Organic & Biomolecular Chemistry

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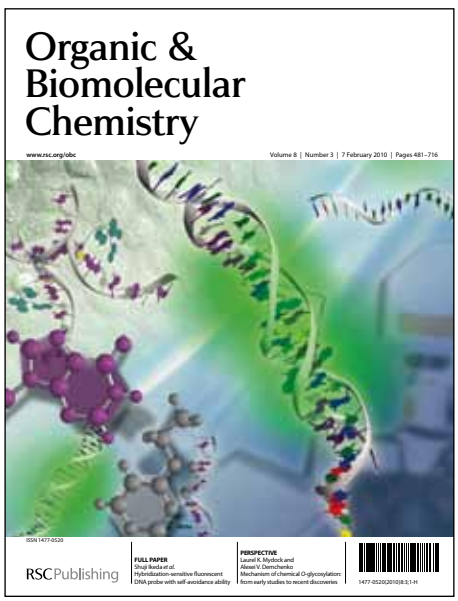

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Bis-vinyl Selenides Obtained via Iron(III) Catalyzed Addition of PhSeSePh to Alkynes: Synthesis and Antinociceptive Activity

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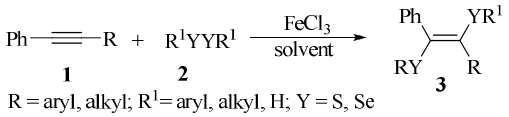
Abstract:

In the present study the synthesis and antinociceptive activity of bis-vinyl selenides, prepared via $FeCl_3$ promoted reaction addition of diorganyl dichalcogenides to alkynes, is described. The pharmacological results demonstrated that bis-vinyl selenides **3a**, **3d**, **3h** and **3t** elicited antinociceptive effect in the mouse formalin test. The antinociceptive effects of bis-vinyl selenides are not sensitive to electronic effects of the substituents on the aromatic ring directly bonded to the selenium atom. Bis-vinyl selenides **3h** and **3t** were the most promising molecules for a pharmacological purposes since these bis-vinyl selenides were effective in both phases of the formalin test and against the edema.A single dose of bis-vinyl selenides **3a**, **3d**, **3h** and **3t** did not cause acute toxicity in mice.

Introduction

Pain is one of the most prevalent, costly and disabling conditions, which reduces quality of life. The major problem in pain management is that effective analgesics may have some unpleasant side-effects. Based on these considerations, research leading to the development of new analgesics is of public health interest. Under this point of view, organoselenium and organotellurium compounds have been reported as pharmacological agents.[1] Among organoselenium compounds, a class of bis and tris selenide alkene derivatives has attracted some attention. The interest in the chemistry of bis-vinyl selenides has increased remarkably due to their chemical properties and pharmaceutical potential.[2] Bis selenide alkene derivatives are known as effective antioxidants. 2,3-Bis(4-chlorophenylselanyl prop-2-en-1-ol) is an effective antinoceptive agent in different chemical[3] and thermal[4] models of pain in mice. The antidepressant-like[5] and neuroprotective[6] actions of 2,3-bis(4-chlorophenylselanyl prop-2-en-1-ol) in rodents has been also reported. Recently, much attention has been devoted to the synthesis of vinylic chalcogenides and their derivatives since they emerged as highly valuable intermediates in a variety of synthetic applications.[7] There are several reasons for this, which include a widely varied synthetic organochemical potential and the fact that the chalcogen atom exercises a stabilizing effect on neighbouring positive as well as negative charges. This makes the double bond in vinylic chalcogenides responsive toward both nucleophilic and electrophilic attack, an extremely useful feature for organic synthetic purposes. In this sense, metal-catalyzed cross-coupling[8] and transmetalation reactions[9] have shown to be the most reliable strategy for the formation of a new carbon-carbon bond since the method allows the reaction to proceed under very mild conditions and with very high stereoselectivities. Although various methods are reported for the preparation of vinylic chalcogenides, the more useful procedure has centred on the nucleophilic or electrophilic organochalcogen addition to terminal or internal alkynes.[10] For example, the nucleophilic addition of chalcogenolate anions to alkynes affords, preferentially, the *Z*-vinylic chalcogenides after longer reaction times at room temperature. The reaction is faster at a high temperature; however, the mixture of *Z* and *E* vinylic chalcogenide is obtained in an almost 1:1 ratio.[11] On the other hand, the eletrophilic addition of organochalcogenyl halides to alkynes gave a mixture of Markownikov and anti-Markownikov adducts, depending on the nature of the substituents at the triple bond.[12] Conversely, vinylic chalcogenides can be prepared by transition-metal-catalyzed cleavage of selenium–selenium bond and addition to alkynes.[13] These well-known methods, however, suffer from several drawbacks such as the use of extremely strong reducing agents, expensive transition-metal reagents, low stereoselectivity, and mainly the lack of environmental friendliness. Realizing the importance in the development of environmentally benign protocols to the preparation of vinyl chalcogenides applying green, mild and relatively cheaper methods, this study aimed at the preparation of bis-vinyl selenides **3** via reaction of alkynes **1** with diorganyl dichalcogenides promoted by iron salts (Scheme 1). The pharmacological potential of bis-vinyl selenides was investigated by screening the antinociceptive activity in mice.



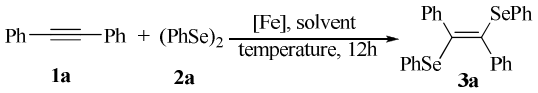
Scheme 1: General scheme.

Chemistry

Our preliminary studies started with the determination of the influence of reaction atmosphere. Thus, a mixture of diphenyl diselenide (0.25 mmol) and $FeCl_3$ (1 equiv), using $MeNO_2$ as solvent, was reacted with diphenylacetylene **1a** (1 equiv) at room temperature. A comparison of reaction runs using rigorously

dried systems (Table 1, entry 1) versus those run in an ambient atmosphere (Table 1, entry 2) showed that the yield was slightly higher in the latter case. To better understand if the activity of the iron system is due to the different ligand partner type on the iron complex or to the effect of dry iron salt, some experiments were also carried out using other iron sources and a very sluggish reactivity was observed (Table 1, entries 3-6). In an effort to improve on these conversions and subsequent isolated yields and to reduce the catalyst loading, we turned our attention to the use of 0.5, 0.25 and 0.1 equiv (10 mol%) of $FeCl_3$. We were pleased to observe that $FeCl_3$ (10 mol%) in $MeNO_2$ efficiently catalyzed the formation of **3a** in an excellent isolated yield (Table 1, entries 7-9). These results are significant since it suggests that the two portions of diphenyl diselenide (PhSe) were incorporated in the final product, the reaction was carried out at ambient atmosphere and required only 10 mol% of $FeCl_3$, which makes our method more attractive from an economic standpoint, and indicates an atom economy which is an important concept of green chemistry philosophy. Next, we evaluated various solvents as reaction media for the iron-catalyzed addition of diphenyl diselenide to alkynes. A set of solvents including dichloromethane, dichloroethane, toluene, ethanol, dimethyl sulfoxide, dimethylformamide, acetonitrile, dioxane and tetrahydrofuran were examined, and nitromethane gave the best results as solvent, although dichloromethane, dichloroethane and toluene also gave the products in acceptable yields (Table 1, entries 10-18). Finally, neither running the reaction at solvent reflux (Table 1, entry 19) nor changing the concentration (Table 1, entries 20-21) gave better yields than those obtained in table 1, entry 9.

