 80 °C (Table 1, entries 18 and 19). Additionally, it was also observed that the presence of base did not positively affect the catalytic efficiency of this cross-coupling reaction (entries 20–22). By analyzing the above results, we have established the ideal reaction conditions as the use of CuI (10 mol%) as catalyst, diphenyl diselenide (**2a**) (0.6 equiv) as organochalcogen source, using DMSO as solvent in the absence of base, under air at 25 °C. Under these conditions the desired 3-(phenylselanyl)prop-2-yn-1-yl benzoate (**3a**) was isolated in 88% yield after 24 hours (entry 2).

To study the versatility and generality of the methodology several experiments have been screened by using the combination of different prop-2-yn-1-yl esters **1** and diorganyl dichalcogenides **2** for the preparation of 3-(organoselanyl)prop-2-yn-1-yl esters **3** (Table 2). First, the substrate **1a** was submitted to the reaction conditions in the presence of different diorganyl diselenides **2** (Table 2, entries 1–11). In terms of electronic effects, the methodology showed tolerance to the presence of electron-donating and -withdrawing groups into the aromatic ring, affording the corresponding products in good yields (entries 2–7). The reac-

tion seems to be slightly sensitive to steric effects in the aromatic rings of diorganyl diselenides since the presence of methyl groups at the *ortho*-position of the aromatic ring lead to a decrease in the reaction yield (entries 8, 9). On the other hand, when bis(1-naphthyl) diselenide (**2j**) was used the corresponding product **3j** was obtained in good yield (entry 10). Furthermore, by employing the dibutyl diselenide (**2k**) as organochalcogen source it was possible to isolate the 3-(butylselanyl)prop-2-yn-1-yl benzoate (**3k**) bearing an alkyl group directly bonded to the selenium atom (entry 11).

Next, we evaluated the influence of substituents into the aromatic ring of the prop-2-yn-1-yl benzoates **1** in the cross-coupling reaction, by treating these terminal alkynes with diphenyl diselenide (**2a**) under the same reaction conditions (Table 2, entries 12–14). Generally, the reaction was applicable for electron-donating and -withdrawing groups, affording the corresponding products in reasonable yields (entries 12–14). In particular, when a substrate bearing a withdrawing fluorine atom was employed the corresponding selenoacetylene **3n** was achieved in 87% (entry 14). Additionally, considering the well-known pharmacological and biological potential of nicotinic and cinnamic acids derivatives,[23] prop-2-yn-1-yl nicotinate (**1e**) and prop-2-yn-1-yl cinnamate (**1f**) were submitted to the cross-coupling conditions by reacting with diphenyl diselenide (**2a**) and the corresponding products **3o** and **3p** were efficiently obtained in 60 and 92% yield, respectively (entries 15, 16).

Table 1 Determination of the Ideal Reaction Parameters for the Copper-Catalyzed Cross-Coupling of **1a** and **2a**[a]

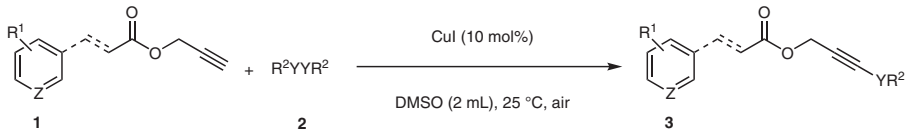


1a **2a** **3a**

Entry	Catalyst (mol%)	PhSeSePh (equiv)	Base (equiv)	Solvent (2 mL)	Yield (%)[b]
1	CuI (10)	0.5	–	DMSO	69
2	CuI (10)	0.6	–	DMSO	88
3	CuI (10)	0.75	–	DMSO	80
4	CuI (5)	0.6	–	DMSO	81
5	CuI (15)	0.6	–	DMSO	73
6	CuBr (10)	0.6	–	DMSO	trace
7	CuCl (10)	0.6	–	DMSO	trace
8	$CuBr_2$ (10)	0.6	–	DMSO	–
9	CuO (10)	0.6	–	DMSO	–
10	CuO_{nano} (10)	0.6	–	DMSO	–
11	CuI (10)	0.6	–	DMSO	68[c]
12	CuI (10)	0.6	–	DCM	–
13	CuI (10)	0.6	–	MeCN	trace
14	CuI (10)	0.6	–	EtOH	–
15	CuI (10)	0.6	–	1,4-dioxane	–
16	CuI (10)	0.6	–	THF	–
17	CuI (10)	0.6	–	DMF	42
18	CuI (10)	0.6	–	DMSO	77[d]
19	CuI (10)	0.6	–	DMSO	73[e]
20	CuI (10)	0.6	K_2CO_3 (1.5)	DMSO	75
21	CuI (10)	0.6	$NaHCO_3$ (1.5)	DMSO	61
22	CuI (10)	0.6	Et_3N (1.5)	DMSO	27

[a] The reaction was performed by using **1a** (0.25 mmol), under air (open flask) at 25 °C for 24 h. The consumption of **1a** was monitored by TLC.
[b] Yield for isolated products.
[c] The reaction was carried out under argon atmosphere.
[d] The reaction was carried out at 80 °C.
[e] The reaction was carried out at 50 °C.

Table 2 Synthesis of 3-(Organoselanyl)prop-2-yn-1-yl Esters **3**[a]



