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Synthesis of isoxazolines by the electrophilic chalcogenation of β,γ-unsaturated oximes: fishing novel anti-inflammatory agents

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ABSTRACT

We describe herein a new strategy to prepare chalcogen-functionalized isoxazolines. The strategy involves the reaction of β,γ-unsaturated oximes with electrophilic selenium and tellurium species, affording 19 new selenium- and tellurium-containing isoxazolines in good yields after 1 hour at room temperature. The method was efficiently extended to the synthesis of 5 new (bis)isoxazoline ditellurides. One of the prepared compounds, 3-phenyl-5-((phenylselanyl)methyl)-isoxazoline, demonstrated better anti-inflammatory and anti-edematogenic effects than the reference drug Celecoxib.

INTRODUCTION

Heterocyclic compounds play an important role in several areas of chemical industry, including the development of agrochemicals and dyes.[1] Besides, 70% of marketed drugs, and 8 in 10 of the most consumed ones present at least one heterocyclic unity.[2] In this context, isoxazole and its derivatives are a valuable class of heterocyclic compounds, which are ranked among the top 25 nitrogen-containing frequently found motifs in drugs approved by the U. S. FDA.[3] Among them, Valdecoxib and Parecoxib are alluring examples of selective COX-2 inhibitors, used against inflammatory processes. In the mid-2000s, Valdecoxib was removed from the market due to adverse effects.[4] The close-related isoxazoline derivatives, in turn, are quite interesting compounds, showing a

variety of activities, including COX-2 inhibitory effects (like compound ISO-1),[5] cytotoxic activity towards HT-29, HeLa, MCF-7 and PC-3 cancer cells (like compound I),[6] and are present in a new class of the highly-active oomycete fungicide Zorvec® (Figure 1).[7]

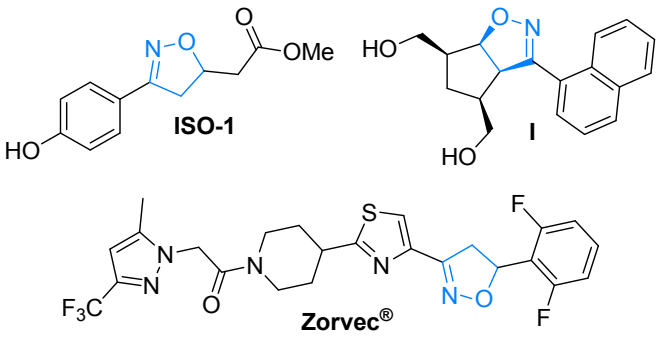
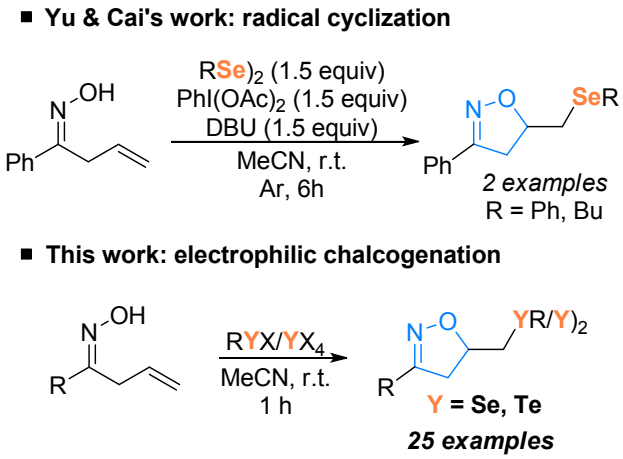


Figure 1. Biologically active isoxazolines.

The first general method for the selective synthesis of isoxazolines was developed by Quilico in 1950[8] and it involves the 1,3-cycloaddition of nitrile oxides to alkenes. During many years this was the method of choice to prepare differently substituted isoxazoline derivatives.[9] More recently, new methods do access isoxazolines have emerged, ranging from metal-catalyzed[10] to metal-promoted cyclization of oximes, using overstoichiometric amounts of transition metals.[11] The radical cyclization of alkenyl oximes using a diversity of radical initiators was also explored[12] and the fluoro- and iodo-promoted cyclizations of alkenyl oximes to prepare fluoro-[13] and iodo-isoxazolines[14] were recently developed.

Organochalcogen compounds are widely known to be versatile intermediates in organic synthesis.[15] For instance, vinyl selenides were employed in 1,3-cycloaddition reactions to construct selenium-containing isoxazolines, which were further converted to isoxazole derivatives through selenoxide elimination pathways.[16] Recently, Yu and Cai[17] have disclosed a radical cyclization/sulfanylation and selenylation of β,γ-unsaturated oximes using iodine hypervalent species (PIDA) in the presence of base to access chalcogen-containing isoxazolines in moderate to good yields (Scheme 1).



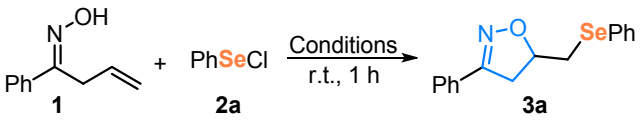
Scheme 1. Synthetic methods to chalcogen-containing isoxazolines.

Despite the biological importance of isoxazolines and organochalcogen compounds,[5,18] there are no general protocols to prepare selenium and tellurium-functionalized isoxazolines. This causes a limitation in the study of the biological activities of such molecular hybrids. Thus, based on the efficiency of chalcogen electrophilic species to construct new C-Y bonds (Y = S, Se or Te) by the reaction with electron-rich substrates,[19] we present herein a general electrophilic cyclization of β,γ-unsaturated oximes to access chalcogen-containing isoxazolines, through a simple, fast and open-air protocol. The methodology was extended to unprecedented tellurium-containing isoxazolines.

RESULTS AND DISCUSSION

(*E*)-1-Phenylbut-3-en-1-one oxime **1a** and PhSeCl **2a** were chosen as the standard substrates to determine the best reaction conditions to prepare the respective isoxazoline **3a** (Table 1). We started by determining the best solvent for the reaction at room temperature under argon atmosphere (Table 1, entries 1-6). The desired product **3a** was accessed in 82% yield using MeCN as the solvent (Table 1, entry 1). Solvents like hexane, DMSO, γ-valerolactone and EtOAc did not present better results and the expected product **3a** was obtained in a yield range of 71-80% (Table 1, entries 2 to 5). In addition, based on previous works in the use of deep eutectic solvents (DES) in the synthesis of organochalcogen compounds,[20] the choline chloride (ChCl):urea-based DES was tested as the reaction medium; however, the isoxazoline **3a** was obtained in only 49% yield (Table 1, entry 6).

Table 1: Optimization of the reaction conditions.[a]



Entry	Solvent	Yield (%)[b]
1	MeCN	82
2	hexanes	74
3[c]	DMSO	72
4	γ-valerolactone	80
5	EtOAc	71
6[d]	1 ChCl: 2 Urea	49
7[c]	MeCN	74
8[d]	MeCN	81
9[d,e]	MeCN	82

[a] In a test tube saturated with argon was added β,γ-unsaturated oxime **1a** (0.5 mmol), solvent (0.5 mL) and PhSeCl **2a** (0.6 mmol). The reaction was carried out at room temperature for 1 h. [b] The yields refer to the isolated product obtained by column chromatography, except when noted. [c] PhSeBr was used instead PhSeCl **2a**. [d] The reaction was carried out in an open-air flask. [e] The crude reaction was quenched with a saturated K_2CO_3 and extracted with EtOAc. After evaporation of the solvent, the resulting solid was rinsed with hexanes and dried under vacuum, to yield pure **3a**.