Table 1: Influence of reaction conditions in the formation of **3a**



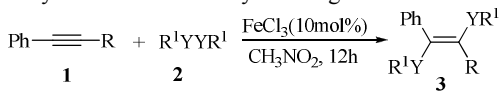
1a **2a** **3a**

entry	[Fe] (equiv)	solvent	yield (%)[a]
1	$FeCl_3$ (1)	CH_3NO_2	73[b]
2	$FeCl_3$ (1)	CH_3NO_2	89
3	$FeCl_2.4H_2O$ (1)	CH_3NO_2	45
4	$FeCl_2.6H_2O$ (1)	CH_3NO_2	74
5	Fe° (1.0)	CH_3NO_2	-[c]
6	$Fe(acac)_3$ (1.0)	CH_3NO_2	-[c]
7	$FeCl_3$ (0.5)	CH_3NO_2	88
8	$FeCl_3$ (0.25)	CH_3NO_2	89
9	$FeCl_3$ (0.1)	CH_3NO_2	92
10	$FeCl_3$ (0.1)	CH_2Cl_2	77
11	$FeCl_3$ (0.1)	DCE	79
12	$FeCl_3$ (0.1)	toluene	74
13	$FeCl_3$ (0.1)	EtOH	-[c]
14	$FeCl_3$ (0.1)	DMSO	-[c]
15	$FeCl_3$ (0.1)	DMF	-[c]
16	$FeCl_3$ (0.1)	CH_3CN	57
17	$FeCl_3$ (0.1)	dioxane	9
18	$FeCl_3$ (0.1)	THF	-[c]
19[d]	$FeCl_3$ (0.1)	CH_3NO_2	20
20[e]	$FeCl_3$ (0.1)	CH_3NO_2	79
21[f]	$FeCl_3$ (0.1)	CH_3NO_2	73

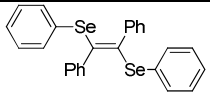
[a] Yields for isolated products. [b] Reaction was carried out at argon atmosphere. [c] **1a** was recovered quantitatively. [d] Reaction carried using reflux temperature of CH_3NO_2. [e] Reaction was performed in 2 mL of solvent. [f] Reaction was performed in 5 mL of solvent.

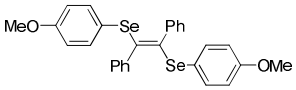
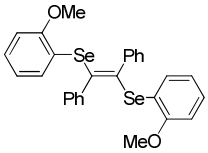
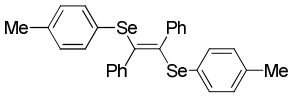
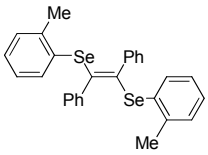
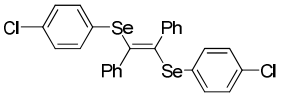
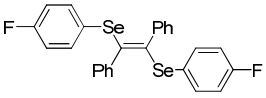
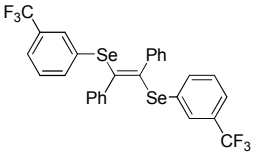
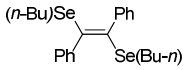
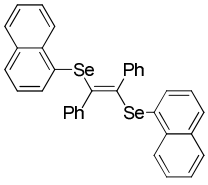
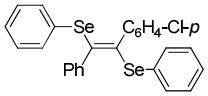
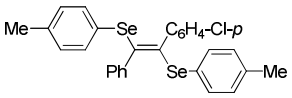
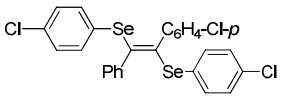
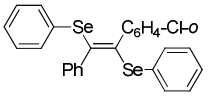
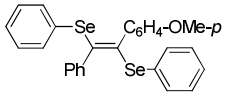
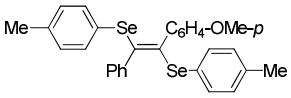
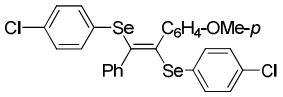
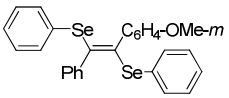
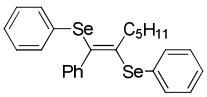
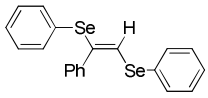
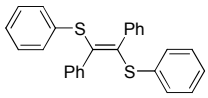
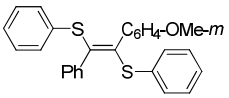
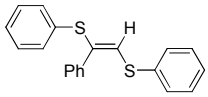
The results described above suggested that the reaction of diphenyl diselenide **2a** with substrate **1a** gave the desired bis-vinyl selenides **3a** in better yields when the reaction was carried out using a 1:1 substrate stoichiometry, $FeCl_3$ (10 mol%), in nitromethane (1 mL) at room temperature for 12 h, under ambient atmosphere. On the basis of these results, we undertook a systematic study applying the conditions of entry 9, table 1, to several substituted alkynes **1a-g** in order to test the tolerance of functional groups as well as their effects on the conversion. These results are collected in table 2. The yields of bis-vinyl selenides **3** varied depending on the nature of diorganoyl diselenide used. While diaryl diselenides bearing a neutral, electron-donating or electron-withdrawing group on the aromatic ring provided the best yields of **3** (Table 2, entries 1-8), the presence of the alkyl or bulky naphthyl group directly bonded to the selenium atom, decreased the yield to 58 and 51% respectively (Table 2, entries 9-10). The results also indicated that the reaction seems not to be sensitive to electronic effects of the substituents in the aromatic ring directly bonded to the triple bond. For example, alkynes having the aromatic ring substituted by Cl or MeO group gave good yields (Table 2, entries 11-18). Furthermore, we found that the reaction with substrate **1f** having an alkyl substituent directly bonded to the triple bond and the terminal alkyne **1g** also worked well under the standard reaction conditions; although the terminal alkyne gave the product in moderated 60% yield (Table 2, entries 19-20). Moreover, the reaction of diorganyl disulfides with alkynes using the standard reaction conditions yielded the addition product only in moderated yields, while the use of diorganyl ditellurides did not give any amount of desired bis-vinyl tellurides (Table 2, entries 21-25).