1 **2** **3**

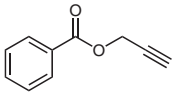
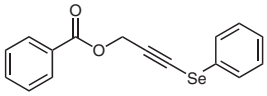
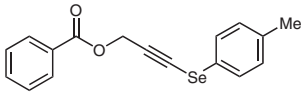
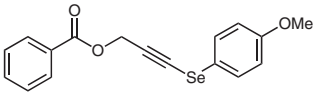
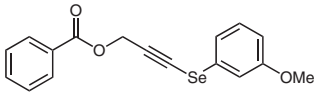
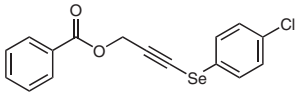
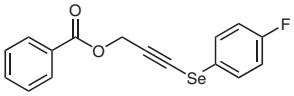
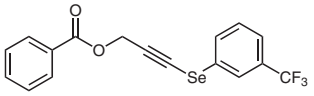
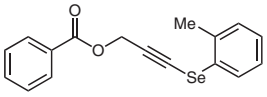
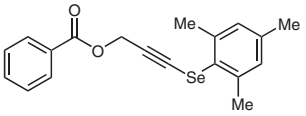
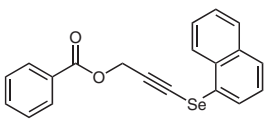
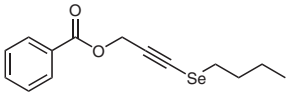
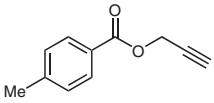
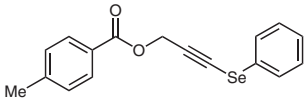
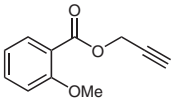
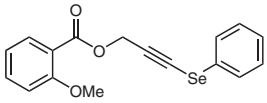
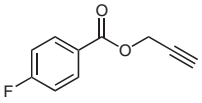
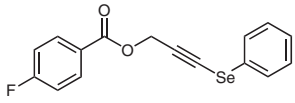
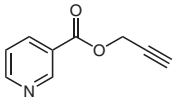
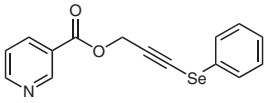
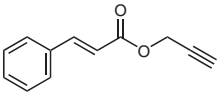
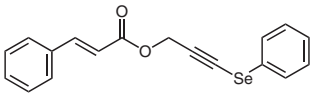
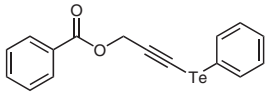
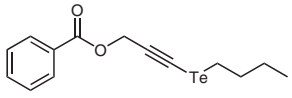
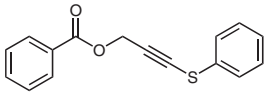
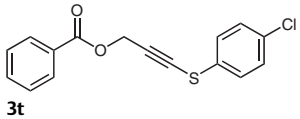
Entry	Substrate **1**	**2** $(R^2Y)_2$	Product **3**	Time (h)	Yield (%)[b]
1	 **1a**	**2a** $(PhSe)_2$	 **3a**	24	88
2	**1a**	**2b** $(p\text{-}MeC_6H_4Se)_2$	 **3b**	24	56
3	**1a**	**2c** $(p\text{-}MeOC_6H_4Se)_2$	 **3c**	22	87
4	**1a**	**2d** $(m\text{-}MeOC_6H_4Se)_2$	 **3d**	22	65
5	**1a**	**2e** $(p\text{-}ClC_6H_4Se)_2$	 **3e**	22	83
6	**1a**	**2f** $(p\text{-}FC_6H_4Se)_2$	 **3f**	22	61
7	**1a**	**2g** $(m\text{-}CF_3C_6H_4Se)_2$	 **3g**	22	62
8	**1a**	**2h** $(o\text{-}MeC_6H_4Se)_2$	 **3h**	20	55
9	**1a**	**2i** $(2,4,6\text{-}Me_3C_6H_2Se)_2$	 **3i**	22	32
10	**1a**	**2j** $(\alpha\text{-}C_{10}H_7Se)_2$	 **3j**	22	76

Table 2 (continued)

Entry	Substrate **1**	**2** $(R^2Y)_2$	Product **3**	Time (h)	Yield (%)[b]
11	**1a**	**2k** $(nC_4H_9Se)_2$	 **3k**	22	58
12	 **1b**	**2a**	 **3l**	48	46
13	 **1c**	**2a**	 **3m**	21	60
14	 **1d**	**2a**	 **3n**	22	87
15	 **1e**	**2a**	 **3o**	24	60
16	 **1f**	**2a**	 **3p**	24	92
17	**1a**	**2l** $(PhTe)_2$	 **3q**	24	64
18	**1a**	**2m** $(nC_4H_9Te)_2$	 **3r**	24	40
19	**1a**	**2n** $(PhS)_2$	 **3s**	24	0[c]
20	**1a**	**2o** $(p\text{-}ClC_6H_4S)_2$	 **3t**	24	0[c]

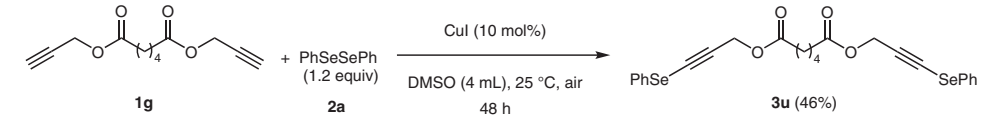
[a] The reaction was carried out using the prop-2-yn-1-yl ester **1** (0.25 mmol), diorganyl diselenide **2** (0.6 equiv), CuI (10 mol%) in DMSO (2 mL), at 25 °C under air (open flask). The consumption of **1** was monitored by TLC.
[b] Yield for isolated products.
[c] Only the starting materials were detected by GCMS analysis of the crude reaction mixture.

In order to extend the scope to other organochalcogen derivatives, the substrate **1a** was reacted under the same reaction conditions, in the presence of different diorganyl ditellurides and disulfides (Table 2, entries 17–20). When diphenyl and dibutyl ditellurides (**2l** and **2m**) were employed as organochalcogen sources the expected 3-(phenyltellanyl)prop-2-yn-1-yl benzoate (**3q**) and 3-(butyltellanyl)prop-2-yn-1-yl benzoate (**3r**) were isolated in 60 and 40% yield, respectively (entries 17 and 18). The lower yield observed in the presence of an alkyl group bonded to the tellurium atom could be explained by the relatively lack of stability of the product **3r**. On the other hand, the reaction system has failed to promote the cross-coupling reaction using aromatic disulfides **2n** and **2o** since no products were observed using the same reaction conditions (entries 19 and 20). This lack of reactivity of disulfides is most likely explained due the higher strength of sulfur–sulfur bond when compared with selenium analogues.[24]

