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Review

Seleno- and Telluro-Functionalization of Quinones: Molecules with Relevant Biological Application

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Quinones and organochalcogens are classes of compounds with great biological applicability, such as antioxidant, anticancer, anti-Alzheimer, and antidepressant activities, among others. Thus, the combination of these two classes of compounds is important to obtain new hits with biological activities that are additive or synergistic. Several methodologies for the preparation of this class of hybrid compound have been widely described. Many of the prepared hybrid molecules have shown increased biological activities and, in some cases, to act as two distinct pharmacophores. In this review, methods for the preparation of selenium-quinones, tellurium-quinones and their biological applications are highlighted.

Keywords: selenides, tellurides, naphthoquinones, organochalcogens, biological activity

1. Introduction

Quinones are pigments found in different living organisms and in a wide variety of plant families, such as Ranunculaceae,[1] Aphodelaceae,[2] Fabaceae,[3] Ebenaceae[4] and Rhamnaceae.[5] They are also present in bacteria, fungi, higher plants and some animals. Compounds with this core could be used as chemical intermediates, polymerization inhibitors, oxidizing agents, photographic chemicals, tanning agents, and chemical reagents.[6] The pharmacological properties of these compounds have been studied in depth, and they are considered privileged structures in medicinal chemistry. Quinones have been assessed for their biological activity against cancer and for their antiallergic,[7] antifungal,[8] antiviral,[9] antibacterial[10] and anti-inflammatory properties.[11] In addition, the quinone class also plays an important role in the prevention of chronic diseases such as Parkinson's and cardiovascular diseases, with a mechanism of action involving the fight against cell damage caused by reactive oxygen species (ROS).[12] Recent studies continue to show important applications of quinones, such as the use of mitochondrial ubiquinone as a potential treatment or adjuvant therapy in the context of coronavirus disease 2019 (COVID-19).[13] It is worth mentioning the importance that various quinones represent in the vitamin K family, being responsible for the function in several biological processes, and vitamin K3 being of vital importance in blood clotting.[14] Currently, there are already several commercialized drugs in which quinones form part of their molecular structures, as is the case of doxorubicin (**1**), a drug with the widest scope of anticancer activity in humans. Another promising quinone is β-lapachone (**2**), which is in phase II clinical trials under code ARQ501 for the treatment of pancreatic cancer (Figure 1).[15-17]

Tellurium- and selenium-containing organic compounds were for a long time considered dangerous to the environment and human health, and for this reason the interest in organochalcogen compounds has been growing only in recent decades. The importance of molecules

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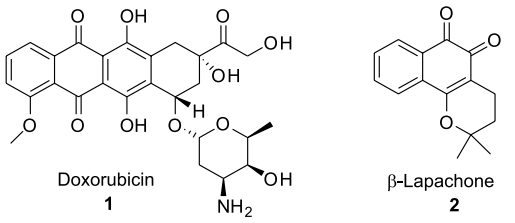


Figure 1. Doxorubicin and β-lapachone structures.

containing chalcogens is highlighted in different fields, including materials science, organic synthesis, medicine and biology.[18-22]

In this review, several organochalcogens will be highlighted: more specifically, tellurium- and selenium-containing quinones, since they themselves have undergone more recent and unique chemical and biological studies in relation to their counterparts containing sulfur. Currently, it is possible to consider that chemists have managed to master the preparative chemistry of tellurium- and selenium-containing compounds, and their biological applications are quite widespread. This can be seen in the increase in the number of publications dedicated to organoselenium and organotellurium compounds.[23-25]

It is important to show that organoselenium compounds have already proven to be valuable reagents in various chemical reactions, such as selenylation, selenocyclization, selenoxide elimination, cross-coupling reactions and 2,3-sigmatropic rearrangement processes, as well as in asymmetric catalysis.[26-31] The biological profile of selenium compounds is established, and their use as bioactive molecules is emerging as an even more attractive field of research. The selenide ALT2074 (**3**) was identified as a glutathione peroxidase (GPx)-mimic able to prevent endothelial changes and myocardial ischemia-reperfusion injury.[32] In addition, ethaselen (**4**) is in phase II of clinical trials for the treatment of non-small cell lung cancers with overexpression thioredoxin reductase (TrxR).[33] One of the most important organoselenium compound is ebselen (**5**), which exhibits hydroperoxide- and peroxynitrite-reducing activity, acting as a glutathione peroxidase and peroxiredoxin enzyme mimetic (Figure 2). This compound has become even more interesting due to its promising potential to inhibit the main protease (M^{pro}) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[34,35]

The large number of studies showing the applications of hybrid compounds between quinones and organochalcogens demonstrate the great interest in the development of synthetic methods toward compounds containing these two moieties in the same structure, aiming at superior additive or synergistic biological effects. Thus, this review has the proposal of emphasizing studies related to quinone structures functionalized with organochalcogens, their synthesis, as well as biological applications. The systematic arrangement of this review explores the possibility of providing practical guidance to synthetic chemists for further research, while emphasizing the possible biological applications of quinones functionalized with organochalcogens.