Table 2: Synthesis of *E*-bis-vinyl chalcogenides **3**[a]



1 **2** **3**

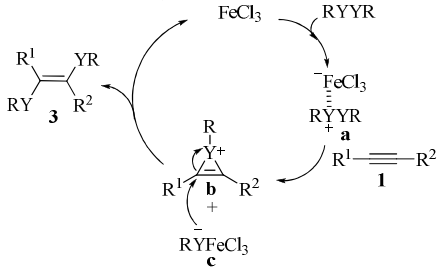
Entry	R	R^1Y	Product (yield)[b]
1	C_6H_5 **1a**	C_6H_5Se **2a**	 **3a**-92%

2	**1a**	*p*-MeOC$_6$H$_4$Se **2b**	 **3b**-60%
3	**1a**	*o*-MeOC$_6$H$_4$Se **2c**	 **3c**-71%
4	**1a**	*p*-MeC$_6$H$_4$Se **2d**	 **3d**-75%
5	**1a**	*o*-MeC$_6$H$_4$Se **2e**	 **3e**-70%
6	**1a**	*p*-ClC$_6$H$_4$Se **2f**	 **3f**-64%
7	**1a**	*p*-FC$_6$H$_4$Se **2g**	 **3g**-75%
8	**1a**	*m*-CF$_3$C$_6$H$_4$Se **2h**	 **3h**-81%
9	**1a**	*n*-BuSe **2i**	 **3i**-58%
10	**1a**	1-naphthylSe **2j**	 **3j**-51%
11	*p*-ClC$_6$H$_4$ **1b**	**2a**	 **3k**-91%
12	**1b**	**2d**	 **3l**-64%
13	**1b**	**2f**	 **3m**-78%
14	*o*-ClC$_6$H$_4$ **1c**	**2a**	 **3n**-78%
15	*p*-MeOC$_6$H$_4$ **1d**	**2a**	 **3o**-72%
16	**1d**	**2d**	 **3p**-63%
17	**1d**	**2f**	 **3q**-76%
18	m-MeOC$_6$H$_4$ **1e**	**2a**	 **3r**-62%
19	n-C$_5$H$_{11}$ **1f**	**2a**	 **3s**-85%
20	H **1g**	**2a**	 **3t**-60%
21	**1a**	C$_6$H$_5$S **2k**	 **3u**-62%
22	**1e**	**2k**	 **3v**-42%
23	**1g**	**2k**	 **3w**-40%
24	**1a**	C$_6$H$_5$Te **2l**	-[c]
25	**1a**	*n*-BuTe **2m**	-[c]

[a] Reaction condition: the reaction was carried out using ambient atmosphere, alkyne (0.5 mmol), diorganoyl dichalcogenides (1.0 equiv), $FeCl_3$ (0.1 equiv) in CH_3NO_2 (1 mL) at room temperature for

12 hours. [b] Yields for isolated products. [c] **1a** was recovered quantitatively.

Based on understanding that in the iron-catalyzed cross coupling that iron is easily admitted as a complex having an oxidation state +3 and that this complex could be stabilized by the selenium atom,[14] we proposed a plausible mechanism to support the current Fe(III)-catalyzed selenium addition, as illustrated in Scheme 2. (i) The iron trichloride coordinates with diorganyl diselenides to form selenonium-like specie **a**; (ii) the alkyne coordination to the selenium atom provides the seleniranium ion **b** and selenolate specie **c**; (iii) nucleophilic anti-attack of the species **c** on the activated triple bond leads to *E*-vinyl selenides **3**. In this context, in view of the high activation of the triple bond by the selenium group, our methodology showed to be high stereoselective, providing exclusively the desired *E*-vinyl selenides **3**, via an anti-addition process, as the unique isomer, which was confirmed by X-ray diffraction analysis (Figure 1). The radical pathway was not discarded; however, when the reaction of diphenylacetylene **1a** with diphenyl diselenide was carried out in the presence of TEMPO, a radical inhibitor, bis-vinyl selenide **3a** was obtained in 87% yield. This result indicates that the pathway does not follow the typical radical addition, where the radical source is PhSe.[15]



Scheme 2: Plausible mechanism.

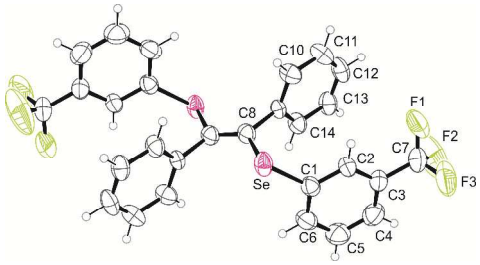


Figure 1: ***ORTEP*** view of the compound **3h**.

Results and Discussion

In an attempt to investigate the potential antinociceptive and anti-inflammatory effects of bis-vinyl selenides, the formalin test was carried out. The formalin test consists in two phases: the first phase, also called neurogenic phase, which results basically from the direct activation of nociceptors, and the second phase, which involves a period of sensitization during which an inflammatory phenomena occurs.[16]

The majority of bis-vinyl selenides tested exhibited effect on the first phase of the formalin test (p<0.05), except for one compound which is *p*-chloro substituted (**3f**, Figure 2). At 2 h of pre-treatment, bis-vinyl selenides **3h** at a dose equal to 50 mg/kg (i.g) decreased the time that mice spent licking the hind paw in the first ($p \leq 0.011837$) (Figure 2) and second phases ($p \leq 0.0029$) (Figure 3) of the formalin test. Bis-vinyl selenide **3t** elicited similar effects of **3h** in first ($p \leq 0.009658$) (Figure 2) and second phases of test ($p \leq 0.0467$) (Figure 3). **3a** and **3d** significantly decreased licking time in the first phase (Figure 2) but had no effect in the second phase of the formalin test (Figure 3).

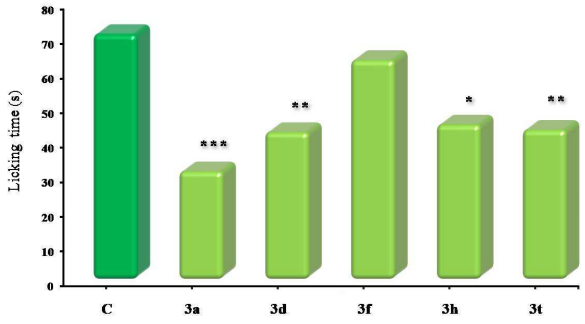


Figure 2. Effect of bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** on licking behavior induced by formalin in the first (0–5 min) phase of the formalin test. Each column represents the mean ± S.E.M. of 5–7 mice in each group. Asterisks denote significance levels when compared to the control group (one-way ANOVA followed by the Duncan's test) (*) $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$. **C** means control, a group of mice treated with canola oil. Standard error (S.E.M.) of all groups represents <10% of means.