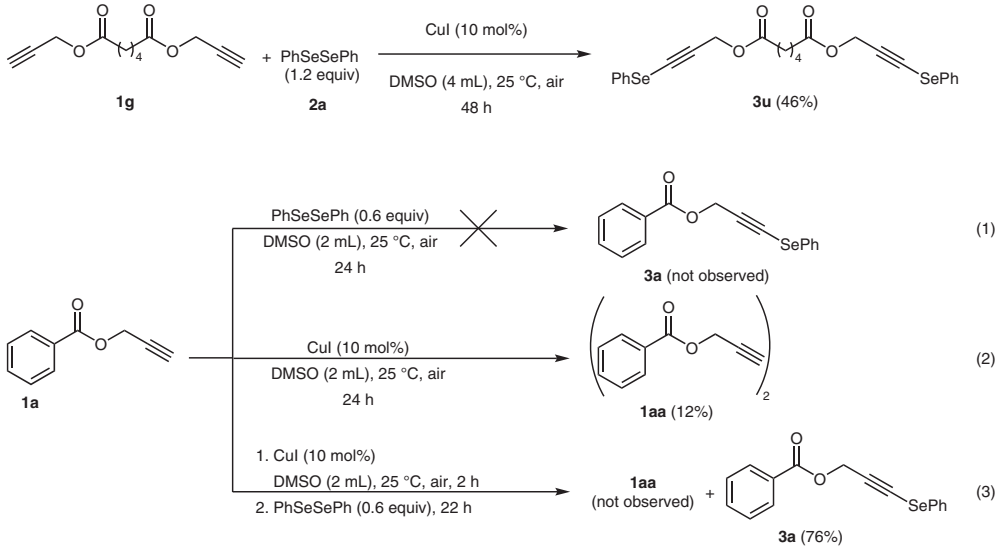
The versatility and efficiency of the catalytic system has been affirmed by submitting the di(prop-2-yn-1-yl) adipate (**1g**) to the reaction conditions (Scheme 2). Particularly, this double catalyzed cross-coupling process was conducted by employing 1.2 equivalents of diphenyl diselenide (**2a**) and 10 mol% of the copper iodide leading to the desired bis[3-(phenylselanyl)prop-2-yn-1-yl] adipate (**3u**) in 46% yield, after 48 hours.

To secure more information about the mechanism some control experiments have been accomplished (Scheme 3). First, when the reaction was carried out in the absence of CuI, no product formation was observed and the starting materials **1a** and **2a** were totally recovered (Scheme 3, eq. 1). To check whether the cross-coupling reaction could involve copper acetylide species,[25] a Glaser-type reaction was performed. Thus, when the substrate **1a** was submitted to standard conditions, in the absence of any diorganyl dichalcogenide, the formation of the homo-coupling product **1aa** was observed in only 12% yield even after 24 hours of reaction time (Scheme 3, eq. 2). To evaluate the possibility of a nucleophilic attack of the copper acetylide intermediate to the diorganyl diselenide, compound **1a** was stirred in the presence of CuI (10 mol%) in DMSO for 2 hours followed by the subsequent diphenyl diselenide (**2a**) addition, then the reaction mixture was stirred for an additional 22 hours (Scheme 3, eq. 3). In this case, only the cross-coupling product **3a** was obtained in 76% yield and not even traces of the homo-coupling product **1aa** was detected. Moreover, by analyzing these results and considering that no homo-coupling were detected during the scope development, the in situ formation of a copper acetylide seems to be unlikely for this synthetic transformation.

Considering the results achieved in the control experiments and based on previous reports[26] a plausible reaction mechanism is shown in Scheme 4. First, a Cu(III)-complex **A**

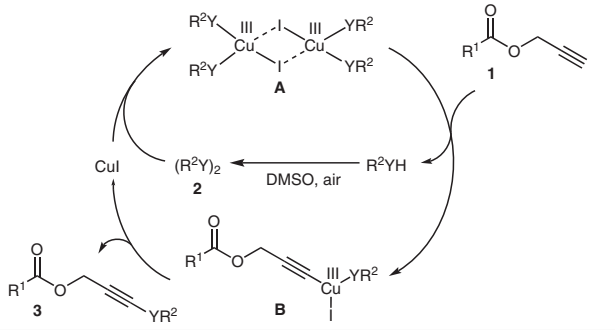


Scheme 2 CuI-catalyzed double cross-coupling reaction of **1g** and **2a**



Scheme 3 Mechanistic control experiments

could be formed through the interaction of the diorganyl dichalcogenide **2** and CuI. Next, this complex would react with the alkyne **1** to generate the intermediate **B** with concomitant formation of the organochalcogenol specie (R^2YH), which is immediately converted into the corresponding diorganyl dichalcogenide **2** via an oxidative step. Subsequently, the intermediate **B** might lead to the expected product **3** through reductive elimination process replacing the copper(I) specie to the catalytic cycle. The in situ formation of diorganyl dichalcogenides from oxidation of chalcogenol species (R^2YH) seems to be a reasonable explanation since the reaction media required only 0.6 equivalent of diorganyl dichalcogenide.

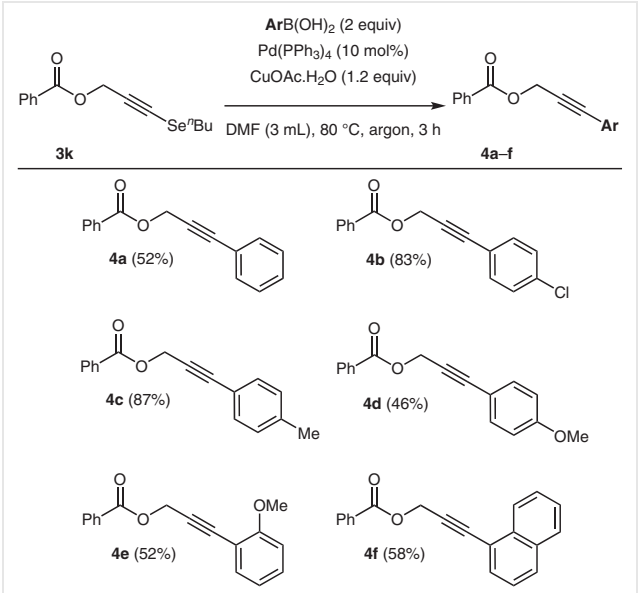


Scheme 4 Plausible reaction mechanism

The presence of carbon–chalcogen bond into an organic structure allows the use of these substances as synthetic precursors for the preparation of new target compounds generally trough the replacement of the organochalcogen moiety by other organic functions via transition-metal-catalyzed transformations.[27] In this way, the 3-(butylselanyl)prop-2-yn-1-yl benzoate (**3k**) underwent palladium-catalyzed Suzuki type cross-coupling reaction using different arylboronic acids to form new carbon–carbon bonds (Scheme 5). To our delight, the corresponding the products **4a–f** were efficiently achieved in moderate to excellent yields.