2. Functionalization of Quinones with Organoselenium and Organotellurium

In 1987, Stone and co-workers[36] described the first selenohydroquinone **8** through a Diels-Alder reaction between benzoquinone (**6**) and 2-phenylseleno-l,3-butadiene (**7**) previously synthesized. Hydroquinone **8** was obtained with 64% yield, proving that seleno-1,3-butadiene (**7**) reacts with electron-deficient dienophiles, being an excellent method of synthesis of selenohydroquinones (Scheme 1).

Ueno and co-workers[37] discovered an innovative method of selenylation to obtain selenonaphthoquinones and selenoquinolinequinones by addition of phenylselenolate ion in chloroquinones. The selenolate ions were obtained by reaction of the corresponding diselenides, tributylphosphine (Bu_3P), and sodium hydroxide, with tetrahydrofuran (THF) as solvent. The different selenoquinones **11** were produced from naphthoquinones **9** with yields varying from 68 to 98% (Scheme 2a). The two selenoquinolinequinones **13a-13b** were synthesized from chloroquinoline quinones **12a** and **12b**, in 47 and 38% yield, respectively (Scheme 2b). As a mechanistic suggestion, the authors believe that the phenylselenolate ion (nucleophile of the reaction) is generated from the breakdown of diphenyl diselenides for the complexation of phenylselenide with Bu_3P and its subsequent release in the basic medium. This ion then performs substitution at the C-2 and/or C-3 of the quinone, depending on the position of the halogen (Scheme 2c).

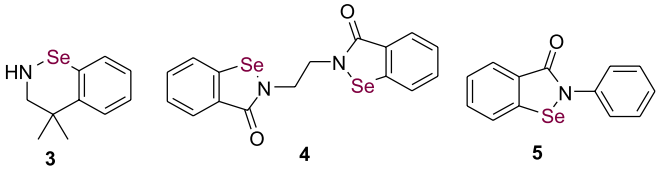
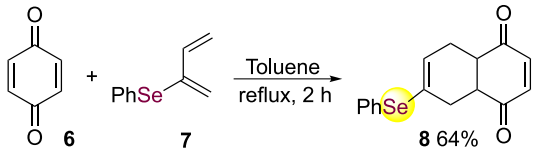


Figure 2. Structure of organoselenium compounds.