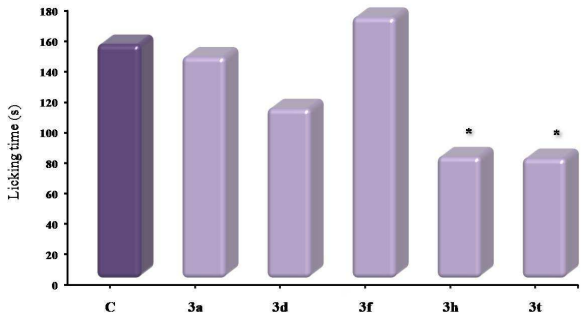


Figure 3. Effect of bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** on licking behavior induced by formalin in the second (15–30 min) phase of the formalin test. Each column represents the mean ± S.E.M. of 5–7 mice in each group. Asterisks denote significance levels when compared to the control group (one-way ANOVA followed by the Duncan's test) (*) $p < 0.05$. **C** means control, a group of mice treated with canola oil. Standard error (SEM) of all groups represents <20% of means.

Administration of morphine (2.5 mg/kg, i.g.) as a positive control was effective in decreasing the time that mice spent licking the hind paw in both phases of the formalin test (data not shown). Studies have demonstrated that the antinociceptive action of other organoselenium compounds, such as diphenyl diselenide and bis-selenide derivatives, remain significant up to 2h and 45 min, respectively[17] and that morphine, diacetylmorphine and 6-acetylmorphine, known analgesic drugs, have approximately 2.5h, 1.8h and 1.7h of the effect duration, respectively.[18]

The hindpaw edema from animals was assessed to further confirm the anti-inflammatory activity of bis-vinyl selenides. Figure 4 shows that only **3h** and **3t**, administered to mice 2h before the formalin test, significantly reduced (about 25%) paw edema induced by intraplantar injection of formalin. Accordingly, the anti-edematogenic effect of **3h** and **3t** could be associated to the reduction of nociception by these bis-vinyl selenides in the inflammatory phase (second phase) of the

formalin test. All the other bis-vinyl selenides tested, **3a**, **3d** and **3f**, had no anti-edematogenic effect in mice.

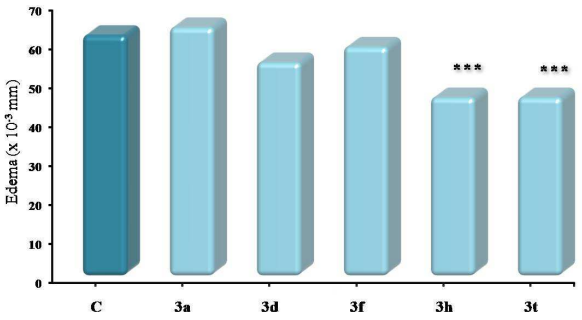


Figure 4. Effect of bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** on edema-induced by formalin in mice. Each column represents the mean ± S.E.M. of 5–7 mice in each group. Asterisks denote significance levels when compared to the control group (one-way ANOVA followed by the Duncan's test) *** P <0.001. **C** means control, a group of mice treated with canola oil. Standard error (SEM) of all groups represents <10% of means.

Taking these results together it is possible to infer that bis-vinyl selenides **3h** and **3t** are the most promising molecules for a pharmacological propose since these bis-vinyl selenides were effective in both phases of the formalin test and against the edema. Evidence has been found to suggest that the antinociceptive effects of bis-vinyl selenides are not sensitive to electronic effects of the substituents on the aromatic ring directly bonded to the selenium atom. A inspection of bis-vinyl selenides tested revealed that compounds **3a**, **3d**, **3h** and **3t** showed antinociceptive effects despite the differences of the substituents on the aromatic ring directly bonded to the selenium atom. While **3h** is a bis-vinyl selenide with a CF_3 group substituted in the aromatic ring directly bonded to the selenium atom, **3a** has a methyl group substituted in the aromatic ring directly bonded to the selenium atom and **3d** has no substituent in the aromatic ring, ruling out the possibility of a structure-activity relationship. In support of this idea are the results obtained with **3t**, which has the hydrogen atom in the place of the aromatic ring bonded to the vinyl portion of the molecule.

In addition, antinociceptive effects of bis-vinyl selenides (50 mg/kg, i.g.) at other times of pre-treatment (30 and 60 min) were demonstrated (see supporting information, Table 1). Bis-vinyl selenides **3t** and **3a** administered 30 and 60 min before the test decreased the time that mouse spent licking hind paw in the first phase. By contrast, only **3t** showed the same effect in the second phase at 60 min of pre-treatment ($p \leq 0.05$). Interestingly, **3h** and **3d** pre-administered at 30 and 60 min before the test diminished the time that mouse spent licking hind paw in the second phase. **3h**, but not **3d**, administered 30 min before the test to mice elicited the antinociceptive effect in the first phase of the formalin test ($p<0.05$) (see supporting information, Table 1). Moreover, bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** administered to mice at 30 or 60 min before the formalin test had no anti-edematogenic (see supporting information, Table 1).

Concerning the possible toxicity caused by bis-vinyl selenides, the potential acute toxicity and the locomotor activity after a single oral dose of **3a**, **3d**, **3f**, **3h** and **3t** were investigated. Most of the bis-vinyl selenides showed neither acute toxicity nor nonspecific locomotor disturbances in mice (see supporting information, Table 2). The results obtained with the bis-vinyl selenide substituted with the chlorine group in the aromatic ring bonded to the selenium atom **3f** indicated minor hepatic toxicity, demonstrated by an inhibition (about 15%) in hepatic δ-ALA-D activity and an increase in AST activity, a biochemical marker of acute hepatic damage (see supporting information, Table 2). δ-ALA-D is a sulfhydryl-containing enzyme, which is extremely sensitive to oxidizing agents and to situations associated with oxidative stress.[19] Similar to δ-ALA-D, Na^+, K^+-ATPase is a sulfhydryl enzyme sensitive to oxidizing agents.[20] However, none of bis-vinyl selenides tested inhibited the Na^+, K^+-ATPase activity even the compound **3f** (see supporting information, Table 2).

Conclusion

In summary, we have explored the addition reaction behavior of of diorganyl dichalcogenides to alkynes in presence of catalytic amount of FeCl3 and established a steroselectivity route to obtain highly substituted bis-vinyl chalcogenides. The reaction works well with a wide range of substituents in both diorganyl dichalcogenides and alkynes, generally resulting in good yields, and proceed under relatively mild conditions. Furthermore, since the reactions was carried out at room temperature, under ambient atmosphere and iron salts are easily available commercially, less expensive and relative non-toxic our method could be considered an economic and eco-friendly protocol. The pharmacological results demonstrated that bis-vinyl selenides **3a**, **3d**, **3h** and **3t** elicited antinociceptive effect in the mouse formalin test. The antinociceptive effects of bis-vinyl selenides were not sensitive to electronic effects of the substituents on the aromatic ring directly bonded to the selenium atom. Bis-vinyl selenides **3h** and **3t** were the most promising molecules for a pharmacological propose since these bis-vinyl selenides were effective in both phases of the formalin test and against the edema. Bis-vinyl selenide **3f** has no anitinociceptive effect in mice. A single dose of bis-vinyl selenides **3a**, **3d**, **3h** and **3t** did not cause acute toxicity in mice.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz on a DPX-200 NMR spectrometer or at 400 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in CDCl3 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of CDCl3 or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 50 MHz on a DPX-200 NMR spectrometer or at 100 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in CDCl3 solutions. All synthesized and tested compounds were obtained in purity superior to 98% determined by combustion analysis, HPLC and gas chromatography.