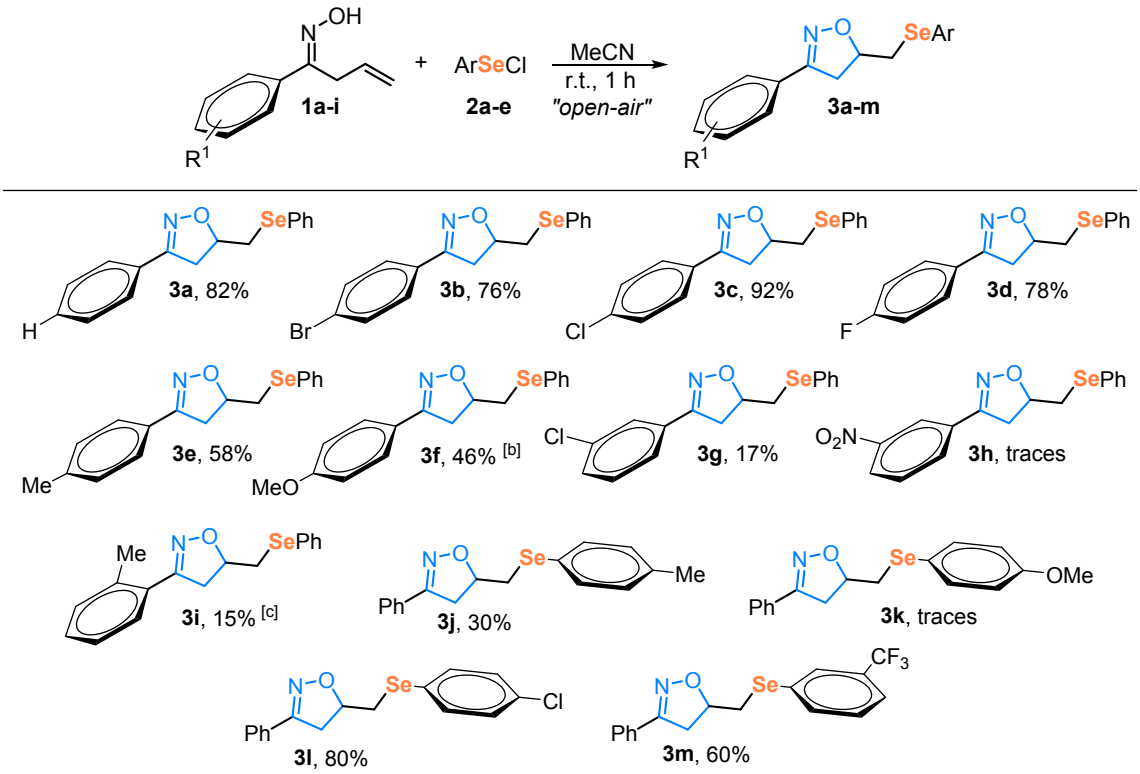
Following, the reaction was performed using PhSeBr as the selenium electrophilic source instead PhSeCl, giving the product **3a** in 74% yield (Table 1, entry 7). When the reaction was carried out in an open-air flask, **3a** was obtained in 81% yield, showing that the reaction is not sensible to air atmosphere (Table 1, entry 8).

It is worth to mention that using hexane or acetonitrile as solvent caused the precipitation of the product **3a** that, after a simple filtration, could be obtained in 40% yield. However, the yield of **3a** was increased to 82% after the crude reaction was quenched with a saturated solution of K_2CO_3 and extracted with EtOAc. After evaporation of the solvent, the resulting solid was rinsed with hexanes and dried under vacuum (Table 1, entry 9).

Based on these results, the best reaction condition was defined as stirring a mixture of unsaturated oxime **1a** and PhSeCl **2a** (1.2 equiv) in MeCN in an open-air vessel for 1 h at room temperature. Additionally, purification of the product was performed just by rinsing it with hexanes after extraction.

With the best reaction conditions in hand, a study on the reaction scope was performed by varying the substituents in the aromatic ring of the β,γ-unsaturated oxime **1** in the reaction with PhSeCl **2a** (Table 2, **1b-i**). As shown in Table 2, β,γ-unsaturated oximes bearing halogen groups in the *para*-position were good substrates for the reaction, affording the respective products **3b** (R^1 = 4-Br), **3c** (R^1 = 4-Cl) and **3d** (R^1 = 4-F) in 76%, 92% and 78% yield. On the other hand, the electron-rich β,γ-unsaturated oximes **1e** (R^1 = 4-Me) and **1f** (R^1 = 4-OMe) were less reactive substrates, affording the expected products **3e** and **3f** in 58% and 46% yield, respectively. Some limitations were found by employing *meta*- and *ortho*-substituted β,γ-unsaturated oximes, accessing the products **3g** (R^1 = 3-Cl) and **3i** (R^1 = 2-Me) in 17% and 15% yield, respectively. Unfortunately, the *meta*-NO_2 substituted oxime **1h** was not a suitable substrate to our protocol, and only trace amounts of product **3h** were detected (Table 2).

Table 2. Scope for selenium-containing isoxazolines **3**.[a]



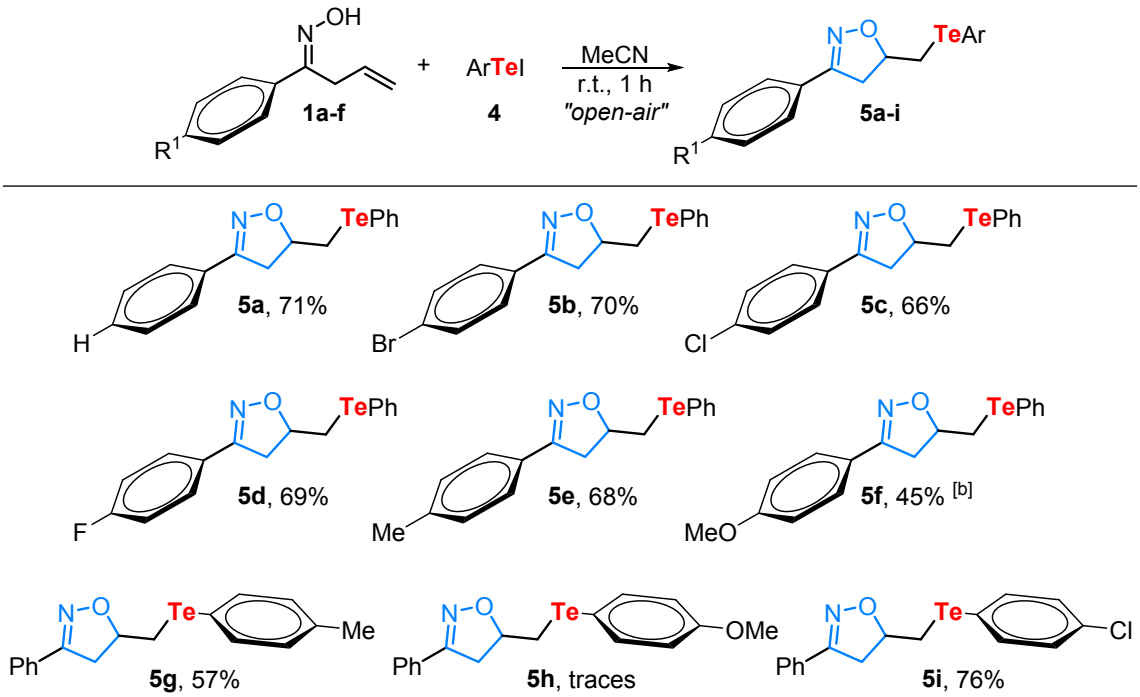
[a] In a test tube was added β,γ-unsaturated oxime **1** (0.5 mmol), MeCN (0.5 mL) and ArSeCl **2** (0.6 mmol). The reaction was carried out at room temperature for 1 h. Isolated yields were obtained

by rinsing the crude reaction mixture with hexanes solvent. [b] The product was purified by column chromatography (1:9 mixture of AcOEt/hexanes as eluent).[c] Obtained in a mixture 2:1 with the respective oxime.

Following, the reactivity of differently substituted arylselenyl chlorides **2** was evaluated in the reaction with (*E*)-1-phenylbut-3-en-1-one oxime **1a** under the optimal conditions. It was observed that the presence of electron-donor groups in the *para*-position of the benzene ring, like in **2b** (Ar = 4-Me-C_6H_4) and **2c** (Ar = 4-MeO-C_6H_4) reduced the reactivity, and the respective products **3j** and **3k** were obtained in 30% yield and trace amounts, respectively. These results can be explained in part by the lower electrophilicity of the selenium atom in these species and by the stabilization of the *in situ* formed seleniranium intermediate, once in both cases the total consumption of oxime **1a** was observed (see Scheme 2 for a plausible mechanism). On the other hand, the presence of electron-withdrawing groups positively affects the reaction and products **3l** (Ar = 4-Cl-C_6H_4) and **3m** (Ar = 3-CF_3-C_6H_4) were obtained in 80% and in 60% yield (Table 2). These results demonstrate that the electron-withdrawing effect enhances the electrophilicity of the selenium atom, facilitating the reaction.