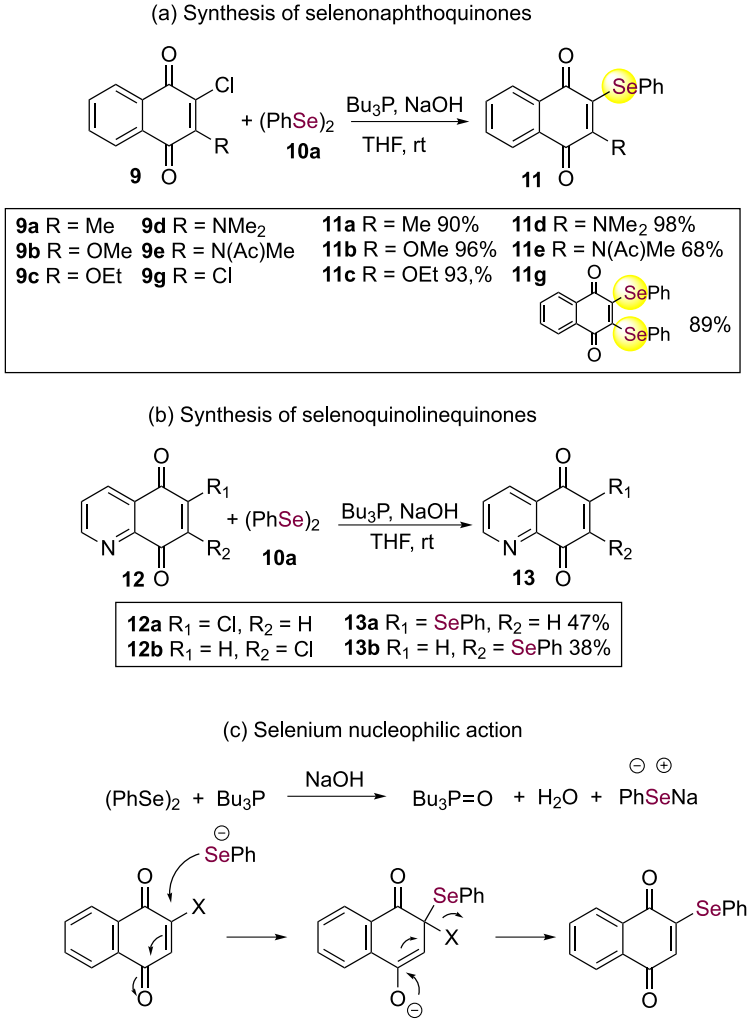


Scheme 1. Synthesis of selenoquinone via Diels-Alder reaction (adapted from reference 36).

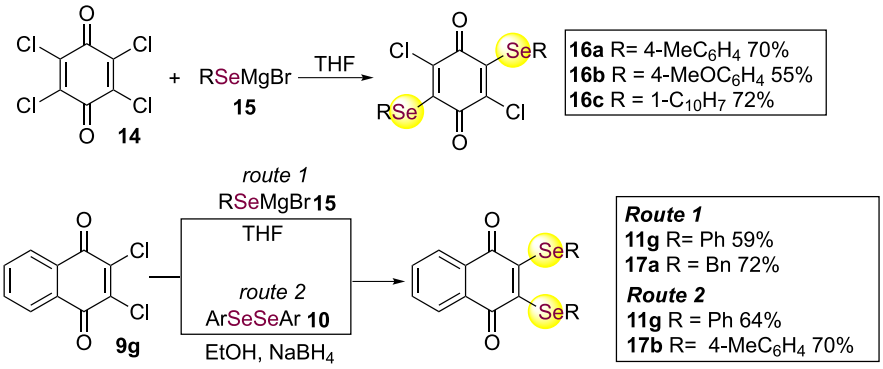
Tetrachloro-1,4-benzoquinone **14** and 2,3-dichloro-1,4-naphthoquinone **9g** are versatile compounds with reactive chlorine atoms, and their chemistry is of great synthetic interest. They have been widely used as reagents in nucleophilic substitution. Quinone compounds containing an organoselenium moiety were obtained through reactions of chloroquinones with selenolates. Initially, using route 1, compound **14** was treated with aryl and alkyl selenolates, generated by the reaction of Grignard reagents and selenium powder to provide **16a-16c** in yields of 55-72% and **11g** and **17a** in yields of 59 and 72%, respectively. However, when **9g** was reacted with phenyl and benzyl selenolate, in the route 2, generated by the reduction of diselenides with $NaBH_4$, compounds **11g** and **17b** were also obtained in good yields of 59 and 72%, respectively. However, using diselenides **10**, the products **11g** and **17b** were also obtained in good yields (Scheme 3).[38]

Joseph and co-workers[39] have successfully demonstrated another method to introduce selenium atoms through a reaction between benzeneseleninic anhydride and hexamethyldisilazane (Scheme 4). This methodology provides a reactive intermediate, oligomeric $(PhSeN)_4$, that oxidizes the phenol derivatives to selenoiminoquinones **21**. In addition, these selenoiminoquinones were investigated, and both spectroscopic and crystallographic studies proved that the oxygen from the carbonyl group is involved in an attractive interaction with the selenium atom. Therefore, the electronic structure around the selenium atom can be described in terms of the model with a 3-center and 4-electron connection and correlated with other hypervalent molecules.

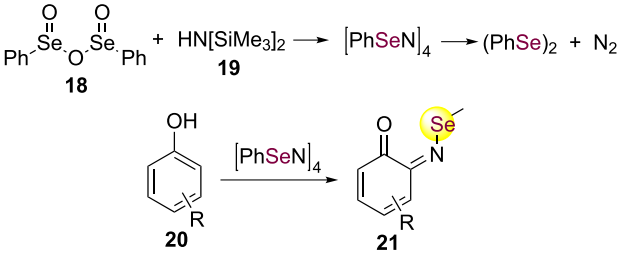
Naphthoquinone-fused selenazoles **24** and 2-aryl-4,9-dioxonaphtho[2,3-*d*] selenazoles **23** can be easily



Scheme 2. Selenonaphthoquinones and selenoquinolinequinones (adapted from reference 37).