General Procedure for Iron-Promoted Addition of Diorganoyl Dichalcogenides to Alkynes: To a Schlenk tube, under ambient atmosphere, containing a mixture of the appropriate diorganoyl dichalcogenide (0.55 equiv) in CH_3NO_2

(0.5 mL) was added, at room temperature, the $FeCl_3$ (0.1 equiv, 10 mol%). The resulting solution was stirred for 15 min at this temperature. After that the corresponding alkyne (0.5 mmol) in CH_3NO_2 (0.5 mL) was added and resulting solution was stirred under reflux for 12 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with a saturated solution of NH_4Cl (3 x 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography eluted with hexane/acetate (95:5).

(*E*)-1,2-Diphenyl-1,2-bis(phenylselenyl)ethene (3a): Yield: 0.226 g (92%). White solid. mp = 155-158 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm):7.24-7.21 (m, 4H), 7.19-7.03 (m, 12H), 7.01-6.96 (m, 4H). RMN ^{13}C ($CDCl_3$, 100 MHz), δ (ppm): 140.5, 135.0, 133.1, 130.0, 129.5, 128.3, 127.6, 127.4, 102.3. MS (relative intensity) *m*/*z*: 492 (13), 335 (25), 254 (27), 178 (100), 152 (19), 77 (10). Anal. (%) calcd. for $C_{26}H_{20}Se_2$: C 63.68, H 4.110. Found: C 63.74, H 4.18.

(*E*)-1,2-Bis(4-methoxyphenylselenyl)-1,2-diphenylethene(3b): Yield: 0.165 g (60%). Yellow solid. mp = 164-167 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.20-7.11 (m, 10H), 7.08-7.05 (m, 4H), 6.54-6.49 (m, 4H), 3.68 (s, 6H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm): 159.9, 140.5, 137.2, 132.5, 129.4, 127.7, 127.2, 120.3, 113.9, 55.1. MS (relative intensity) *m*/*z*: 552 (9), 373 (7), 365 (25), 281 (30), 253 (25), 207 (100), 186 (58), 178 (75), 133 (17), 77 99). Anal. HRMS calcd. for $C_{28}H_{24}O_2Se_2$ (M+Na^+): 552.0107. Found: 552.0113.

(*E*)-1,2-Bis(2-methoxyphenylselenyl)-1,2-diphenylethene (3c): Yield: 0.196 g (71%). White solid. mp = 156-159 °C. ^{1}H RMN ($CDCl_3$, 200 MHz), δ (ppm): 7.37-7.25 (m, 6H), 7.16-7.07 (m, 8H), 6.71-6.63 (m, 2H), 6.58-6.53 (m, 2H), 3.69 (s, 6H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm):158.2, 141.2, 135.5, 133.5, 129.4, 129.0, 128.9, 127.3, 127.2, 120.7, 119.9, 110.2, 55.5. MS (relative intensity) *m*/*z*: 551 (17), 365 (29), 284 (14), 207 (21), 178 (100), 159 (17), 107 (36), 77 (33). Anal. HRMS calcd. for $C_{28}H_{24}O_2Se_2$ (M+Na^+): 551.0107. Found: 552.0117.

(*E*)-1,2-Diphenyl-1,2-bis(*p*-tolylselenyl)ethene (3d): Yield: 0.195 g (75%). Yellow solid. mp = 133-136 °C. ^{1}H RMN ($CDCl_3$, 200 MHz), δ (ppm): 7.32-7.08 (m, 10H), 7.05 (d, J = 8.1 Hz, 4H), 6.79 (d, J = 7.8 Hz, 4H), 2.17 (s, 6H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 140.8, 137.3, 135.1, 133.0, 125.5, 129.1, 129.6, 127.3, 126.4, 21.0. MS (relative intensity) *m*/*z*: 518 (16), 353 (7), 372 (16), 353 (12), 207 (28), 178 (100), 152 (22), 133 (5), 76 (4). Anal. (%) calcd. for $C_{28}H_{24}Se_2$: C 64.87, H 4.67. Found: C 64.96, H 4.72.

(*E*)-1,2-Diphenyl-1,2-bis(*o*-tolylselenyl)ethene (3e): Yield: 0.182 g (70%). White solid. mp = 190-193 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.25-7.20 (m, 5H), 7.16-7.09 (m, 5H), 6.97-6.95 (m, 2H), 6.84-6.80 (m, 2H), 2.23 (s, 6H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm):141.3, 140.9, 136.6, 133.5, 131.0, 129.5, 129.0, 128.1, 127.48, 127.3, 125.8, 22.8. MS (relative intensity) *m*/*z*: 520 (7), 349 (16), 281 (27), 253 (28), 107 (100), 178 (80), 152 (19), 133 (17), 91 (66), 73 (40). Anal. (%) calcd. for $C_{28}H_{24}Se_2$: C 64.87, H 4.67. Found: C 64.93, H 4.71.

(*E*)-1,2-Bis(4-chlorophenylselenyl)-1,2-diphenylethene (3f): Yield: 0.179 g (65%). Yellow solid. mp = 178-181 °C. ^{1}H RMN ($CDCl_3$, 200 MHz), δ (ppm): 7,23-7,13 (m, 10H), 7,08 (d, J = 8,3 Hz, 4H), 6,96 (d, J = 8,6 Hz, 4 H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm):140,2, 136,3, 133,9, 133,1, 129,4, 129,1, 128,1, 129,9, 127,7. MS (relative intensity) *m*/*z*: 553 (5), 348 (15), 281 927), 253 (21), 214 (12), 207 (100), 176 (28), 151 (10), 96 (3), 91 (54), 73 (40). Anal. HRMS calcd. for $C_{26}H_{18}Cl_2Se_2$ (M+Na^+): 559.9113. Found: 559.9141.

(*E*)-1,2-Bis(4-fluorophenylselenyl)-1,2-diphenylethene (3g): Yield: 0.198 g (75%). White solid. mp = 134-137 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.22-7.01(m, 14H), 6.71-6.65 (m, 4H), ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 162.5 (d, ^1J = 248 Hz), 140.2, 135.5 (d, ^3J = 8.7 Hz), 132.7 ,128.4, 127.8, 127.6, 124.5 (d, ^4J = 3.6 Hz), 115.5 (d, ^2J = 21.9 Hz). MS (relative intensity) *m*/*z*: 528 (8), 353 (20), 281 (4), 253 (28), 207 (100), 178 (80), 152 (19), 133 917), 91 (66), 73 (40). Anal. (%) calcd. for $C_{26}H_{18}F_2Se_2$: C 59.33, H 3.45. Found: C 59.48, H 3.51.