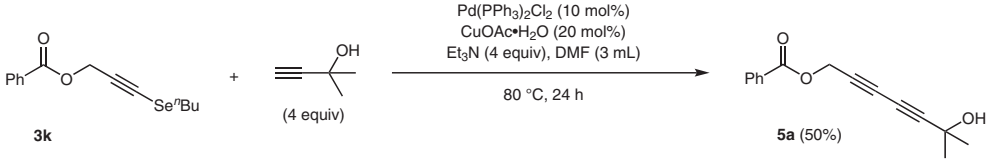
Aware of the synthetic importance of diynes as building blocks to obtain several organic substances,[28] the benzoate **3k** was also submitted to palladium-catalyzed Sonogashira type reaction with a tertiary propargylic alcohol, which provided the expected unsymmetrical diyne **5a** in 50% yield (Scheme 6).

Glioma is a neuroepithelial tumor originating from the glial or supporting cells of the central nervous system. Gliomas are classified as ependymomas, astrocytomas [including glioblastoma (GBM)], oligodendrogliomas, mixed gliomas, and a few others.[29] Despite the aggressive treatment including surgical resection, chemotherapy with Temozolomide (Tmz) and radiotherapy, median survival time for patients with GBM is only 14.6 months.[30] GBM is an incurable disease that almost invariably leads to neurological demise and death. Due to its high degree of invasiveness, radical resection of the primary tumor mass is not curative. Infiltrating tumor cells invariably remain within the surrounding brain, leading to disease progression or recurrence, either locally or distant from the primary tumor.[31] Therefore, treatment of GBM remains one of the hardest challenges to be tackled by oncotherapy.[32]



Scheme 5 Suzuki type cross-coupling reactions of **3k** and different arylboronic acids

In order to evaluate the anticancer activity of the synthesized compounds, the 3-(phenylselanyl)prop-2-yn-1-yl benzoate (**3a**) was chosen to initial studies due its great synthetic availability in our research laboratory. Thus, the treatment with **3a** in the concentration of 10 μM for 24 hours and the concentration of 50 and 100 μM for 24, 48 and 72 hours significantly decreased the number of Human GBM cell line A172 (Figure 1). The effects of 50 μM (after 24 h of treatment) and 100 μM (24 and 72 h) were similar to that observed with the standard treatment used in the clin-



Scheme 6 Sonogashira type cross-coupling reaction of **3k** and a tertiary propargylic alcohol

ic with Tmz. The greatest effect was observed after 24 hours of treatment. This may have occurred due to the low instability of the compound **3a** at 37 °C, which was experimentally observed by GC-MS analysis, since the compound was applied only once and left in contact with the cells for up to 72 hours.

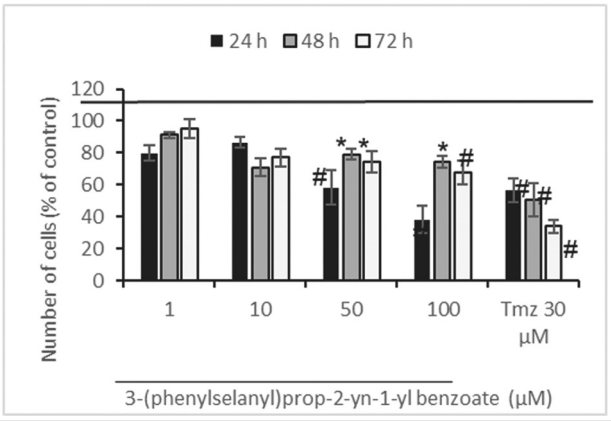


Figure 1 3-(Phenylselanyl)prop-2-yn-1-yl benzoate (**3a**) induced cell number decrease in GBM cell line A172. GBM cells were treated with **3a** at concentrations 1, 10, 50, and 100 µM and Tmz at concentration 30 µM for 24, 48 and 72 h. The upper line indicates the control cells treated with vehicle DMSO. Bars indicates mean ± SEM of at least three independent experiments. * p <0.05; # p <0.01.

Some studies have demonstrated the antitumor effect of organochalcogens[33] in bladder carcinoma,[34] cervical cancer,[35] breast cancer,[36] and chronic lymphocytic leukemia.[37] Other studies have shown the effect of organoselenium, such as diphenyl diselenide and selenadiazole in gliomas.[38,39] However, to our knowledge, this is the first work showing the antiglioma potential of an organochalcogen-containing propynyl benzoates. The main mechanism by which organochalcogen, mainly organoselenium compounds, are considered promising antitumor agents is in their broad antioxidant effect.[33,34,36,40] The promising anticancer activity exhibited by the benzoate **3a** has encouraged our research group to proceed with the structure–activity relationship studies of this class of organic substances, which are still under investigation in our laboratories.

In summary, we have described an efficient catalytic system to promote the carbon–chalcogen bond formation by reacting prop-2-yn-1-yl esters derivatives with differently substituted diorganyl diselenides and ditellurides, under mild reaction conditions. The reactions were conducted under ambient temperature and atmosphere (open flask) under base-free conditions. The incorporation of both organochalcogen moieties from diorganyl dichalcogenides into the target product structures gives an atom-economic aspect to this synthetic methodology. Generally, the present protocol have furnished a series of 3-(organochalcogenyl)prop-2-yn-1-yl esters bearing aromatic, aromatic substituted and alkyl groups bonded to the chalcogen atoms in very good yields. Besides, the synthetic potential of the carbon–chalcogen bond was also proved by employing the 3-(butylselanyl)prop-2-yn-1-yl benzoate as a substrate in palladium-catalyzed Suzuki and Sonogashira type reactions, which provided the generation of new carbon–carbon bonds. In addition, we have demonstrated for the first time the antitumor effect of the 3-(phenylselanyl)prop-2-yn-1-yl benzoate (**3a**) in human glioma cell line, indicating a promising molecule for the development of drugs that help fight this disease.

^{1}H NMR spectra were obtained at 400 MHz on a DPX-400 NMR spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or TMS as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in hertz and integrated intensity. ^{13}C NMR spectra were obtained at 100 MHz on a DPX-400 NMR spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Standard abbreviations were used to denote the multiplicity of a particular signal. Column chromatography was performed using silica gel (230–400 mesh). TLC was performed using silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with I_2 vapor, or acidic vanillin. Most reactions were monitored by TLC for disappearance of starting material. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques.

3-(Organochalcogenyl)prop-2-yn-1-yl)benzoates 3a–r and 3u; General Procedure

In a reaction tube, under ambient atmosphere (air), containing the appropriated diorganyl diselenide **2** (0.15 mmol, 0.60 equiv, for **3u** 1.2 equiv) and CuI (10 mol%) at 25 °C was added DMSO (2 mL). To the stirred reaction mixture was added the proper benzoate **1** (0.25 mmol) diluted in DMSO (1 mL), in one portion. The mixture was stirred for the required time at 25 °C (Table 2). After that, the mixture was quenched with sat. aq NH_4Cl (5 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL) and dried ($MgSO_4$). After filtering, the organic solution was concentrated using a rotary evaporator under reduced pressure. The product was purified by flash chromatography in silica gel using hexane/EtOAc as eluent.