Based on the positive results obtained in the synthesis of the selenium-containing isoxazolines **3** (Table 2), we were encouraged to expand the reaction scope to tellurium-containing isoxazolines **5** (Table 3). For this purpose, since tellanyl halides are not bench stable, aryltellanyl iodides **4** were prepared *in situ* in a solution of THF, and the reaction was subsequently performed in the presence of β,γ-unsaturated oximes **1**.[21]

Table 3. Scope for tellurium-containing isoxazolines **5**.[a]



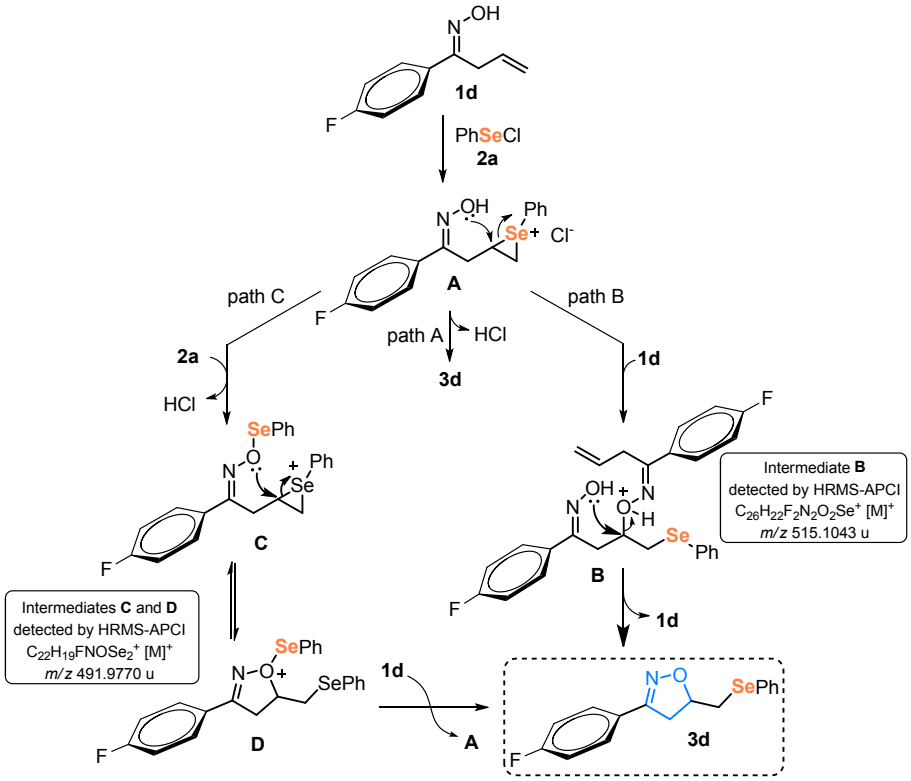
[a] The ArTeI **4** (1.0 mL, 1*M* in THF) was prepared immediately before the use, in a separate vessel, from a mixture of ArTeTeAr (0.5 mmol) and I_2 (0.5 mmol) in THF (1.0 mL). This solution was added to a solution of β,γ-unsaturated oxime **1** (0.5 mmol) in MeCN (0.5 mL), and the resulting mixture was stirred at room temperature for 1 h. The crude reaction was quenched (sat. K_2CO_3) and extracted with EtOAc. After evaporation of the solvent, the resulting solid was rinsed with hexanes. [b] Yield after rinsing the crude with a 1:9 mixture of AcOEt/hexanes.

The yields of the tellurium-containing isoxazolines were slightly lower than those observed for the selenium-analogues **3**. Thus, neutral (*E*)-1-phenylbut-3-en-1-one oxime **1a** reacted smoothly with phenyltellanyl iodide **4a** (Ar = C_6H_5) to give the product **5a** in 71% yield (Table 3). Unlike the observed in the synthesis of selenium- isoxazolines **3b-d** (Table 2), halogen-substituted β,γ-unsaturated oximes **1b-d** (R^1 = Br, Cl and F) presented a similar reactivity in the reaction with PhTeI **4a**, giving the respective products **5b-d** in 70%, 66% and 69% yield, similar to the unsubstituted analogue **4a** (Table 3). The presence of electron-donor groups negatively influences the reaction, as observed for the selenium analogues, and *para*-methyl-substituted oxime **1e** (R^1 = Me) reacted with **4a** to give **5e** in 68% yield, while oxime **1e** (R^1 = OMe) afforded the respective product **5f** in only 45% yield (Table 3).

Regarding the ArTeI **4** counterpart, the reactivity was less sensible to electronic effects, except in the case when the strong electron-donor methoxy group was present (**4h**, Ar = 4-$OMeC_6H_4$), that completely inhibited the reaction with oxime **1a**, with only trace amounts of **5h** being detected (Table 3). The

presence of *para*-chlorine substituent (**4i**, Ar = 4-Cl-C_6H_4) increased the reactivity, and product **5i** was obtained in 76% yield. In an attempt to extend the methodology, PhSCl and ArS-succinimides (Ar = Ph, *p*-$MeOC_6H_4$ and *p*-ClC_6H_4) were used as electrophiles in the reaction with oxime **1a**. However, the expected sulfur-containing isoxazolines were not formed under the optimal conditions.

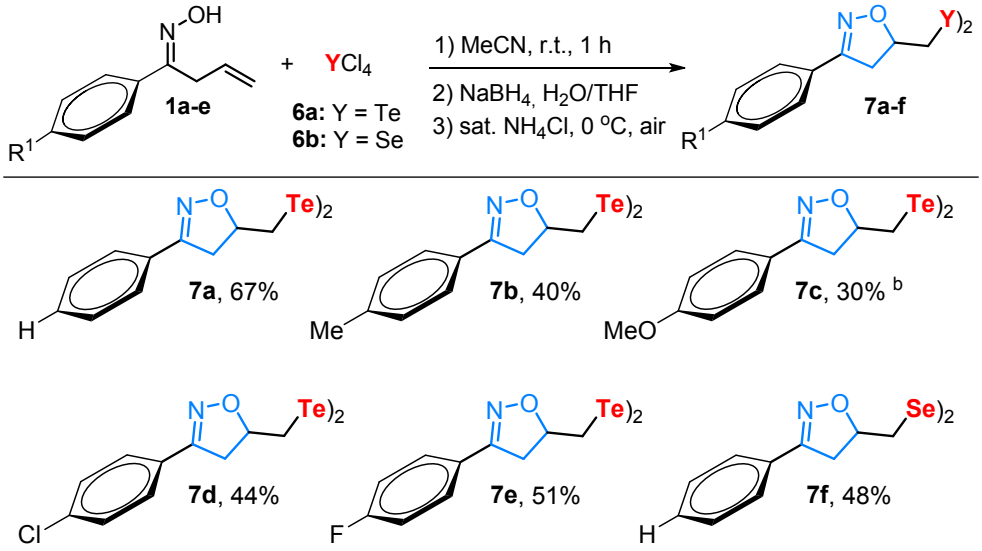
Based on the literature reports,[23] HRMS data and in our observations, a plausible mechanism for the formation of the chalcogen-containing isoxasoline **3d** is proposed in Scheme 2. Initially, the β,γ-unsaturated oxime **1d** reacts with the electrophilic selenium species **2a**, giving the seleniranium cation intermediate **A**. From the intermediate **A**, the reaction can follow three different pathways to access the product **3d**. I the path A, the seleniranium species **A** is directly converted to **3d** through the intramolecular nucleophilic attack by the oxygen and elimination of HCl. Alternatively, the seleniranium **A** undergoes a ring-opening reaction by the intermolecular attack by oxime **1d**, giving the oxonium intermediate **B** (detected by HRMS; Figures S1 and S2). Finally, an intramolecular annulation occurs, releasing oxime **1d** as leaving group, and giving the desired product **3d** (Scheme 2, path B). A third pathway involves the attack of the seleniranium specie **A** to a second PhSeCl **2a** to give the intermediate **C**, which is easily converted to **D** (detected by HRMS; Figures S1 and S3) by an intramolecular cyclization. Finally, another unit of β,γ-unsaturated oxime **1d** reacts with the intermediate **D** to give the desired product **3d** and releasing the key intermediate **A** for a new reaction (Scheme 2, path C).



Scheme 2. Mechanism proposal for the electrophilic chalcogenation.

Inspired by the results above, we envisioned to accomplish the synthesis of diisoxazoline ditellurides **7**, by using $TeCl_4$ **6a** as electrophile in the annulation of the β,γ-unsaturated oximes **1**, followed by a sequential reduction-oxidation step, as previously described by Comasseto et al.[22] To our delight, the reaction between (*E*)-1-phenylbut-3-en-1-one oxime **1a** and $TeCl_4$ **6a** under our optimal conditions (r.t., 1 h), followed by the Comasseto's reaction, gave the expected diisoxazoline ditelluride **7a** in an overall 67% yield (Table 4).