Scheme 3. Synthesis of quinone compounds containing alkyl aryl (or benzyl)selenide (adapted from reference 38).



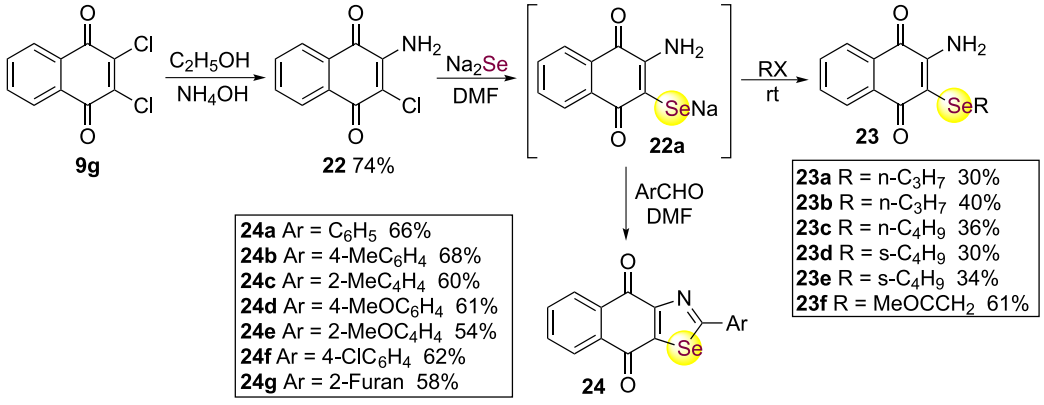
Scheme 4. Synthesis of selenoiminoquinones (adapted from reference 39).

prepared through simple protocols. In the method described by Zhou and co-workers,[40] the synthetic approach begins with the conversion of 1,2-dichloronaphthoquinone **9g** to the aminochlorinated intermediate **22** in the presence of ammonium hydroxide. Compound **22** was heated with sodium selenide in *N*,*N*-dimethylformamide (DMF), producing intermediate **22a** *in situ*, via a nucleophilic substitution reaction, to then be reacted with aromatic aldehydes to give the selenonaphthoquinones **24a-24f** with yields varying from 54-68%. When **22a** was reacted with alkyl halides, 2-amino-3-alkylseleno-1,4-naphthoquinones **23a-23g** were produced in 30-61% yield (Scheme 5).

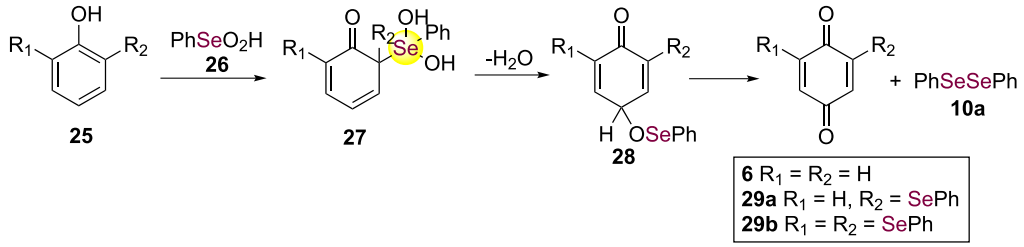
In the same year, Henriksen[41] studied the first *o*-oxidation of phenols using benzeneselenenyl acid **26** as a specific oxidizing agent, producing **28** after subsequent reactions of dehydration and rearrangement. Intermediate **28** was oxidized in a final step to give a mixture of three compounds (benzoquinone **6** and selenium-quinones **29a** and **29b**), in the proportion 3:4:3 (Scheme 6).

As a further expansion of this promising area of research, a simple and efficient method for the synthesis of selenocyanoquinones has been described. Quinone imines **31a-31e** were reacted with triselenodicyanide in a one-pot selenocyanation reaction in a quinoid kernel of pyridobenzimidazole system and showed selectivity at C-9 due to the presence of the electron-donor substituent in the *ortho* position (Scheme 7). The method involves an aromatic electrophilic substitution reaction in the quinoidal structure and presented several advantages, such as mild reaction conditions, simple procedure, and good yields (66-96%).[42]