3-(Phenylselanyl)prop-2-yn-1-yl Benzoate (3a)

Yield: 0.069 g (88%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.06–8.03 (m, 2 H), 7.53–7.48 (m, 3 H), 7.40–7.36 (m, 2 H), 7.29–7.19 (m, 3 H), 5.10 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.5, 133.0, 129.6, 129.4, 129.2, 129.0, 128.2, 127.7, 127.1, 97.9, 68.1, 53.4.

MS (EI, 70 eV): *m*/*z* (%) = 316 (4), 211 (3), 193 (19), 159 (25), 115 (32), 105 (100), 77 (41), 51 (21).

HRMS: *m*/*z* calcd for $C_{16}H_{12}O_2Se$ $[M + H]^+$: 317.0081; found: 317.0076.

3-(4-Tolylselanyl)prop-2-yn-1-yl Benzoate (3b)

Yield: 0.046 g (56%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.08–8.06 (m, 2 H), 7.58–7.54 (m, 1 H), 7.45–7.41 (m, 4 H), 7.13–7.11 (m, 2 H), 5.12 (s, 2 H), 2.32 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 137.5, 133.2, 130.3, 129.8, 129.7, 129.5, 128.3, 123.9, 97.2, 68.7, 53.6, 21.0.

MS (EI, 70 eV): *m*/*z* (%) = 330 (6), 207 (14), 159 (23), 128 (44), 116 (8), 105 (100), 77 (32), 51 (11).

HRMS: *m*/*z* calcd for $C_{17}H_{14}NO_2Se$ [M + H]$^+$: 331.0237; found: 331.0232.

3-[(4-Methoxyphenyl)selanyl]prop-2-yn-1-yl Benzoate (3c)

Yield: 0.067 g (87%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07–8.04 (m, 2 H), 7.57–7.52 (m, 1 H), 7.50–7.46 (m, 2 H), 7.44–7.40 (m, 2 H), 6.87–6.83 (m, 2 H), 5.08 (s, 2 H), 3.76 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.7, 159.6, 135.3, 133.1, 132.2, 129.7, 128.3, 117.3, 115.3, 96.3, 69.4, 55.3, 53.5.

MS (EI, 70 eV): *m*/*z* (%) = 346 (8), 223 (7), 209 (7), 159 (10), 145 (19), 105 (100), 77 (29), 51 (8).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_3Se$ [M + H]$^+$: 347.0186; found: 347.0182.

3-[(3-Methoxyphenyl)selanyl]prop-2-yn-1-yl Benzoate (3d)

Yield: 0.056 g (65%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09–8.06 (m, 2 H), 7.60–7.54 (m, 1 H), 7.46–7.42 (m, 2 H), 7.25–7.19 (m, 1 H), 7.12–7.07 (m, 2 H), 6.81–6.78 (m, 1 H), 5.14 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 160.3, 133.2, 130.2, 129.8, 129.5, 128.9, 128.4, 121.3, 114.5, 113.4, 98.4, 68.1, 55.3, 53.5.

MS (EI, 70 eV): *m*/*z* (%) = 346 (7), 223 (8), 75 (24), 145 (11), 115 (12), 105 (100), 77 (36), 51 (10).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_3Se$ [M + H]$^+$: 347.0186; found: 347.0182.

3-[(4-Chlorophenyl)selanyl]prop-2-yn-1-yl Benzoate (3e)

Yield: 0.072 g (83%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07–8.04 (m, 2 H), 7.57–7.53 (m, 1 H), 7.47–7.41 (m, 4 H), 7.29–7.25 (m, 2 H), 5.12 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 133.6, 133.2, 130.7, 129.8, 129.7, 129.6, 128.4, 126.2, 96.5, 67.7, 53.4.

MS (EI, 70 eV): *m*/*z* (%) = 350 (3), 227 (10), 193 (8), 159 (18), 149 (17), 136 (7), 105 (100), 77 (36), 51 (15).

HRMS: *m*/*z* calcd for $C_{16}H_{11}ClO_2Se$ [M + H]$^+$: 350.9691; found: 350.9684.

3-[(4-Fluorophenyl)selanyl]prop-2-yn-1-yl Benzoate (3f)

Yield: 0.051 g (61%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09–8.06 (m, 2 H), 7.60–7.51 (m, 3 H), 7.47–7.43 (m, 2 H), 7.06–7.02 (m, 2 H), 5.12 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 162.5 (d, $^1J_{C,F}$ = 247.5 Hz), 133.3, 131.8 (d, $^3J_{C,F}$ = 8.0 Hz), 129.8, 129.5, 128.4, 122.2 (d, $^4J_{C,F}$ = 3.3 Hz), 116.8 (d, $^2J_{C,F}$ = 22.1 Hz), 97.7, 68.4, 53.5.

MS (EI, 70 eV): *m*/*z* (%) = 334 (4), 211 (19), 209 (11), 159 (20), 133 (29), 105 (100), 77 (30), 51 (11).

HRMS: *m*/*z* calcd for $C_{16}H_{11}FO_2Se$ [M + H]$^+$: 331.0237; found: 334.9982.

3-{[3-(Trifluoromethyl)phenyl]selanyl}prop-2-yn-1-yl Benzoate (3g)

Yield: 0.059 g (62%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09–8.08 (m, 1 H), 8.07–8.06 (m, 1 H), 7.79 (s, 1 H), 7.73–7.71 (m, 1 H), 7.58–7.54 (m, 1 H), 7.52–7.50 (m, 1 H), 7.46–7.43 (m, 2 H), 7.42–7.40 (m, 1 H), 5.14 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 133.3, 132.3, 131.9 (q, $^4J_{C,F}$ = 32.7 Hz), 129.8, 129.7, 129.5, 129.4, 128.4, 125.7 (q, $^3J_{C,F}$ = 4.1 Hz), 124.1 (q $^3J_{C,F}$ = 3.7 Hz), 123.5 (q, $^1J_{C,F}$ = 272.9 Hz), 99.4, 66.9, 53.4.