(*E*)-1,2-Diphenyl-1,2-bis(3-(trifluoromethyl)phenylselenyl)ethene (3h): Yield: 0.255 g (81%). White solid. mp = 128-131 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.39-7.35 (m, 4H), 7.32-7. 29 (m, 2H), 7.25-7.08 (m, 12H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 139.8, 138.1, 133.0, 131.8 (q, J = 4.4 Hz), 131.0, 130.7(q, J = 32.2 Hz), 129.4, 128.6, 128.0, 127.9, 124.2 (q, J =3.6 Hz), 123.5 (q, J = 272.2 Hz). MS (relative intensity) *m*/*z*:628 (3), 625 (7), 403 (16), 363 (9), 322 (8), 178 (100), 152 (13), 126 (34). Anal. HRMS calcd. for $C_{28}H_{18}F_6Se_2$ (M+Na^+): 697.9643. Found: 697.9758.

(*E*)-1,2-Bis(butylselenyl)-1,2-diphenylethene (3i): Yield: 0.132 g (58%). Yellow solid. mp = 80-83 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.41-7.35 (m, 8H), 7.32-7.28 (m, 2H), 2.14 (qui, J = 7.3 Hz, 4H), 1.33 (qui, J = 7.6 Hz, 4H), 1.12 (sex, J = 7.6 Hz, 4H), 0.71 (t, J = 7.6 Hz, 6H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 141.1, 130.6, 129.5, 128.1, 127.5, 32.3, 27.0, 22.7, 13.4. MS (relative intensity) *m*/*z*: 352 (10), 304 (23), 228 (21), 207 (53), 178 (84), 152 (18), 91 (5), 55 (14). Anal. HRMS calcd. for $C_{22}H_{28}Se_2$ (M+Na^+): 452.0521. Found: 452.0530.

(*E*)-1,2-Bis(naphthalen-1-ylselenyl)-1,2-diphenylethene (3j): Yield: 0.151 g (51%). White solid. mp = 167-170 °C. ^{1}H RMN ($CDCl_3$, 200 MHz), δ (ppm): 8.19 -8.12 (m, 2H), 7.71-7.54 (m, 4H), 7.51-7.38 (m, 6H), 7.12-6.95 (m, 12H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 150.5, 135.7, 134.9, 133.7, 133.5, 129.5, 129.1, 129.0, 128.4, 128.2, 127.2, 126.3, 125.8, 125.1. MS (relative intensity) *m*/*z*: 392 (5), 304 (23), 228 (21), 207 (53), 178 (84), 152 (18), 128 (22), 126 (19) 115 (100), 77 (7). Anal. (%) calcd. for $C_{34}H_{24}Se_2$: C 69.16, H 4.10. Found: C 69.28, H 4.17.

(*E*)-(1-(4-Chlorophenyl)-2-phenylethene-1,2-diyl)bis(phenylselene) (3k): Yield: 0.255 g (91%). White solid. mp = 80-83 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.22-7.10 (m, 14H), 6.72-6.65 (m, 4H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm): 140.5, 139.2, 135.1, 135.6, 134.7, 134.0, 133.2, 131.4, 130.9, 129.9, 129.4, 128.8, 128.6, 128.4, 127.9, 127.7, 127.6. MS (relative intensity) *m/z*: 525 (9), 368 (14), 333 (27), 331 (15), 252 (22), 211 (100), 176 (80), 156 (22), 150 (26), 77 (14). Anal. (%) calcd. for $C_{26}H_{19}ClSe_2$: C 59.60, H 3.65. Found: C 59.62, H 3.69.

(*E*)-(1-(4-Chlorophenyl)-2-phenylethene-1,2-diyl)bis(p-tolylselene) (3l): Yield: 0.177 g (64%). White solid. mp = 135-138 °C. ^{1}H RMN ($CDCl_3$, 200 MHz), δ (ppm): 7.23-6.99 (m, 13H), 6.88-6.77 (m, 4H), 2.22-1.14 (m, 6H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 140.7, 139.4, 137.7, 137.6, 135.2, 134.1, 133.0, 131.8, 130.9, 130.8, 129.5, 129.4, 129.2, 128.8, 127.8, 127.7, 127.4, 126.6, 126.2, 21.0 (2C). MS (relative intensity) *m/z*: 556 (5), 553 (10), 383 (19), 383 (19), 348 (31), 281 (16), 268 (10), 212 (86), 176 (59), 170 (20), 151 (21), 83 (10), 91 (100), 73 (25). Anal. HRMS calcd. for $C_{29}H_{26}ClSe_2$ ($M+Na^+$): 553.9819. Found: 553.9829.

(*E*)-(1-(4-Chlorophenyl)-2-phenylethene-1,2-diyl)bis((4-chlorophenyl)selene) (3m): Yield: 0.232 g (78%). White solid. mp = 131-139 °C. RMN ^{1}H ($CDCl_3$, 400 MHz), δ (ppm): 7.23-7.14 (m, 9H), 7.01-7.05 (m, 4H), 7.02-6.95 (m, 4H). RMN ^{13}C ($CDCl_3$, 100 MHz), δ (ppm):140.2, 138.8, 136.5, 136.27, 134.6, 134.3, 134.3, 133.7, 130.8, 129.4, 129.9, 128.7, 128.2, 127.9, 127.8. MS (relative intensity) *m/z*: 596 (4), 593 (5), 403 (12), 370 (10), 366 (11), 281 (17), 153 (16), 212 (100), 207 (62), 190 (21), 176 (70), 156 (14), 133 (11), 77 (7). Anal. HRMS calcd. for $C_{26}H_{17}Cl_3Se_2$ ($M+Na^+$): 593.8726. Found: 593.8738.

(*E*)-(1-(4-Chlorophenyl)-2-phenylethene-1,2-diyl)bis(phenylselene) (3n): Yield: 0.205 g (78%). White solid. mp = 115-118 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.36-7.15 (m, 10H), 7.12-6.96 (m, 9H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 139.9, 138.8, 136.6, 134.98, 132.8, 132.7, 131.2, 131.1, 129.7, 129.5, 129.3, 128.7, 128.6, 128.4, 128.3, 128.1, 127.8, 127.7, 127.4, 125.9. MS (relative intensity) *m/z*: 525 (5), 341 (12), 334 (16), 332 (10), 282 (10), 212 (63), 207 (100), 176 (49), 116 (16), 77 (19). Anal. HRMS calcd. for $C_{26}H_{19}ClSe_2$ ($M+Na^+$): 525.9506. Found: 525.9533.