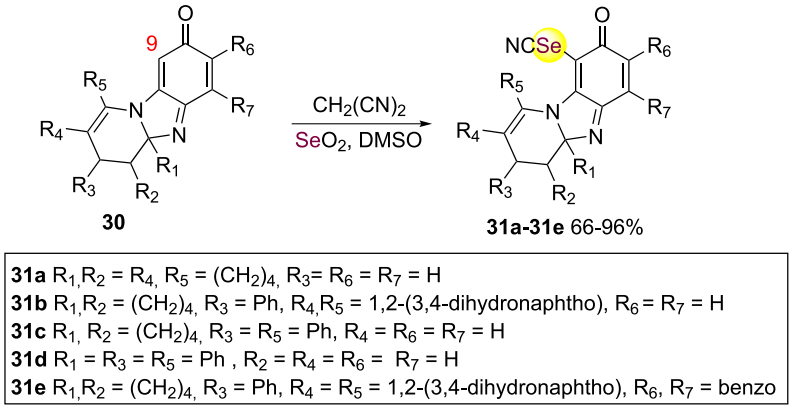
Selenium-lapachol derivatives can be synthetized via a solvent-free and metal-free methodology, as reported by Braga and co-workers in 2015.[43] The synthesis involved the use of molecular iodine as a catalyst, dimethyl sulfoxide (DMSO) as a stoichiometric oxidizing agent and diselenides as nucleophiles, under microwave irradiation. Lapachol (**32**) and C-allyl lawsone (**34**) were employed



Scheme 5. Preparation of naphthoquinone-fused selenazoles and 2-aryl-4,9-dioxonaphtho[2,3-*d*] selenazoles (adapted from reference 40).



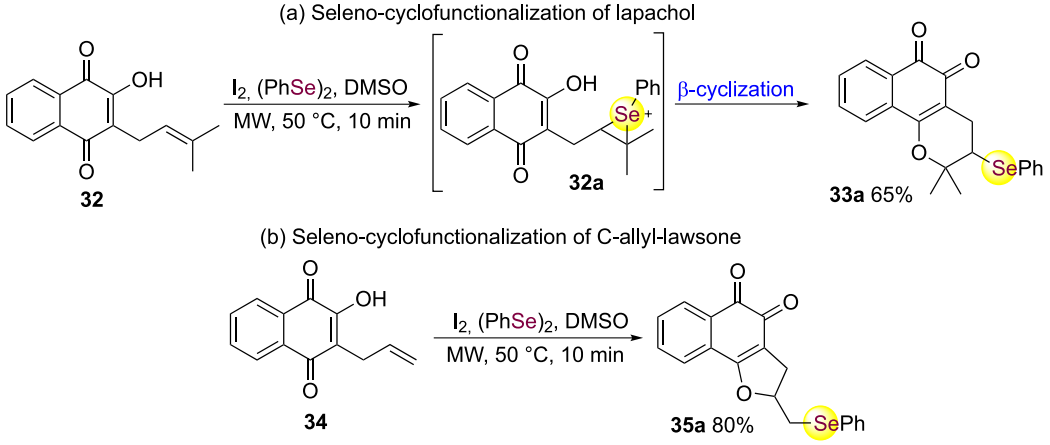
Scheme 6. *o*-Oxidation of phenols using benzeneselenenyl acid (adapted from reference 41).



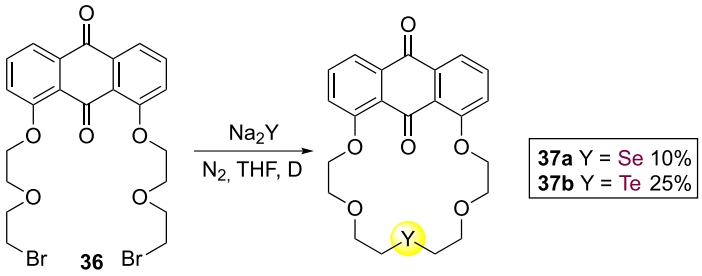
Scheme 7. Selenocyanation reaction of quinone imines (adapted from reference 42).

as substrates for the seleno-functionalization. This system allows the formation of PhSeI species, which is the source of electrophilic selenium for the formation of the seleniranium intermediate **32a**. When **32** was used, the respective 3-selenophenyl-β-lapachone **33a** was obtained in 65% yield in a 6-endo-trig fashion (Scheme 8a). Applying the chalcogenylation method to C-allyl lawsone (**34**), the selenium product **35a** was obtained in 80% yield (Scheme 8b). The compounds were obtained through β-cyclization; however, α-cyclization is also possible. In general, β-lapachone analogs are synthesized preferentially in reactions without heating and in a shorter reaction time than α-lapachone derivatives (thermodynamic product).[43]