MS (EI, 70 eV): *m*/*z* (%) = 384 (2), 261 (12), 183 (14), 159 (17), 117 (7), 105 (100), 77 (33), 51 (13).

HRMS: *m*/*z* calcd for $C_{17}H_{15}NO_2Se$ [M + H]$^+$: 384.9954; found: 384.9945.

3-(2-Tolylselanyl)prop-2-yn-1-yl Benzoate (3h)

Yield: 0.045 g (55%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.09–8.06 (m, 2 H), 7.76–7.54 (m, 1 H), 7.58–7.53 (m, 1 H), 7.45–7.41 (m, 2 H), 7.20–7.12 (m, 3 H), 5.14 (s, 2 H), 2.32 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 136.8, 133.2, 130.2, 129.8, 129.7, 129.5, 128.6, 128.4, 127.4, 127.2, 97.8, 68.0, 53.6, 20.9.

MS (EI, 70 eV): *m*/*z* (%) = 330 (3), 159 (6), 128 (73), 115 (11), 105 (100), 91 (9), 77 (24), 51 (8).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_2Se$ [M + H]$^+$: 331.0237; found: 331.0232.

3-(Mesitylselanyl)prop-2-yn-1-yl Benzoate (3i)

Yield: 0.029 g (32%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.06–8.05 (m, 1 H), 8.03–8.02 (m, 1 H), 7.58–7.54 (m, 1 H), 7.46–7.41 (m, 2 H), 6.95–6.94 (m, 2 H), 4.99 (s, 2 H), 2.56 (s, 6 H), 2.27 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 142.2, 139.4, 133.1, 129.8, 129.0, 128.4, 125.1, 92.1, 69.9, 53.7, 29.7, 24.1, 20.9.

MS (EI, 70 eV): *m*/*z* (%) = 358 (2), 236 (3), 141 (20), 119 (4), 105 (100), 91 (6), 77 (19), 51 (5).

HRMS: *m*/*z* calcd for $C_{19}H_{18}O_2Se$ [M + H]$^+$: 359.0550; found: 359.0546.

3-(Naphthylselanyl)prop-2-yn-1-yl Benzoate (3j)

Yield: 0.069 g (76%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07–8.05 (m, 2 H), 8.01–7.96 (m, 2 H), 7.85–7.83 (m, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.58–7.49 (m, 3 H), 7.45–7.41 (m, 3 H), 5.12 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 134.1, 133.2, 132.2, 129.8, 129.6, 129.5, 128.7, 128.6, 128.4, 126.9, 126.4, 126.2, 125.5, 97.6, 68.1, 53.6, 29.7.

MS (EI, 70 eV): *m*/*z* (%) = 366 (6), 261 (4), 243 (20), 165 (18), 152 (9), 128 (9), 105 (100), 77 (24), 51 (5).

HRMS: *m*/*z* calcd for $C_{20}H_{14}O_2Se$ [M + H]$^+$: 367.0237; found: 367.0233.

3-(Butylselanyl)prop-2-yn-1-yl Benzoate (3k)

Yield: 0.043 g (58%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.08–8.06 (m, 2 H), 7.59–7.54 (m, 1 H), 7.46–7.42 (m, 2 H), 5.01 (s, 2 H), 2.82 (t, *J* = 7.4 Hz, 2 H), 1.82 (quint, *J* = 7.3 Hz, 2 H), 1.44 (sext, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 133.1, 129.8, 129.7, 128.3, 94.2, 69.2, 53.7, 32.1, 29.0, 22.4, 13.4.

MS (EI, 70 eV): *m*/*z* (%) = 296 (1), 239 (2), 174 (2), 159 (1), 118 (7), 105 (100), 77 (38), 51 (16).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_2Se$ [M + H]$^+$: 297.0394; found: 297.0389.

4-Methyl-[3-(phenylselanyl)prop-2-yn-1-yl] Benzoate (3l)

Yield: 0.038 g (46%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.89–7.87 (m, 2 H), 7.47–7.45 (m, 2 H), 7.25–7.21 (m, 2 H), 7.20–7.14 (m, 3 H), 5.04 (s, 2 H), 2.32 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 144.0, 129.8, 129.5, 129.2, 129.1, 128.0, 127.3, 126.7, 98.1, 68.0, 53.4, 21.6.

MS (EI, 70 eV): *m*/*z* (%) = 330 (3), 193 (16), 173 (15), 119 (100), 115 (30), 91 (24), 77 (8), 51 (9).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_2Se$ $[M + H]^+$: 331.0237; found: 331.0232.

2-Methoxy-[3-(phenylselanyl)prop-2-yn-1-yl] Benzoate (3m)

Yield: 0.052 g (60%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.59–6.57 (m, 1 H), 6.28–6.27 (m, 1 H), 6.26–6.25 (m, 1 H), 6.22–6.17 (m, 1 H), 6.05–6.01 (m, 2 H), 5.99–5.97 (m, 1 H), 5.71–5.68 (m, 2 H), 3.84 (s, 2 H), 2.61 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.1, 159.4, 133.9, 131.8, 129.5, 129.1, 128.0, 127.2, 120.0, 119.1, 112.0, 98.1, 67.8, 55.9, 53.3.

MS (EI, 70 eV): *m*/*z* (%) = 346 (1), 194 (12), 193 (12), 189 (9), 135 (100), 115 (37), 92 (7), 77 (22), 51 (11).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_3Se$ $[M + H]^+$: 347.0186; found: 347.0182.

4-Fluoro-*N*-[3-(phenylselanyl)prop-2-yn-1-yl] Benzoate (3n)

Yield: 0.072 g (87%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.12–8.07 (m, 2 H), 7.55–7.52 (m, 2 H), 76.34–7.24 (m, 3 H), 7.14–7.09 (m, 2 H), 5.13 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.2, 164.8 (d, $^1J_{C,F}$ = 233.2 Hz), 132.4 (d, $^3J_{C,F}$ = 9.4 Hz), 129.6, 129.3, 127.9, 127.4, 125.7 (d, $^4J_{C,F}$ = 2.9 Hz), 115.6 (d, $^2J_{C,F}$ = 22.1 Hz), 97.7, 68.5, 53.7.

MS (EI, 70 eV): *m*/*z* (%) = 334 (4), 254 (1), 193 (20), 177 (26), 123 (100), 95 (35), 75 (15), 51 (20).

HRMS: *m*/*z* calcd for $C_{16}H_{11}FO_2Se$ $[M + H]^+$: 334.9986; found: 334.9982.