Table 4. Scope for diisoxazoline dichalcogenides **7**.[a]

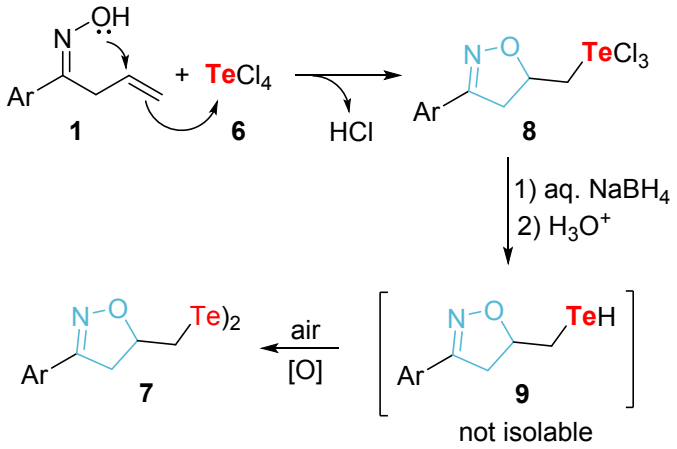


[a] In a test tube was added β,γ-unsaturated oxime **1a** (0.5 mmol), 0.5 mL of MeCN and $TeCl_4$ **6a** (0.6 mmol). The reaction mixture was stirred at room temperature for 1 h. Then, 3 mL of THF was added, followed by the dropwise addition of an aqueous solution of $NaBH_4$ (0.75 M) at 0 °C. The resulting mixture was stirred for additional 20 min and quenched (sat. NH_4Cl) under air atmosphere.[22] The solvent was removed under reduced pressure and the resulting solid was rinsed with hexanes. [b] Yield after rinsing the crude with a 3:7 mixture ratio of AcOEt/hexanes.

The reaction was extended to *para*-substituted β,γ-unsaturated oximes **1** bearing electron-releasing and electron-withdrawing groups. In all cases, the expected ditellurides were obtained in slightly lower yields compared to the unsubstituted oxime **1a**. There is no a clear effect caused by the substituents and products **7b** (R^1 = 4-Me), **7d** (R^1 = 4-Cl) and **7e** (R^1 = 4-F) were obtained in 40%, 44% and 51% yield, respectively. The strong electron-donating methoxy group caused an even more decreasing in the reaction yield, affording the respective product **7c** (R^1 = 4-MeO) in only 30% yield. In order to expand the scope of this approach to the diselenide analogue, $SeCl_4$ **6b** was satisfactorily employed as an electrophile under the optimal conditions, affording the expected diisoxazoline diselenide **7f** in 48% yield (Table 4).

Based in the literature[22] and in our own findings, a plausible mechanism for the formation of ditellurides **7a-e** (and by extension to diselenide **7f**) involves the initial formation of the tellurium trichloride isoxazoline **8**, after attack by the oxime **1** to $TeCl_4$ **6**. Following, the Te(IV) trichloride **8** is reduced to the unstable tellurol **9**, that rapidly is oxidized by air to the respective ditelluride **7** (Scheme 3). The formation of the tellurium trichloride isoxazoline **8** as an intermediate was

confirmed by ^{125}Te NMR and HRMS analysis (Figure S4). The registered ^{125}Te NMR of tellurium tetrachloride **6** (in CD_3CN) showed one signal at δ 1707 ppm. After the addition of the unsaturated oxime **1**, almost instantaneous consumption of $TeCl_4$ and the appearance of a new signal at δ 1248 ppm are observed. Using HRMS analysis it was possible to confirm that the signal observed in the ^{125}Te NMR is in fact the tellurium trichloride **8**.



Scheme 3. Mechanism proposal for the formation of ditellurides **7**.

As mentioned before, in the introduction, a number of biological activities are attributed to the isoxazoline core and to organoselenium compounds. The similarity of the chalcogen-containing isoxazolines **3** and **5** with ISO-1, a potent anti-inflammatory agent,[5] we wonder if the new prepared compounds could present such bioactivity. To test our hypothesis, 3-phenyl-5-[(phenylselanyl)methyl]-isoxazoline **3a** (PPSEI45) was chosen and evaluated for its antiedematogenic and anti-inflammatory effects in mice (Figs. 2 and 3). Here, ear edema was induced by croton-oil application, as described elsewhere.[24-25]

Importantly, treatment with PPSEI45, at dose of 50 mg/kg, or Celecoxib, only at dose of 100 mg/kg, reduced the ear edema induced by croton oil, presenting anti-edematogenic effect (ANOVA: $F(4, 25) = 93.17$, $p < 0.0001$). The inhibition of ear edema by PPSEI45 (50 mg/kg) was 51%, while by Celecoxib (100 mg/kg) was 36% (Figure 2).

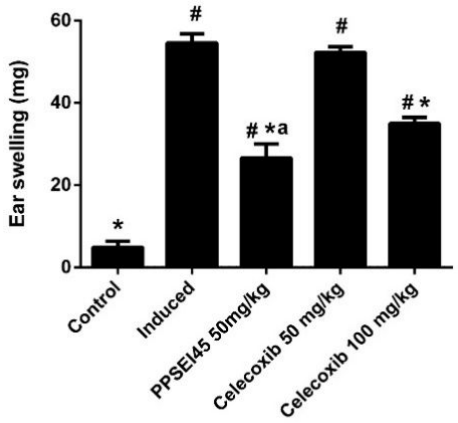


Figure 2. Ear swelling treatment with PPSEI45 (**3a**) and Celecoxib.

In order to extend our knowledge about the anti-inflammatory potential of PPSEI45, the MPO activity was determined. An elevated level of MPO is considered as an indicator of neutrophil activation under the influence of pro-oxidative and pro-inflammatory conditions.[26-30] As demonstrated in Figure 3, the data analysis revealed that croton oil significantly increased the MPO activity in ears of mice, when compared to the control group. Here, pre-treatment with PPSEI45 (**3a**, 50 mg/kg) or Celecoxib (100 mg/kg) protected against the increase on the MPO activity in mouse ear induced by croton oil (ANOVA: $F(4, 25) = 7.313$, $p < 0.001$). PPSEI45 (50 mg/kg) and Celecoxib (100 mg/kg) reduced around 74% and 79% of the MPO activity, respectively. This result suggests that PPSEI45 suppressed the severity of croton oil via inhibition of MPO activity.

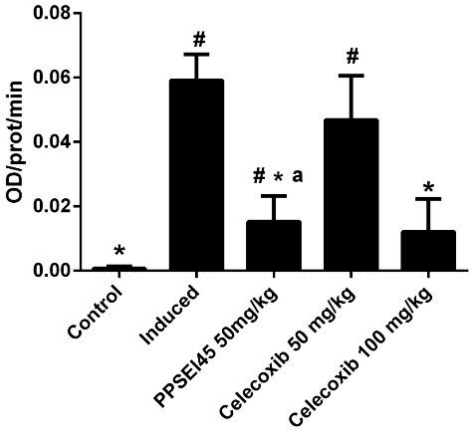


Figure 3. MPO activity for PEPSEI45 (**3a**) and Celecoxib.

Of particular importance is that the single oral administration of PPSEI45 (300 mg/kg) did not cause death of animals. The alanine aminotransferase ALT

(df = 0.4070; t = 2, p > 0.05) and aspartate aminotransferase AST (df = 2; t = 1.016, p > 0.05) activities, as well as the levels of urea (df = 2; t = 1.110, p > 0.05) remained unaltered after treatment with PPSEI45, when compared to those mice of the control group (Table S1). An increasing of plasmatic AST activity is a marker of cardiac damage,[31] which is one of the adverse effects of coxibs.[32] Additionally, the ability of organoselenium compounds to oxidize sulfhydryl groups from biological molecules can be involved both in their pharmacological and/or toxicological effects. δ-ALA-D is a sulfhydryl-containing enzyme that is extremely sensitive to oxidizing agents.[33] A single oral administration of compound PPSEI45, at dose 300mg/kg, did not alter the enzyme activity in samples of brain, kidney or liver (Table S2).

The findings of the present study indicated, for the first time, that PPSEI45, an organoselenium compound possessing structural elements of Valdecoxib, exerts anti-inflammatory action in mice. Importantly, PPSEI45 (**3a**) reduced ear edema formation and protected against the increase on the myeloperoxidase (MPO) activity in mouse ear. Indeed, our results are consistent with the fact that PPSEI45 was more effective than Celecoxib, a reference drug, in this model of acute inflammation.