(*E*)-(1-(4-Methoxyphenyl)-2-phenylethene-1,2-diyl)bis(phenylselene) (3o): Yield: 0. 188 g (72%). Yellow solid. mp = 52-55 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.28-6.94 (m, 16 H), 6.9-6.84 (m, 1H), 6.76-6.63 (m, 2H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 158.9, 140.8, 135.1, 134.2, 134.0, 133.2, 131.4, 130.9, 130.5, 130.3, 130.17, 128.5, 128.6, 128.3, 127.6, 127.2, 126.2, 113.1, 55.1. MS (relative intensity) *m/z*: 522 (11), 365 (42), 284 (12), 208 (100), 193 (62), 165 (66), 139 (9), 77 (9). Anal. HRMS calcd. for $C_{27}H_{22}OSe_2$ ($M+Na^+$): 522.0001. Found: 522.0012.

(*Z*)-(1-(4-Methoxyphenyl)-2-phenylethene-1,2-diyl)bis(p-tolylselene) (3p): Yield: 0.173 g (63%). Yellow solid. mp = 121-123 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.24-7.09 (m, 7H), 7.06-7.03 (m, 4H), 6.82-7.78 (m, 4H), 6.719-6.69 (m, 2H), 3.74 (s, 3H), 2.19 (s, 6H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm): 158.6, 140.8, 137.3,137.1, 135.2, 137.7, 133.2, 132.5, 130.8, 129.5, 129.2, 129.1, 127.5, 127.2, 126.7, 126.4, 113.0, 55.1, 21.1. MS (relative intensity) *m/z*: 550 (14), 348 (13), 379 (52), 364 (9), 298 (17), 208 (100), 193 (78), 165 (79), 139 (10), 91 (35). Anal. (%) calcd. for $C_{29}H_{26}OSe_2$: C 63.51, H 4.78. Found: C 63.74, H 4.82.

(*E*)-(1-(4-Methoxyphenyl)-2-phenylethene-1,2-diyl)bis((4-chlorophenyl)selene)(3q): Yield: 0.224 g (76%). Yellow solid. mp = 80-86 °C. ^{1}H RMN ($CDCl_3$, 400 MHz). δ (ppm): 7.25-7.05 (m, 10H), 7.03-6.92 (m, 4H), 6.83-6.81 (m, 1H), 6.76-6.68 (m, 2H), 3.73 (s, 3H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm): 159.0, 141.3, 140.0, 136.3, 136.2, 133.9, 133.8, 129.3, 128.9, 128.5(2C), 128.1, 128.0, 127.8, 127.7, 121.9, 114.8, 113.5, 55.2. MS (relative intensity) *m/z*: 591 (4), 401 (13), 399 (29), 364 (19), 208 (100), 193 (60), 165 (64), 139 (9), 73 (11). Anal. HRMS calcd. for $C_{27}H_{20}Cl_2OSe_2$ ($M+Na^+$): 589.9222. Found: 589.9230.

(*E*)-(1-(3-Methoxyphenyl)-2-phenylethene-1,2-diyl)bis(phenylselene) (3r): Yield: 0.162 g (62%). White solid. mp = 112-115 °C. RMN ^{1}H ($CDCl_3$, 400 MHz), δ (ppm): 7.24-6.97 (m, 16H), 6.87-6.85 (m, 1H), 6.72 (s, 1H), 6.68-6.65 (m, 1H), 3.69 (s, 3H). RMN ^{13}C ($CDCl_3$, 100 MHz), δ (ppm):158.9, 141.8, 140.5, 135.1, 134.3, 134.0, 128.7, 127.5, 127.4 (2C),122.0, 114.7, 113.6, 55.2. MS (relative intensity) *m/z*: 522 (23), 520 (21), 350 (13), 313 (10), 285 (19), 253 (17), 208 (100), 178 (73), 165 (65), 152 (14), 77 (23). Anal. HRMS calcd. for $C_{27}H_{22}OSe_2$: C 62.32, H 4.26. Found: C 62.45, H 4.30.

(*E*)-(1-Phenylhept-1-ene-1,2-diyl)bis(phenylselene) (3s): Yield: 0.206 g (85%). Yellow oil. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.48-7.45 (m, 2H), 7.29-7.23 (m, 5H), 7.13-7.05 (m, 8H), 2.64 (t, J = 7.8 Hz, 2H), 1.57 (qui, J = 7.6 Hz, 2H), 1.27-1.19 (m, 4H), 0.85 (t, J = 6.6 Hz, 3H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 141.8, 137.3, 134.6, 134.2, 131.3, 130.5, 130.3, 129.5, 129.9, 128.6, 127.6, 127.5, 127.2, 127.1, 37.7, 31.3, 29.0, 22.4, 13.9. MS (relative intensity) *m/z*: 488 (4), 486 (13), 258 (35), 207(17), 178 (100), 156 (17), 143 (40), 129 (48), 115 (78), 91 (64), 71 (22), 65 (6), 55 (7), 51 (6). Anal. HRMS calcd. for $C_{25}H_{26}Se_2$: C 486.0365. Found: 486.0378.

(*E*)-(1-Phenylethene-1,2-diyl)bis(phenylselene) (3t): Yield: 0.124 g (60%). Yellow oil. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.55-7. 14 (m, 15H), 7.07 (s, 1H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm): 139.5, 133.0, 132.1, 131.1, 130.6, 130.4, 129.3, 129.2, 128.6, 128.3, 128.4, 127.5, 127.4, 126.0. MS (relative intensity) *m/z*: 415 (9), 280 (10), 258 (19), 252 (9), 206 (25), 178 (100), 156 (48), 151 (10), 77 (66). Anal. HRMS calcd. for $C_{20}H_{16}Se_2$: C 415.9582. Found: 415.9602.

(*E*)-1,2-Diphenyl-1,2-bis(phenylthio)ethene) (3u): Yield: 0.123 g (62%). White solid. mp = 106-106 °C. ^{1}H RMN ($CDCl_3$, 400 MHz) , δ (ppm): 7.49-7.37 (m, 3H), 7.19-6.99 (m, 16H), 7.00-6.89 (m, 1H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm): 138.9, 134.4, 131.7, 130.6, 129.9, 128.1, 128.3, 127.3, 126.8. MS (relative intensity) *m*/*z*: 396 (49), 287 (30), 271 (13), 253 (41), 209 (51), 206 (56), 178 (100), 165 (43), 152 (42), 108 (29), 77 (18). Anal. HRMS calcd. for $C_{26}H_{20}S_2$ (M+Na$^+$): 396.1006. Found: 396. 1019.

(*E*)-(1-(2-Chlorophenyl)-2-phenylethene-1,2-diyl)bis(phenylsulfide) (3v): Yield: 0.091 g (42%). White solid. mp = 43-46 °C. ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.54-6.99 (m, 19H). ^{13}C RMN ($CDCl_3$, 100 MHz), δ (ppm):137.6, 137.0, 134.7, 134.2, 133.3, 132.5, 132.0, 131.5, 130.1, 129.6, 129.3, 129.0, 128.8, 128.3 (2C), 127.8, 127.7, 127.1, 126.0. MS (intensidade relativa) *m*/*z*: 430 (3), 341 (5), 281 (21), 253 (17), 207 (100), 190 (16), 133 (17), 96 (15), 73 (26). Anal. HRMS calcd. for $C_{26}H_{19}ClS_2$: 430.0617. Found: 430.0629.