3-(Phenylselanyl)prop-2-yn-1-yl Nicotinate (3o)

Yield: 0.048 g (60%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.26–9.25 (m, 1 H), 8.79–8.77 (dd, *J* = 4.9, 1.7 Hz, 1 H), 8.33–8.30 (m, 1 H), 7.55–7.52 (m, 2 H), 7.40–7.36 (m, 1 H), 7.34–7.29 (m, 2 H), 7.30–7.25 (m, 1 H), 5.17 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.5, 153.6, 151.0, 137.1, 129.5, 129.4, 127.8, 127.4, 125.5, 123.2, 97.3, 69.0, 53.9.

MS (EI, 70 eV): *m*/*z* (%) = 318 (2), 317 (10), 211 (8), 193 (24), 160 (43), 117 (11), 106 (100), 78 (44), 51 (26).

HRMS: *m*/*z* calcd for $C_{15}H_{11}NO_2Se$ $[M + H]^+$: 318.0033; found: 318.0028.

3-(Phenylselanyl)prop-2-yn-1-yl Cinnamate (3p)

Yield: 0.078 g (92%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, *J* = 16.0 Hz, 1 H), 7.46–7.45 (m, 1 H), 7.44–7.40 (m, 3 H), 7.30–7.27 (m, 3 H), 7.25–7.14 (m, 3 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 4.94 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.0, 145.7, 134.1, 130.4, 129.5, 129.3, 128.8, 128.1, 127.9, 127.3, 117.1, 97.9, 68.1, 53.1.

MS (EI, 70 eV): *m*/*z* (%) = 342 (6), 314 (15), 281 (39), 253 (23), 207 (100), 157 (26), 117 (4), 77 (26), 51 (12).

HRMS: *m*/*z* calcd for $C_{18}H_{14}O_2Se$ $[M + H]^+$: 343.0237; found: 343.0233.

3-(Phenyltellanyl)prop-2-yn-1-yl Benzoate (3q)

Yield: 0.058 g (64%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07–8.05 (m, 2 H), 7.71–7.68 (m, 2 H), 7.57–7.52 (m, 1 H), 7.44–7.40 (m, 2 H), 7.27–7.22 (m, 3 H), 5.18 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.7, 135.5, 133.2, 129.8, 129.7, 129.5, 128.3, 128.1, 112.2, 108.8, 53.7, 46.5.

MS (EI, 70 eV): *m*/*z* (%) = 365 (1), 244 (8), 159 (21), 131 (8), 114 (63), 105 (100), 77 (57), 51 (26).

HRMS: *m*/*z* calcd for $C_{16}H_{12}O_2Te$ $[M + H]^+$: 366.9978; found: 366.9973.

3-(Butyltellanyl)prop-2-yn-1-yl Benzoate (3r)

Yield: 0.034 g (40%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.08–8.06 (m, 2 H), 7.58–7.54 (m, 1 H), 7.46–7.42 (m, 2 H), 5.15 (s, 2 H), 2.84 (t, *J* = 7.4 Hz, 2 H), 1.86 (quint, *J* = 7.5 Hz, 2 H), 1.42 (sext, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.8, 133.1, 129.8, 128.3, 105.8 74.9, 53.8, 43.2, 33.6, 24.6, 13.2, 9.6.

MS (EI, 70 eV): *m*/*z* (%) = 346 (1), 289 (3), 287 (3), 168 (16), 105 (100), 77 (31), 51 (9), 29 (22).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_2Te$ $[M + H]^+$: 347.0291; found: 347.0286.

Bis[3-(phenylselanyl)prop-2-yn-1-yl] Adipate (3u) (Scheme 2)

Yield: 0.061 g (46%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.53–7.50 (m, 4 H), 7.33–7.27 (m, 6 H), 4.91 (s, 2 H), 4.88 (s, 2 H), 2.69–2.62 (m, 4 H), 2.53–2.48 (m, 2 H), 2.37–2.33 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.4, 169.9, 162.7, 160.7, 129.5, 129.1, 127.9, 127.3, 117.5, 117.4, 98.0, 97.9, 68.0, 67.9, 53.0, 52.9, 33.6, 29.3, 24.1, 23.8.

HRMS: *m*/*z* calcd for $C_{22}H_{22}O_4Se_2$ $[M + H]^+$: 534.9927; found: 534.9926.

Propynyl Benzoates 4a–f via Suzuki-Type Reaction;[17b] General Procedure

A mixture of 3-(butylselanyl)prop-2-yn-1-yl benzoate (**3k**; 74 mg, 0.25 mmol), $Pd(PPh_3)_4$ (29 mg, 10 mol%), and the proper boronic acid (2.0 equiv) were dissolved in DMF (3 mL). After that, $Cu(OAc)_2{\cdot}H_2O$ (60 mg, 0.3 mmol, 1.2 equiv) was added. This mixture was then heated in an oil bath for 12 h at 80 °C. After this, the reaction was cooled to r.t., diluted with EtOAc (3 mL), and then washed with sat. aq NH_4Cl (20 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane/EtOAc.

3-(Phenyl)prop-2-yn-1-yl Benzoate (4a)

Yield: 0.030 g (52%); colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.12–8.09 (m, 2 H), 7.60–7.56 (m, 1 H), 7.49–7.44 (m, 4 H), 7.34–7.31 (m, 3 H), 5.16 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 159.9, 133.4, 133.2, 129.8, 128.4, 114.2, 113.9, 86.6, 81.7, 55.2, 53.5.

MS (EI, 70 eV): *m*/*z* (%) = 237 (5), 236 (31), 114 (89), 105 (100), 89 (8), 77 (32), 63 (8), 51 (14).

HRMS: *m*/*z* calcd for $C_{16}H_{12}O_2$ $[M + H]^+$: 237.0915; found: 237.0910.

3-(4-Chlorophenyl)prop-2-yn-1-yl Benzoate (4b)

Yield: 0.056 g (83%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.12–8.10 (m, 2 H), 7.61–7.57 (m, 1 H), 7.49–7.45 (m, 2 H), 7.42–7.40 (m, 2 H), 7.31–7.27 (m, 2 H), 5.14 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 133.3, 133.1, 129.8, 129.5, 128.7, 128.4, 84.1, 60.4, 53.2, 21.0, 14.2.

MS (EI, 70 eV): *m*/*z* (%) = 271 (3), 270 (15), 242 (6), 148 (56), 113 (16), 105 (100), 77 (24), 51 (11).