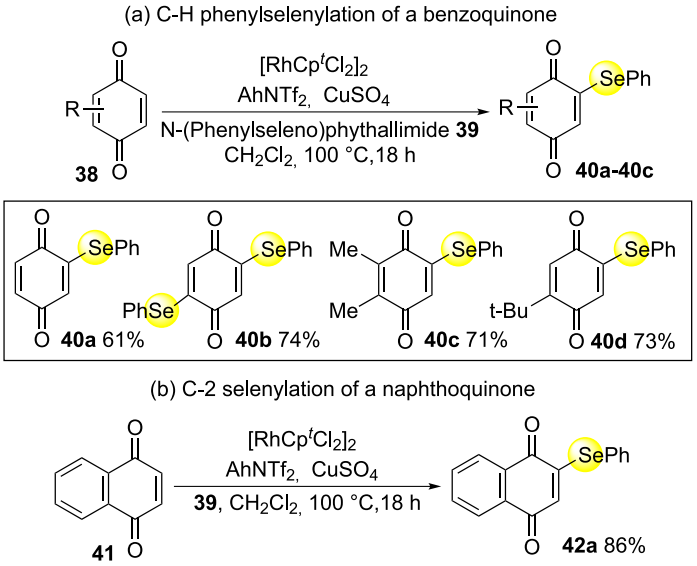
Sykes and co-workers[44] described the synthesis of 1,8-anthraquinone-18-crown-5 containing chalcogenides **37a-37b** and their application as sensors for the selective recognition of Pb^{II}. The structure of these macrocycles is formed by a fluorescent anthraquinone moiety that has a cyclic polyether chain as a receptor. Compounds **37a-37b** were synthesized by the reaction of disodium selenide or disodium telluride with 1,8-bis-(2-bromoethylethylenoxy) anthracene-9,10-dione (**36**) in the proportion of 1:1, in yields of 10 and 25%, respectively (Scheme 9). Several studies have been carried out in relation to optical properties, X-ray diffraction, cyclic voltammetry and nuclear magnetic resonance (NMR) spectroscopy. From



Scheme 8. Seleno-cyclofunctionalization of lapachol and C-allyl lawsone (adapted from reference 43).



Scheme 9. Synthesis of 1,8-anthraquinone-18-crown-5 containing chalcogenides (adapted from reference 44).



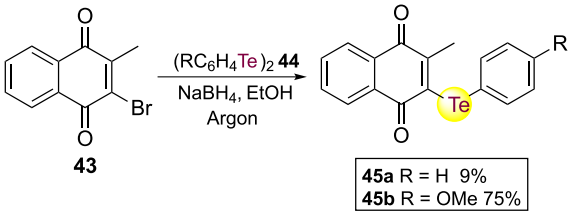
Scheme 10. Phenylselenylation of benzoquinones and 1,4-naphthoquinone (adapted from reference 45).

these results, it was found that **37a** acts as a luminescent sensor for the selective recognition of Pb^{II} in acetonitrile via internal charge transfer. However, compound **37b** does not show the same result, as it does not change luminescence with the addition of lead.[44]

The first methodology that described the C–H phenylselenylation of quinones was described in 2016 by da Silva Junior and co-workers.[45] The reaction was carried out under Rh-catalysis and using *N*-(phenylseleno)-phthalimide (100 mol%) as an electrophile. Selenobenzoquinones **40a-40c** were obtained in satisfactory yields that varied from 61 to 74% (Scheme 10a), and the selenonaphthoquinone **42a** in 86% yield (Scheme 10b). Increasing the loading of *N*-(phenylseleno)-phthalimide to 250 mol% enabled the selective generation of bis-functionalization adduct **40b** in 73% yield. Selenium-containing quinones possess significant antitumor activity, which may be due to their ability to generate intracellular ROS and induce cell death.[45]

In 2005, Jacob and co-workers[46] reported the synthesis of compounds containing a chalcogen and a naphthoquinone as selective enhancers of oxidative stress. Cancer cells proliferate under conditions of oxidative stress and might therefore be selectively targeted by redox catalysts. Scheme 11 describes the synthetic methodology for obtaining tellurium-menadione compounds **45a** and **45b** using $NaBH_4$ as reducing agent and ditellurides **44**, in yields of 9 and 75%, respectively. These compounds combine the specific electrochemical features of quinones and tellurium, and respond to the presence of oxidative stress. The high efficiency and selectivity shown by compounds **45a-45b** make them interesting in the development of anticancer drugs.