CONCLUSIONS

In conclusion, we have developed a new and general method to prepare chalcogen-containing (Se and Te) isoxazolines. A simple and mild electrophilic cyclization of β,γ-unsaturated oximes allowed the preparation of 25 isoxazolines, including unprecedented tellurium-functionalized ones and diisoxazoline ditellurides. HRMS and NMR analysis afforded information on the reaction mechanism, showing the involvement of cationic species. One of the prepared compounds, 3-phenyl-5-((phenylselanyl)methyl)-isoxazoline, exerts anti-inflammatory effect in an applicable experimental model and at lower doses than the reference drug (Celecoxib).

EXPERIMENTAL SECTION

General Information

The reactions were monitored by TLC carried out on pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV_{254} by using UV light as visualization agent and the mixture of 5% vanillin in 10% H_2SO_4 under heating conditions as developing agent. Merck silica gel (particle size 63-200 μm) was used to flash chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker Nuclear Ascend 400 spectrometer. The spectra were recorded in $CDCl_3$ and DMSO-d_6 solutions. The chemical shifts are reported in ppm, referenced to tetramethysilane (TMS) as the external reference. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of doublet of doublet of doublets (dddd) and multiplet (m). Coupling constants (*J*) are reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or DMSO-d_6. Electrospray ionization (ESI-QTOF) high resolution mass spectrometry (EMAR) analyzes were performed on a Bruker Daltonics micrQTOF-Q II instrument in positive or negative modes. The samples were solubilized in HPLC grade acetonitrile and injected into the APCI source via a syringe at a flow rate of 5.0 μL min^{-1}. The following instrument parameters were applied: the capillary and cone voltages were adjusted to +3500 V and -500 V, respectively, with a desolvation temperature of 180 °C. Compass 1.3 software for micrOTOF-Q II (Bruker Daltonics, USA) was used for data acquisition and processing. Data were collected in the m/z range of 50-1200 at the rate of two sweeps per second. The starting oximes **1a-l** were prepared as previously described in the literature.[10a,35-37]

General Procedure for the synthesis aryl selanyl chlorides 2: Reactions using diphenyl diselenide were performed in a 5 mmol scale; the other reactions were carried out in a 2.5 mmol scale. In a 50 mL round-bottomed flask saturated with argon, containing a solution of the diaryl diselenide (5 mmol) in DCM (10.0 mL) at 0 ºC, it was added dropwise 50% of a solution of sulfuryl chloride (0.67 g, 5.0 mmol) in DCM (10.0 mL) under stirring. Following, the remaining solution of

SO_2Cl_2 in the addition funnel was diluted with 10.0 mL of DCM and the resulting solution was added dropwise under vigorous stirring at 0 ºC. The system was stirred for additional 1 h at room temperature. Finally, the obtained mixture was concentrated under reduced pressure to give an orange solid, which was used as substrate without further purification.[38]

General Procedure for the synthesis of selenium-containing isoxazolines 3: In a round-bottomed flask were added the β,γ-unsaturated oxime **1** (0.5 mmol), MeCN (0.5 mL) and ArSeCl **2** (0.6 mmol). The resulting mixture was stirred at room temperature for 1 h. After reaction completion, a saturated solution of K_2CO_3 (2.0 mL) was added carefully and the product was extracted with ethyl acetate (4x 2.0 mL). The solvent was removed under reduced pressure and the resulting solid was rinsed with hexanes (8x 1.0 mL). Following, the solid was dried in a vacuum pump to access the product **3** in the tabulated yields (Table 2). Product **3f** was isolated by column chromatography (a 9:1 mixture of hexanes/AcOEt was used as eluent).

3-Phenyl-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3a). Yield: 130 mg (82%); white solid; mp 94-96 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.6 - 7.62 (m, 2H); 7.57 - 7.55 (m, 2H); 7.41 - 7.39 (m, 3H); 7.29 - 7.26 (m, 3H); 4.91 (dddd, *J* = 10.3, 9.1, 6.9, 4.5 Hz, 1H); 3.44 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.31 (dd, *J* = 12.6, 4.5 Hz, 1H); 3.20 (dd, *J* = 16.8, 6.9 Hz, 1H); 3.00 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 156.3, 133.4, 130.3, 129.6, 129.5, 128.8, 127.7, 126.8, 80.5, 40.2, 31.5 (d, $^1J_{C\text{-}Se}$ = 68.5 Hz). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{16}NOSe$ 318.0392; Found 318.0391.

3-(4-Bromophenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3b). Yield: 150 mg (76%); white solid; mp 94-96 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.56 - 7.54 (m, 2H); 7.53 - 7.47 (m, 4H); 7.29 - 7.28 (m, 3H); 4.95 - 4.87 (m, 1H); 3.40 (dd, J = 16.8, 10.3 Hz, 1H); 3.30 (dd, J = 12.6, 4.5 Hz, 1H); 3.16 (dd, J = 16.8, 7.0 Hz, 1H); 2.99 (dd, J = 12.6, 9.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 155.5, 133.4, 132.0, 129.4, 128.7, 128.5, 128.2, 127.7, 124.5, 80.8, 39.9, 31.4 (d, $^1J_{C\text{-}Se}$ = 68.6 Hz). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{15}BrNOSe$ 394.9494; Found 394.9500.

3-(4-Chlorophenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3c). Yield: 161 mg (92%); white solid; mp 58-60 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.79 - 7.76 (m, 2H); 7.55 - 7.51 (m, 2H); 7.38 - 7.30 (m, 3H); 7.26 - 7.20 (m, 2H); 4.99 (dddd, *J* = 10.2, 9.1, 7.2, 4.4 Hz, 1H); 3.41 (dd, *J* = 16.8, 10.2 Hz, 1H); 3.29 (dd, *J* = 12.1, 4.5 Hz, 1H); 3.09 - 3.01 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ (ppm) 155.3, 136.1, 133.3, 129.4, 129.0, 128.6, 127.9, 127.9, 127.6, 80.7, 39.9, 31.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}ClNOSe$ 351.9999; Found 351.9998.

3-(4-Fluorophenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3d). Yield: 130 mg (78%); yellow solid; mp 72-74 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.63 - 7.59 (m, 2H); 7.56 - 7.54 (m, 2H); 7.29 - 7.27 (m, 3H); 7.10 - 7.05 (m, 2H); 4.90 (dddd, *J* = 10.3, 9.0, 6.9, 4.5 Hz, 1H); 3.41 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.30 (dd, *J* = 12.6, 4.5 Hz, 1H); 3.17 (dd, *J* = 16.8, 6.9 Hz, 1H); 2.99 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 163.9 (d, ^{1}J = 250.7 Hz), 155.3, 133.3, 129.4, 128.7 (d, ^{3}J = 8.4 Hz), 127.8, 127.7, 125.8 (d, ^{4}J = 3.4 Hz), 116.0 (d, ^{2}J = 22.0 Hz), 80.6, 40.2, 31.5 (d, $^{1}J_{C\text{-}Se}$ = 68.3 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) 112.38 (tt, *J* = 8.3, 5.2 Hz). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ (ppm) 259.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}FNOSe$ 336.0298; Found 336.0298.

5-[(Phenylselanyl)methyl]-3-(*p*-tolyl)-4,5-dihydroisoxazole (3e). Yield: 96 mg (58%); light red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.56 - 7.54 (m, 1H); 7.52 (d, J = 8.3 Hz, 2H); 7.28 - 7.25 (m, 3H); 7.19 (d, J = 8.0 Hz, 2H); 4.87 (dddd, J = 10.3, 9.1, 6.8, 4.6 Hz, 1H); 3.41 (dd, J = 16.8, 10.2 Hz, 1H); 3.30 (dd, J = 12.5, 4.5 Hz, 1H); 3.17 (dd, J = 16.8, 6.8 Hz, 1H); 2.98 (dd, J = 12.5, 9.0 Hz, 1H); 2.37 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.3, 140.5, 133.3, 129.5, 129.4, 128.9, 127.6, 126.8, 126.7, 80.3, 40.3, 31.5 (d, $^{1}J_{C\text{-}Se}$ = 68.5 Hz), 21.6. ^{77}Se NMR ($CDCl_3$, 76 MHz) δ (ppm) 258.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NOSe$ 332.0549; Found 332.0550.