3-(4-Tolyl)prop-2-yn-1-yl Benzoate (4c)

Yield: 0.054 g (87%); white solid; mp 47-49 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11–8.10 (m, 1 H), 8.09–8.08 (m, 1 H), 7.58–7.54 (m, 1 H), 7.46–7.42 (m, 2 H), 7.37–7.35 (m, 2 H), 7.12–7.10 (m, 2 H), 5.14 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 138.9, 133.2, 131.8, 129.8, 129.0, 128.4, 119.1, 86.8, 82.4, 53.4, 29.7, 21.4.

MS (EI, 70 eV): *m*/*z* (%) = 251 (6), 250 (33), 222 (11), 128 (100), 115 (10), 105 (84), 77 (38), 51 (13).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_2$ $[M + H]^+$: 251.1072; found: 251.1067.

3-(4-Methoxyphenyl)prop-2-yn-1-yl Benzoate (4d)

Yield: 0.030 g (46%); white solid; mp 35-37 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07–8.04 (m, 2 H), 7.57–7.52 (m, 1 H), 7.50–7.46 (m, 2 H), 7.44–7.40 (m, 2 H), 6.87–6.83 (m, 2 H), 5.08 (s, 2 H), 3.76 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.7, 159.6, 135.3, 133.1, 132.2, 129.7, 129.5, 128.3, 117.3, 115.3, 114.7, 96.3, 69.3, 55.3, 53.5.

MS (EI, 70 eV): *m*/*z* (%) = 267 (10), 266 (55), 238 (12), 144 (100), 115 (15), 105 (73), 77 (30), 51 (12).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_3$ $[M + H]^+$: 267.1021; found: 267.1016.

3-(2-Methoxyphenyl)prop-2-yn-1-yl Benzoate (4e)

Yield: 0.034 g (52%); colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11–8.09 (m, 2 H), 7.58–7.53 (m, 1 H), 7.45–7.42 (m, 3 H), 7.31–7.25 (m, 1 H), 6.91–6.85 (m, 2 H), 5.20 (s, 2 H), 3.87 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.9, 160.4, 134.0, 133.1, 130.2, 129.8, 128.4, 128.3, 120.4, 111.5, 110.8, 87.0, 83.0, 55.8, 53.6.

MS (EI, 70 eV): *m*/*z* (%) = 267 (4), 266 (21), 238 (13), 144 (24), 115 (82), 105 (100), 77 (34), 51 (11).

HRMS: *m*/*z* calcd for $C_{17}H_{14}O_3$ $[M + H]^+$: 267.1021; found: 267.1016.

3-(Naphthalen-2-yl)prop-2-yn-1-yl Benzoate (4f)

Yield: 0.040 g (58%); colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.15–8.12 (m, 2 H), 7.84 (d, 2 H, *J* = 8.42 Hz), 7.72–7.70 (m, 1 H), 7.60–7.56 (m, 2 H), 7.53–7.40 (m, 4 H), 7.25 (s, 1 H), 5.31 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.0, 133.5, 133.2, 133.1, 131.0, 129.9, 129.8, 129.3, 128.4, 128.3, 126.9, 126.5, 126.1, 125.1, 119.9, 87.9, 84.8, 53.5.

MS (EI, 70 eV): *m*/*z* (%) = 287 (4), 286 (19), 258 (7), 164 (78), 152 (12), 105 (100), 77 (26), 51 (8).

HRMS: *m*/*z* calcd for $C_{20}H_{14}O_2$ $[M + H]^+$: 287.1072; found: 287.1066.

Propynyl Benzoate via Sonogashira-Type Reaction;[17b] 6-Hydroxy-6-methylhepta-2,4-diyn-1-yl Benzoate (5a)

A mixture of 3-(butylselanyl)prop-2-yn-1-yl benzoate (**3k**; 74 mg, 0.25 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 10 mol%), 2-methylbut-3-yn-2-ol (84 mg, 1 mmol, 4 equiv), and Et_3N (101 mg, 1 mmol, 4.0 equiv) were dissolved in DMF (3 mL). After that, $Cu(OAc)_2{\cdot}H_2O$ (10 mg, 20 mol%) was added. The Schlenk tube was then heated in an oil bath for 24 h at 80 °C. Then, the reaction was cooled to r.t., the crude reaction mixture was diluted with EtOAc (3 mL) and then washed with sat. aq NH_4Cl (20 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by flash chromatography and eluted with a mixture of hexane/EtOAc; yield: 0.030 g (50%); colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07–8.04 (m, 2 H), 7.60–7.56 (m, 1 H), 7.47–7.43 (m, 2 H), 4.97 (s, 2 H), 2.16 (s, 1 H), 1.53 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.7, 133.4, 129.8, 129.3, 128.4, 84.1, 73.5, 70.7, 66.3, 65.5, 52.9, 31.0.

MS (EI, 70 eV): *m*/*z* (%) = 243 (2), 242 (15), 120 (5), 105 (100), 91 (7), 77 (42), 65 (2), 51 (11).

In vitro Anticancer Assay

Human GBM cell line A172, obtained from American Tissue Culture Collection (ATCC, Rockville, MD) was kindly provided by Dr. Guido Lenz (Department of Biophysics, Federal University of Rio Grande do Sul (UFRGS), Brazil). All culture material and reagents were purchased from Gibco Laboratories (Grand Island, NY, USA). Cells were cultured in DMEM low glucose supplemented with 10% of Fetal Bovine Serum (FBS), 1% penicillin/streptomycin, and 0.1% amphotericin B at 37 °C and 5% CO_2 in a humidified incubator.

Glioma cells were seeded at 5 × 10^4 cells/well in DMEM/10% FBS in 24-well plates. After reaching subconfluence, the cultures were exposed to 3-(phenylselanyl)prop-2-yn-1-yl benzoate (**3a**) at concentrations of 1, 10, 50, or 100 μM and Tmz (Sigma-Aldrich Chemical Co., St.Louis, MO, USA) at concentration 30 μM, both compounds dissolved in DMSO at different times (24, 48 and 72 h). Control cultures were performed with DMSO (at maximum 0.5% final concentration). At the end of the treatment, cells were counted in a hemocytometer and the number of cells present in the control group was considered as 100%. Statistical analysis was conducted by ANOVA followed by Tukey post-hoc test to multiple comparisons of at least three independent experiments. p-Value under 0.05 was considered significant.

Conflict of Interest

The authors declare no conflict of interest

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1477-6470.

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