The same research group reported the synthesis of redox-active multifunctional selenium and tellurium compounds and the evaluation of their cytotoxicity against cancer cells.[47] The synthetic methodology employed

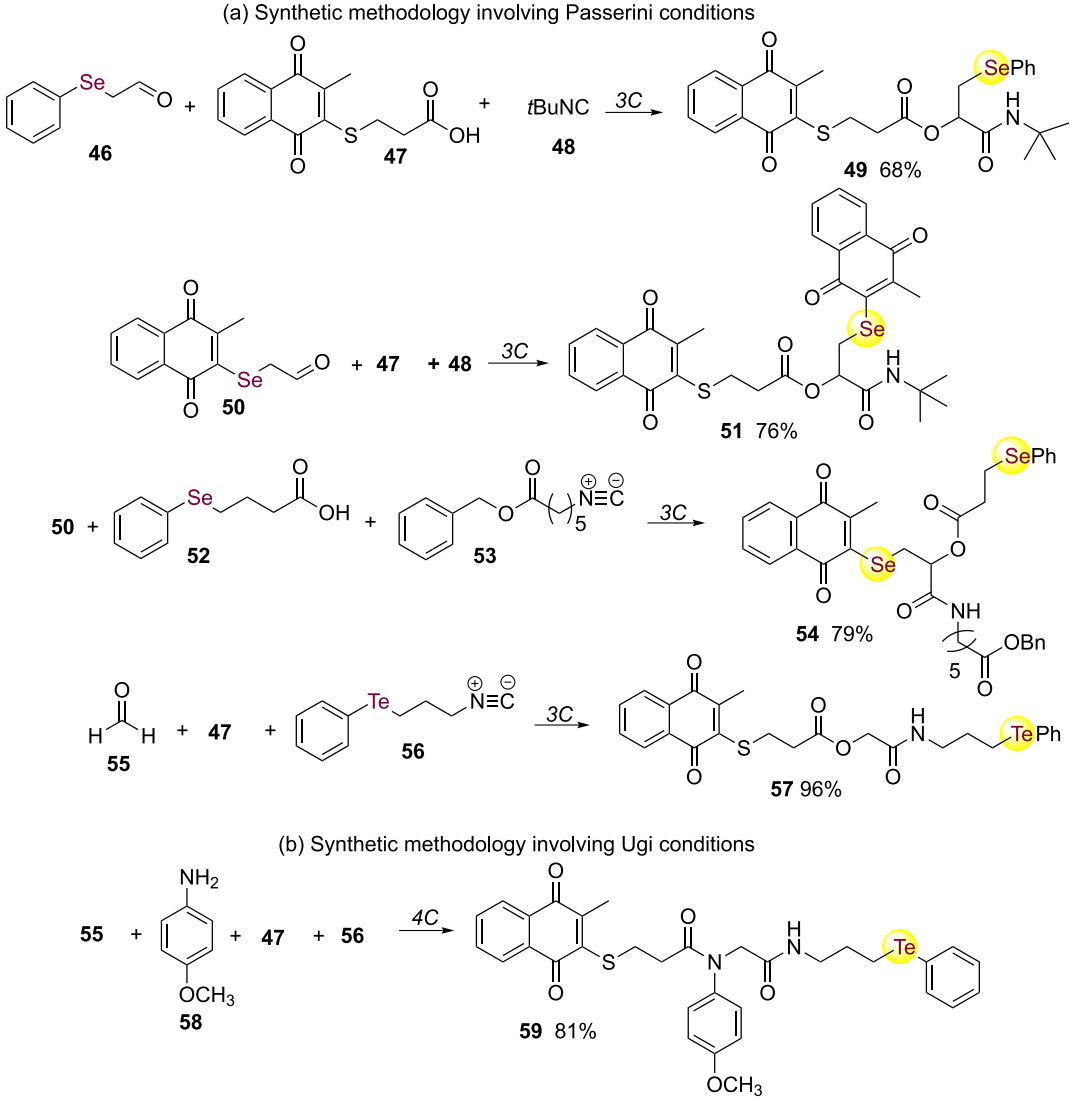


Scheme 11. Synthesis of tellurium-menadione compounds (adapted from reference 46).