3-(4-Methoxyphenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3f). Yield: 79 mg (46%); yellow solid; mp 74-76 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.57 - 7.53 (m, 4H); 7.28 - 7.26 (m, 3H); 6.91 - 6.88 (m, 2H); 4.89 - 4.82 (m, 1H); 3.82 (s, 3H); 3.40 (dd, *J* = 16.7, 10.2 Hz, 1H); 3.29 (dd, *J* = 12.6, 4.5 Hz, 1H); 3.16 (dd, *J* = 16.7, 6.8 Hz, 1H); 2.97 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C{^{1}H} NMR

($CDCl_3$, 100 MHz) δ (ppm) 161.1, 155.9, 133.2, 129.4, 128.9, 128.3, 127.6, 122.0, 114.2, 80.1, 55.4, 40.4, 31.5 (d, $^1J_{C\text{-}Se}$ = 67.9 Hz). ^{77}Se NMR ($CDCl_3$, 76 MHz) δ (ppm) 259.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2Se$ 348.0497; Found 348.0498.

3-(3-Chlorophenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3g). Yield: 25.0 mg (15%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.65 - 7.45 (m, 2H), 7.39 - 7.26 (m, 7H), 4.92 (dddd, *J* = 10.3, 9.0, 6.9, 4.5 Hz, 1H), 3.41 (dd, *J* = 16.9, 10.3 Hz, 1H), 3.31 (dd, *J* = 12.6, 4.5 Hz, 1H), 3.17 (dd, *J* = 16.8, 6.9 Hz, 1H), 2.99 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 155.1, 137.4, 134.7, 133.2, 130.1, 129.9, 129.3, 127.6, 126.7, 124.7, 80.7, 39.7, 31.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}ClNOSe$ 351.9827; Found 351.9825.

5-[(Phenylselanyl)methyl]-3-(*o*-tolyl)-4,5-dihydroisoxazole (3i). Yield: 28 mg (17%), yellowish oil. ^{1}H NMR (CDCl3, 400 MHz) δ (ppm) 7.57 - 7.55 (m, 2H), 7.28 - 7.19 (m, 3H), 4.85 (dddd, *J* = 10.2, 8.8, 6.8, 4.6 Hz, 1H), 3.48 (dd, *J* = 16.7, 10.2 Hz, 1H), 3.30 (dd, *J* = 12.5, 4.6 Hz, 1H), 3.23 (dd, *J* = 16.7, 6.8 Hz, 1H), 3.01 (dd, *J* = 12.6, 8.8 Hz, 1H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (CDCl3 , 100 MHz) δ (ppm) 157.2, 138.1, 133.3, 131.7, 129.5, 129.4, 129.0, 128.6, 127.6, 125.9, 79.4, 42.7, 31.6 (d, 1J C-Se = 68.1 Hz), 23.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NOSe$ 332.0371; Found 332.0374.

3-Phenyl-5-[(*p*-tolylselanyl)methyl]-4,5-dihydroisoxazole (3j). Yield: 49 mg (30%); white solid; mp 83-85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.65 - 7.63 (m, 2H); 7.48 - 7.45 (m, 2H); 7.41 - 7.38 (m, 3H); 7.11 - 7.09 (m, 2H); 4.92 - 4.84 (m, 1H); 3.43 (dd, *J* = 16.8, 10.2 Hz, 1H); 3.27 (dd, *J* = 12.5, 4.5 Hz, 1H); 3.20 (dd, *J* = 16.9, 6.9 Hz, 1H); 2.94 (dd, *J* = 12.5, 9.2 Hz, 1H); 2.34 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.3, 137.8, 133.8, 130.2, 130.2, 129.5, 128.8, 126.8, 124.9 (d, $^1J_{C\text{-}Se}$ = 101.2 Hz), 80.5, 40.1, 31.7 (d, $^1J_{C\text{-}Se}$ = 68.3 Hz), 21.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NOSe$ 332.0549; Found 332.0546.

5-{[(4-Chlorophenyl)selanyl]methyl}-3-phenyl-4,5-dihydroisoxazole (3l). Yield: 140 mg (80%); brown solid; mp 65-67 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.65 - 7.62 (m, 2H); 7.49 (d, *J* = 8.5 Hz, 2H); 7.42 - 7.38 (m, 3H); 7.25 (d,

J = 8.6 Hz, 2H); 4.90 (dddd, *J* = 10.3, 8.6, 6.8, 4.7 Hz, 1H); 3.45 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.27 (dd, *J* = 12.7, 4.7 Hz, 1H); 3.19 (dd, *J* = 16.8, 6.9 Hz, 1H); 3.01 (dd, *J* = 12.6, 8.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) *δ* (ppm) 156.3, 134.7, 134.0, 133.4, 130.4, 129.4, 128.9, 127.1, 126.8, 80.2, 40.3, 32.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}ClNOSe$ 351.9999; Found 352.0001.

3-Phenyl-5-{[(3-(trifluoromethyl)phenyl)selanyl]methyl}-4,5-dihydroisoxazole (3m). Yield: 115 mg (60%); white solid; mp 89-91 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.80 (s, 1H); 7.74 (d, *J* = 7.8 Hz, 1H); 7.66 - 7.63 (m, 1H); 7.53 (d, *J* = 7.8 Hz, 1H); 7.42 - 7.39 (m, 4H); 4.94 (dddd, *J* = 10.3, 8.2, 6.8, 4.8 Hz, 1H); 3.48 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.34 (dd, *J* = 12.7, 4.8 Hz, 1H); 3.21 (dd, *J* = 16.8, 6.8 Hz, 1H); 3.10 (dd, *J* = 12.6, 8.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 156.3, 136.2 (q, ^{4}J = 1.5 Hz), 131.7 (q, ^{2}J = 32.4 Hz), 130.4, 130.3, 129.75, 129.65 (q, ^{3}J = 3.8 Hz), 129.4, 128.9, 126.8, 124.4 (q, ^{3}J = 3.8 Hz), 123.7 (d, ^{1}J = 272.9 Hz), 80.1, 40.4, 31.9. ^{19}F NMR ($CDCl_3$, 376 MHz) *δ* (ppm) 62.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}F_3NOSe$ 386.0266; Found 386.0281.

General Procedure for the synthesis of tellurium-containing isoxazolines 5: The electrophilic species ArTeI was prepared immediately before the use by stirring a mixture of ArTeTeAr (0.5 mmol) and I_2 (0.127 g, 0.5 mmol) in THF (1.0 mL) for 2 h at room temperature.[21] The solution of ArTeI (1.0 mL, 1*M* in THF) was added to the β,γ-unsaturated oxime **1** (0.5 mmol), in MeCN (0.5 mL) and the resulting mixture was stirred for 1 h at room temperature. The extraction and purification were performed as described for the products **3**, above to afford products **5** in the tabled yields (Table 3). Product **5f** was isolated by rinsing the solid with a 9:1 mixture of hexanes/AcOEt.

3-Phenyl-5-[(phenyltellanyl)methyl]-4,5-dihydroisoxazole (5a). Yield: 130 mg (71%); red solid; mp 38-40 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* (ppm) 7.80 - 7.78 (m, 2H); 7.62 - 7.60 (m, 2H); 7.40 - 7.37 (m, 3H); 7.34 - 7.30 (m, 1H); 7.25 - 7.21 (m, 2H); 5.03 - 4.95 (m, 1H); 3.45 (dd, J = 16.8, 10.2 Hz, 1H); 3.30 (dd, J = 12.1, 4.4 Hz, 1H); 3.12 - 3.03 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) *δ* (ppm) 156.2, 139.0, 130.2, 129.6, 129.6, 128.8, 128.3, 126.8, 110.6, 82.1, 41.3, 13.3 (d, $^{1}J_{C\text{-}Te}$ = 173.3 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}NOTe$ 368.0289; Found 368.0287.

3-(4-Bromophenyl)-5-[(phenyltellanyl)methyl]-4,5-dihydroisoxazole (5b). Yield: 155 mg (70%); light orange solid; mp 89 - 91 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.78 - 7.76 (m, 2H); 7.50 (d, J = 8.7 Hz, 2H); 7.44 (d, J = 8.7 Hz, 2H); 7.33 - 7.29 (m, 1H); 7.23 – 7.19 (m, 2H); 4.98 (dddd, J = 10.3, 9.0, 7.3, 4.5 Hz, 1H); 3.39 (dd, J = 16.7, 10.2 Hz, 1H); 3.28 (dd, J = 12.2, 4.5 Hz, 1H); 3.03 - 3.00 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 155.4, 139.0, 132.0, 129.5, 128.5, 128.3, 128.2, 124.4, 110.6, 82.4, 41.0, 13.1 (d, $^{1}J_{C\text{-}Te}$ = 174.1 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}BrNOTe$ 445.9376; Found 445.9375.