(*E*)-(1-Phenylethene-1,2-diyl)bis(phenylsulfide (3w): Yield: 0.064 g (40%). colorless oil . ^{1}H RMN ($CDCl_3$, 400 MHz), δ (ppm): 7.60-7.56 (m, 2 H), 7.34-7.17 (m, 15 H), 7.14-7.09 (m, 1H), 6.89 (s, 1H). ^{13}C RMN ($CDCl_3$, 50 MHz), δ (ppm): 138.9, 137.4, 134.4, 134.2, 131.7, 131.5, 130.6, 129.9, 128.5, 128.3, 127.6 (2C), 127.3, 126.7. MS (relative intensity) *m*/*z*: 331 (4), 281 (12), 253 (15), 209 (13), 207 (100), 191 (13), 123 (14), 96 (14), 73 (7).

Animals: The experiments were conducted using male adult Swiss mice (25-35 g) from our own breeding colony. The animals were kept in a separate animal room, on a 12 h light/dark cycle with lights on at 7:00 a.m., at room temperature (22 ± 1 ^{0}C) with free access to water and food. All manipulations were carried out between 08:00 a.m. and 04:00 p.m. All experiments were performed on separate groups of animals. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil. All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments. Animals were randomly divided into groups of 5-7 animals each.

Drugs: Bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** were dissolved in canola oil and administered intragastrically (i.g.). A single dose of 50 mg/kg was used for all compounds for comparison purposes. Morphine, a positive control, was dissolved in saline and administered at a dose of 2.5 mg/kg by subcutaneous (s.c.) route. Mice received bis-vinyl selenides and morphine in a constant volume of 10 ml/kg of body weight. Appropriate vehicle-treated groups were also simultaneously assessed. All compounds were tested at different pretreatment times of 30 min, 1h and 2h.

Formalin-induced nociceptive behavior and edema: The formalin test was carried out as previously described.[21] Briefly, formalin was administered by intraplantar (i.pl.) injection (2.5%, 20 µl, v/v) into the mouse dorsal right hind paw. The mice were returned to the experimental cage and the time spent licking or biting the injected paw was recorded during the first 5 min (early phase) and 15–30 min (late phase) post-i.pl. Bis-vinyl selenides (50 mg/kg, i.g.) or vehicle (canola oil, p.o., 10 ml/kg) were administered 30 min, 1 h or 2 h before formalin administration. The time spent licking the injected paw, indicative of nociception, was timed with a chronometer. In order to assess if bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** inhibit edema associated with inflammatory pain, paw edema was measured by comparing the difference between the weight of the formalin-treated paw and the weight of the contralateral paw (non-treated paw). Animals were killed by cervical dislocation 30 min after formalin injection and both paws were cut at the ankle joint and weighed in an analytical balance.

Open-field test: With the purpose of excluding sedative or motor abnormality, spontaneous locomotor (number of segments crossed with the four paws) and exploratory activity (number of times reared on the hind limbs) behaviors of mice treated with bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** were assessed in the open-field test. The open-field was made of plywood and surrounded by walls 30 cm in height. The floor of the open field, 45 cm in length and 45 cm in width, was divided by masking tape markers into 9 squares (3 rows of 3). Each animal was placed individually at the center of the apparatus and the number of squares crossed with all paws (crossing) was counted in a 4 min session. The arena floor was cleaned between the trials and the test was carried out in a temperature and light controlled room.[22]

Acute toxicity: The possible acute toxicity of a single dose of bis-vinyl selenides **3a**, **3d**, **3f**, **3h** and **3t** was investigated. Bis-vinyl selenides at a dose of 50 mg/kg (i.g.) or vehicle were administered to mice. After 72 h, mice were anesthetized to blood collection by heart puncture; the blood was collected into heparin containing tubes. Blood samples were centrifuged at 2000×*g* for 10 min and plasma obtained for biochemical assays. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities, biochemical markers of acute hepatic damage, were determined. AST and ALT were expressed as UI/l. The renal function was investigated by determining plasma urea. Urea was expressed as mg/dl. All these parameters were determined by enzymatic colorimetric methods using commercial kits (Labtest Diagnostica, MG, Brazil).

Tissue preparation: Mice were killed and brains and livers were quickly removed and placed on ice. For δ-ALA-D assay brain and liver were homogenized in 50 mM Tris/HCl pH 7.5, 1:2 and 1:5 (w/v), respectively. For Na^+, K^+-ATPase assay brain was homogenized at 1:10 (w/v) in the same buffer. The homogenates were centrifuged at 2400 *x g* and 4000 *x* g for 10 min at 4 ^{0}C for δ-ALA-D and Na^+, K^+-ATPase assays, respectively, to yield a low-speed supernatant fraction (S_1). S1 freshly prepared was used for the enzymatic assays. The protein content in homogenates was quantified by the method of Bradford,[23] using bovine serum albumin (1 mg/ml) as a standard.

Na^+, K^+- ATPase activity: The reaction mixture for Na^+, K^+-ATPase activity assay contained 3 mM $MgCl_2$, 125 mM NaCl, 20 mM KCl, and 50 mM Tris–HCl, pH 7.4, in a final volume of 500 µl. An aliquot of 50 µl of S1 was added to the reaction mixture and pre-incubated at 37 ^{0}C for 10 min. The reaction was initiated by the addition of adenosine triphosphate (ATP) to a final concentration of 3.0 mM and incubated at 37 ^{0}C for 30 min. Controls were carried out under the same conditions with the

addition of 0.1 mM ouabain. Na^+, K^+- ATPase activity was calculated by the difference between the two assays. Released inorganic phosphate (Pi) was measured by the method of Fiske and Subbarow.[24]

δ-Aminolevulinate dehydratase (δ-ALA-D) activity: δ-ALA-D activity was determined according to the method described by Sassa[25] with some modifications. An aliquot of 200 µl of S_1 was pre-incubated for 10 min at 37 ^{0}C. Enzymatic reaction was initiated by adding the substrate (δ-aminolevulinic acid) to a final concentration of 2.2 mM in a medium containing 45 mM phosphate buffer, pH 6.8 and incubated for 1h (liver) and 3 h (brain) at 37 ^{0}C. The incubation was stopped by adding trichloroacetic acid solution 10% with 10 mM $HgCl_2$. The porphobilinogen, which is formed within a fixed time, is mixed with Ehrlich's reagent, and the color developed is measured photometrically (555 nm) against a blank.

Statistical Analysis: All experimental results are given as the mean ± SEM. The statistically significant difference between groups was calculated by means of one-way followed by the Duncan's test when appropriate. A value of $p \leq 0.05$ was considered to be significant.

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Notes and references

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