3-(4-Chlorophenyl)-5-[(phenyltellanyl)methyl]-4,5-dihydroisoxazole (5c). Yield: 132 mg (66%); light orange solid; m. p. 102-103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.79 - 7.77 (m, 2H); 7.53 - 7.51 (m, 2H); 7.36 - 7.30 (m, 3H); 7.24 - 7.20 (m, 2H); 5.03 - 4.95 (m, 1H); 3.40 (dd, J = 16.8, 10.2 Hz, 1H); 3.29 (dd, J = 12.1, 4.5 Hz, 1H); 3.08 - 3.01 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 155.3, 139.0, 136.1, 129.6, 129.0, 128.3, 128.1, 128.0, 110.6, 82.4, 41.1, 13.2. ^{125}Te NMR ($CDCl_3$, 126 MHz) δ (ppm) 433.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}ClNOTe$ 401.9889; Found 401.9889.

3-(4-Fluorophenyl)-5-[(phenyltellanyl)methyl]-4,5-dihydroisoxazole (5d). Yield: 132 mg (69%); light orange solid; mp 95-97 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.79 - 7.77 (m, 2H); 7.60 - 7.57 (m, 2H); 7.34 - 7.30 (m, 1H); 7.24 - 7.20 (m, 2H); 7.09 - 7.05 (m, 2H); 4.98 (dddd, J = 10.2, 9.0, 7.2, 4.5 Hz, 1H); 3.41 (dd, J = 16.7, 10.2 Hz, 1H); 3.29 (dd, J = 12.1, 4.5 Hz, 1H); 3.09 - 3.03 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 163.8 (d, ^{1}J = 250.8 Hz), 155.2, 139.0, 129.5, 128.7 (d, ^{3}J = 8.4 Hz), 128.3, 125.9 (d, ^{4}J = 3.4 Hz), 115.9 (d, ^{2}J = 21.9 Hz), 110.6, 82.2, 41.3, 13.2 (d, $^{1}J_{C\text{-}Te}$ = 173.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) 109.90 (tt, J = 8.7, 5.4 Hz). ^{125}Te NMR ($CDCl_3$, 126 MHz) δ (ppm) 432.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}FNOTe$ 386.0195; Found 386.0189.

5-[(Phenyltellanyl)methyl]-3-(*p*-tolyl)-4,5-dihydroisoxazole (5e). Yield: 129 mg (68%); red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.80 - 7.77 (m, 2H); 7.51 - 7.49 (m, 2H); 7.34 - 7.30 (m, 1H); 7.24 - 7.18 (m, 4H); 4.97 (dddd, J = 10.1, 9.1, 7.1, 4.5 Hz, 1H); 3.43 (dd, J = 16.7, 10.1 Hz, 1H); 3.30 (dd, J = 12.1, 4.5 Hz, 1H); 3.10 - 3.03 (m, 2H); 2.37 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 56.2, 140.5, 139.1, 129.6, 129.5, 128.3, 126.8, 126.7, 110.7, 81.9, 41.4, 21.6, 13.34.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NOTe$ 382.0446; Found 382.0440.

3-(4-Methoxyphenyl)-5-[(phenyltellanyl)methyl]-4,5-dihydroisoxazole (5f). Yield: 89 mg (68%); light brown solid; mp 85-87. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.79 - 7.77 (m, 2H); 7.55 - 7.53 (m, 2H); 7.33 - 7.29 (m, 1H); 7.24 - 7.20 (m, 2H); 6.91 - 6.89 (m, 2H); 4.95 (dddd, J = 10.1, 9.1, 7.1, 4.5 Hz, 1H); 3.83 (s, 3H); 3.41 (dd, J = 16.7, 10.1 Hz, 1H); 3.29 (dd, J = 12.1, 4.5 Hz, 1H); 3.09 - 3.03 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 161.1, 155.8, 139.0, 129.5, 128.3, 128.2, 122.2, 114.2, 110.7, 81.8, 55.5, 41.5, 13.4. ^{125}Te NMR ($CDCl_3$, 126 MHz) δ (ppm) 431.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_2Te$ 398.0395; Found 398.0395.

3-Phenyl-5-[(*p*-tolyltellanyl)methyl]-4,5-dihydroisoxazole (5g). Yield: 108 mg (57%); light orange solid; mp 55-56°C. ^1H RMN ($CDCl_3$, 400 MHz) δ (ppm) 7.69 (d, J = 7.7 Hz, 2H); 7.62 - 7.60 (m, 2H); 7.40 - 7.37 (m, 3H); 7.05 (d, J = 7.7 Hz, 2H); 5.00 - 4.92 (m, 1H); 3.43 (dd, J = 16.7, 10.2 Hz, 1H); 3.27 (dd, J = 12.0, 4.5 Hz, 1H); 3.12 - 2.98 (m, 2H); 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.2, 139.4, 138.5, 130.5, 130.1, 129.7, 128.8, 126.7, 106.4, 82.1, 41.2, 21.3, 13.2 (d, $^1J_{C\text{-}Te}$ = 173.4 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NOTe$ 382.0445; Found 382.0445.

5-{[(4-Chlorophenyl)tellanyl]methyl}-3-phenyl-4,5-dihydroisoxazole (5i): Yield: 152 mg (76%); dark orange solid; mp 90-92 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.72 - 7.68 (m, 2H); 7.62 - 7.60 (m, 2H); 7.41 - 7.38 (m, 3H); 7.20 - 7.186 (m, 2H); 5.01 - 4.94 (m, 1H); 3.45 (dd, J = 16.7, 10.2 Hz, 1H); 3.27 (dd, J = 12.2, 4.8 Hz, 1H); 3.11 - 3.05 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.3, 140.4, 130.3, 129.8, 129.5, 128.8, 126.8, 108.2, 81.7, 41.4, 13.9 (d, $^1J_{C\text{-}Te}$ = 173.0 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}ClNOTe$ 401.9888; Found 401.9892.

General Procedure for the synthesis of diisoxazoline dichalcogenides 7: In a round-bottomed flask were added the β,γ-unsaturated oxime **1** (0.5 mmol), MeCN (0.5 mL) and $TeCl_4$ (0.161 g, 0.6 mmol) or $SeCl_4$ (0.132 g, 0.6 mmol). The resulting mixture was stirred for 1 h at room temperature. Then, the solution was diluted with THF (3.0 mL) and an aqueous solution of $NaBH_4$ (2.0 mL, 0.75*M*) was

added dropwise at 0 ºC.[22] The resulting dark red (for tellurium) or yellowish (for selenium) solution was treated with saturated NH_4Cl (15 mL) and extracted with AcOEt (3x 15 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting solid was rinsed with hexanes (5x 2.0 mL). Following, the solid was dried in a vacuum pump to access the product **7** in the tabulated yields (Table 4). For product **7c**, a 7:3 mixture of hexanes/AcOEt was used in the washing step.

2-Bis[(3-phenyl-4,5-dihydroisoxazol-5-yl)methyl]ditellane (7a). Yield: 97 mg (67%); red solid; mp 35-36 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.68 - 7.64 (m, 2H); 7.41 - 7.39 (m, 3H); 5.02 - 4.91 (m, 1H); 3.66 - 3.45 (m, 3H); 3.20 - 3.12 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ (ppm) 156.4, 156.4, 130.3, 129.5, 128.9, 126.8, 83.0, 83.0, 41.1, 10.0, 9.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2O_2Te_2$ 576.9693; Found 576.9693.

1,2-Bis{[3-(*p*-tolyl)-4,5-dihydroisoxazol-5-yl]methyl}ditellane (7b). Yield: 60 mg (40%); orange solid; mp 125-127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.54 (d, J = 7.8 Hz, 2H); 7.20 (d, J = 7.8 Hz, 2H); 4.98 - 4.89 (m, 1H); 3.63 - 7.57 (m, 1H); 3.50 - 3.44 (m, 2H); 3.17 - 3.10 (m, 1H); 2.37 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.3, 156.3, 140.5, 129.5, 126.7, 126.7, 82.8, 82.8, 41.2, 21.6, 10.1, 9.9. ^{125}Te NMR decoupled ($CDCl_3$, 126 MHz) δ (ppm) 99.4 (t, $^2J_{Te\text{-}H}$ = 33.0 Hz), 97.3 (t, ^2J = 33.6 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_2Te_2$ 605.0007; Found 604.9981.

1,2-Bis((3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)methyl)ditellane (7c). Yield: 47 mg (30%); dark brown solid; mp 140-142 °C. ^{1}H RMN ($CDCl_3$, 400 MHz) δ (ppm) 7.59 - 7.57 (m, 2H); 6.91 - 6.88 (m, 2H); 4.95 - 4.87 (m, 1H); 3.82 (s, 3H); 3.62 - 3.56 (m, 1H); 3.48 - 3.42 (m, 2H); 3.15 - 3.09 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 161.2, 156.0, 155.9, 128.3, 122.0, 114.2, 82.7, 82.6, 55.5, 55.4, 41.3, 10.0, 9.9. ^{125}Te NMR decoupled ($CDCl_3$, 126 MHz) δ (ppm) 99.2 (t, $^2J_{Te\text{-}H}$ = 32.9 Hz), 96.9 (t, ^2J = 32.5 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_4Te_2$ 636.9905; Found 636.9905.

1,2-Bis{[3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl]methyl}ditellane (7d). Yield: 97 mg (44%); orange solid; mp 99-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.61 - 7.56 (m, 2H); 7.39 - 7.35 (m, 2H); 5.03 - 4.92 (m, 1H); 3.65 - 3.58

(m, 1H); 3.51 - 3.42 (m, 2H); 3.16 - 3.08 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 155.9, 136.7, 129.6, 128.5, 118.7, 83.7, 83.7, 41.4, 10.3, 10.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}Cl_2N_2O_2Te_2$ 646.8906; Found 646.8895.

1,2-Bis{[3-(4-fluorophenyl)-4,5-dihydroisoxazol-5-yl]methyl}ditellane (7e). Yield: 78 mg (51%); light yellow solid; mp 120-122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.65 - 7.62 (m, 2H); 7.10 - 7.05 (m, 2H); 5.00 - 4.91 (m, 1H); 3.64 - 3.57 (m, 1H); 3.50 - 3.43 (m, 2H); 3.16 - 3.10 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 163.8 (d, ^{1}J = 251.0 Hz), 155.4, 128.6 (d, ^{2}J = 8.5 Hz), 125.7 (d, ^{4}J = 3.4 Hz), 115.9 (d, ^{3}J = 22.0 Hz), 83.0, 83.0, 41.1, 9.8, 9.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) -109.60 -109.67 (m). ^{125}Te NMR decoupled ($CDCl_3$, 126 MHz) δ (ppm) 101.6 (t, J = 32.4 Hz), 100.0 (t, J = 32.4 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}F_2N_2O_2Te_2$ 612.9505; Found 612.9509.

1,2-Bis[(3-phenyl-4,5-dihydroisoxazol-5-yl)methyl]diselane (7f). Yield: 57 mg (48%), white solid; mp 122 - 124°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.66 - 7.63 (m, 2H), 7.41-7.37 (m, 3H), 5.06 - 4.97 (m, 1H), 3.51 - 3.42 (m, 1H), 3.25 - 3.19 (m, 1H), 3.04 - 2.92 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.5, 130.2, 130.2, 129.4, 128.8, 126.8, 126.7, 81.0, 80.7, 40.4, 40.4, 28.7, 28.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2O_2Se_2$ 478.9942; Found 478.9948.

Bioassays: Animals experimental and drugs

The experiments were conducted using male adult Swiss mice (25-35 g). The animals were kept in a separate animal room, in a 12 h light/dark cycle (with lights on at 7:00 a.m.), at a room temperature of 22 ± 2 °C, with free access to food and water. All procedures were approved by the Committee on Care and Use of Experimental Animal of Federal University of Pelotas, Brazil (CEEA1987). All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments. PPSEI45 (**3a**) was dissolved in canola oil, while Celecoxib was dissolved in 0.9 % saline solution. The mice received oral administration (p.o., by intragastric gavage) in a constant volume of 10 mL/kg body weight. Celecoxib was obtained commercially, and it was used as reference drug. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

Ear edema induced by croton oil.

Ear edema was induced by croton oil based on previous studies with some modifications.[39,40] Mice were treated with compound **3a** (50 mg/kg, p.o.), Celecoxib (50 mg/kg and 100mg/kg, p.o.) or vehicle, before the topical application of 2.5 % croton oil in acetone (20 µL/ear) in the right ear of each mouse. The identical volume (20 µL) of acetone was applied to the left ear. Four hours after the application, animals were euthanized and both ears were cut at the base and the weight difference between the samples of the control ear (left) and the croton oil-treated ear (right) was established on an analytical balance.[41] The results obtained were represented in weight (mg). Subsequently, ears were used to determine the myeloperoxidase (MPO) activity.

MPO assay.

The MPO activity was evaluated according to the method previously proposed with some modifications.[31] The samples of ears were homogenized in potassium phosphate buffer (20 mmol/L, pH 7.4; 1:5, w/v) containing ethylenediaminetetraacetic acid (0.1 mmol/L). After this process, samples were subjected to ultrasonic bath and then frozen and thawed three times and centrifuged at 2.500 rotations per minute (rpm) at 4 °C for 10 min to yield a low speed supernatant fraction. Then, the supernatant fractions were centrifuged again at 14.000 rpm at 4 °C for 15 min to yield a final pellet that was resuspended in medium containing potassium phosphate buffer (50 mmol/L, pH 6.0) and hexadecyltrimethyl ammonium bromide (0.5%). For the enzyme assay, an aliquot of final pellet resuspended (100 µL) was added to a medium containing the medium of resuspension and N,N,N′,N′-tetramethylbenzidine (1.5 mmol/L). The kinetic analysis of MPO was started after H_2O_2 (0.01%) addition and results were expressed as optic density (OD)/mg protein/min.

Acute toxicity

To examine the potential acute toxicity caused by **3a**, mice received a single oral dose of the compound (300 mg/kg) or vehicle (canola oil). After drug administration, animals were observed for up to 72 h to determine the lethal

potential of this compound. After this time of exposure, mice were anesthetized for a heart puncture through which blood was collected in tubes containing heparin. Plasma was obtained by centrifugation at 900×g for 10 min and used for biochemical assays, which were performed with commercial test kits. Plasma aspartate (AST) and alanine (ALT) aminotransferase activities, used as the biochemical markers for early acute hepatic damage were determined by colorimetric method.[42] Here, AST activity was also used as marker of cardiac damage. The values were expressed as U/L. Renal function was analyzed by determining plasma urea levels.[33] The values were expressed as mg/dL.

Samples of liver, kidney and brain were also collected to determine the δ-aminolevulinate dehydratase (δ-ALA-D) activity, a marker of oxidative damage.[43] Samples were homogenized in 50m*M* Tris/HCl pH 7.5, (1:10, w/v) and centrifuged at 900×g for 10 min at 4 °C to yield a supernatant (S1). δ-ALA-D activity was assayed by the method of Sassa.[44] An aliquot of S1 was pre-incubated for 10 min at 37 °C. The enzymatic reaction was initiated by adding the substrate (δ-ALA) to a final concentration of 2.2m*M* in a medium containing 45 m*M* phosphate buffer, pH 6.8 and incubated for 1 h at 37 °C. The incubation was stopped by adding 10% trichloroacetic acid (TCA) solution with 10m*M* $HgCl_2$. The reaction product porphobilinogen (PBG) was measured at 555 nm using modified Ehrlich's reagent. The values were expressed as nmol PBG/mg protein/h. The protein concentration was measured by the method of Bradford,[45] using bovine serum albumin as the standard.

Conflicts of Interest

There are no conflicts to declare.

Associated Content

Support Information: Contains the full spectroscopy (^{1}H, $^{13}C\{^{1}H\}$ NMR) data for all synthesized compounds.

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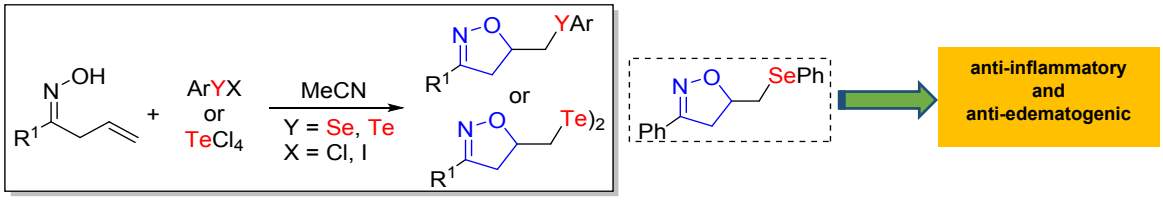

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