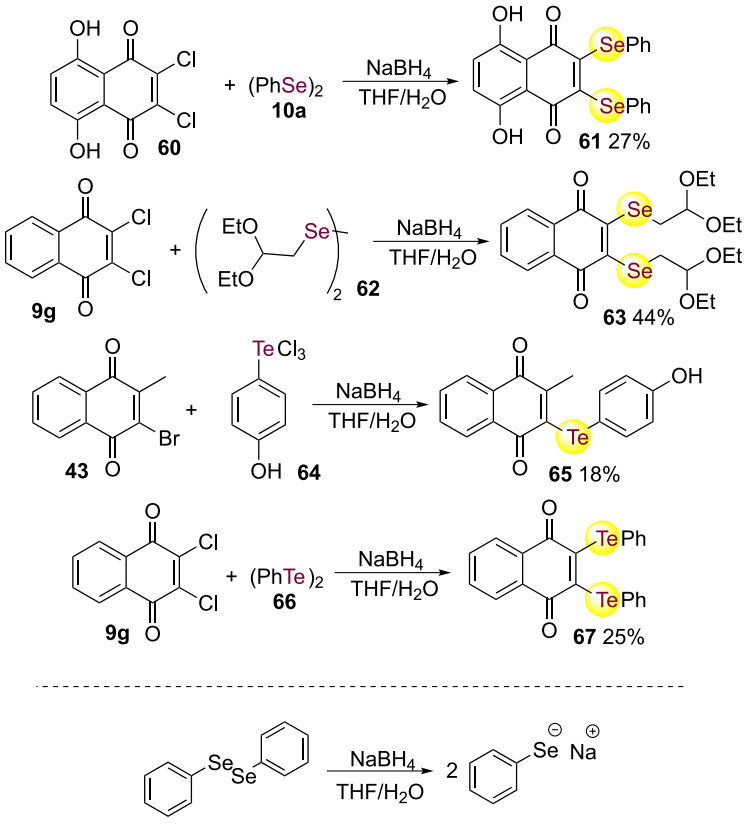
involved the use of multicomponent of Passerini and Ugi reactions, showing that it is an excellent synthetic route for obtaining highly functionalized molecules (Scheme 12). The Passerini reaction is a three-component reaction combining an acid, an aldehyde, and an isonitrile, while the Ugi reaction is a four-component reaction (acid, aldehyde, isonitrile, and amine). It is worth mentioning that acids, aldehydes and amines as building blocks are accessible and variable, which can bring more functionality to multicomponent reaction products. Thus, compounds containing selenium and tellurium were obtained with two to four redox centers, 1,4-naphthoquinone always being one of them. All compounds were evaluated against cancer cells, with **49** and **54** being the most active. In both compounds, the selenium atom is linked directly to the quinonic ring, and this can result in a synergistic effect between the two redox sites.[47]

In 2010, Jacob and co-workers[48] reported a very simple synthesis of a variety of multifunctional redox catalysts designed to target cancer cells by modulating intracellular levels of ROS. Scheme 13 describes the synthetic methodology for obtaining quinone-chalcogen compounds using $NaBH_4$ as a diselenide reducing agent, giving rise to sodium phenylselenolates-reaction nucleophiles. Compounds **61**, **63**, **65** and **67** were obtained with yields ranging from 18 to 44%. Compound **67** has been shown to decrease the proliferation of carcinoma cells. According to human treatment protocols, **67** was combined with other drugs and the result was promising, as it worked in conjunction with these drugs to inhibit the growth of cancer cells and did not increase the toxicity of the drugs.[46,48]

Selenium-containing compounds can be used as potential redox-modulating agents, an effect which may



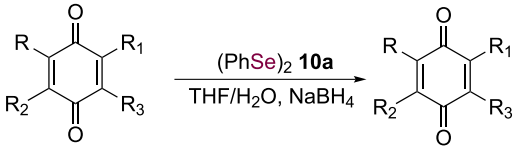
Scheme 12. Multifunctional redox agents synthesized employing the Passerini and Ugi reactions (adapted from reference 47).



Scheme 13. Synthesis of chalcogen-quinone compounds (adapted from reference 48).

be used for the selective targeting of cancer cells, which are naturally under oxidative stress. As macrophages also generate an environment rich in ROS, they may represent a target for such redox-modulating agents. Thus, selenium-containing quinones have been synthesized and tested in macrophage culture. Scheme 14 reports the methodology used to obtain the compounds **69a-69d** using $NaBH_4$ as a reducing agent, in yields varying from 8 to 34%. All compounds were synthesized and subsequently tested in macrophage culture. While tellurium analogs may enable the resolute, effective and fairly selective targeting of macrophages, the selenium agents could act less severely, but equally effectively, by interfering with inflammatory signaling molecules. The studies offer ample opportunities for future investigations in the field of the chemistry and biochemistry of organochalcogens (selenium and tellurium), redox modulation and planning of anti-inflammatories.[49]

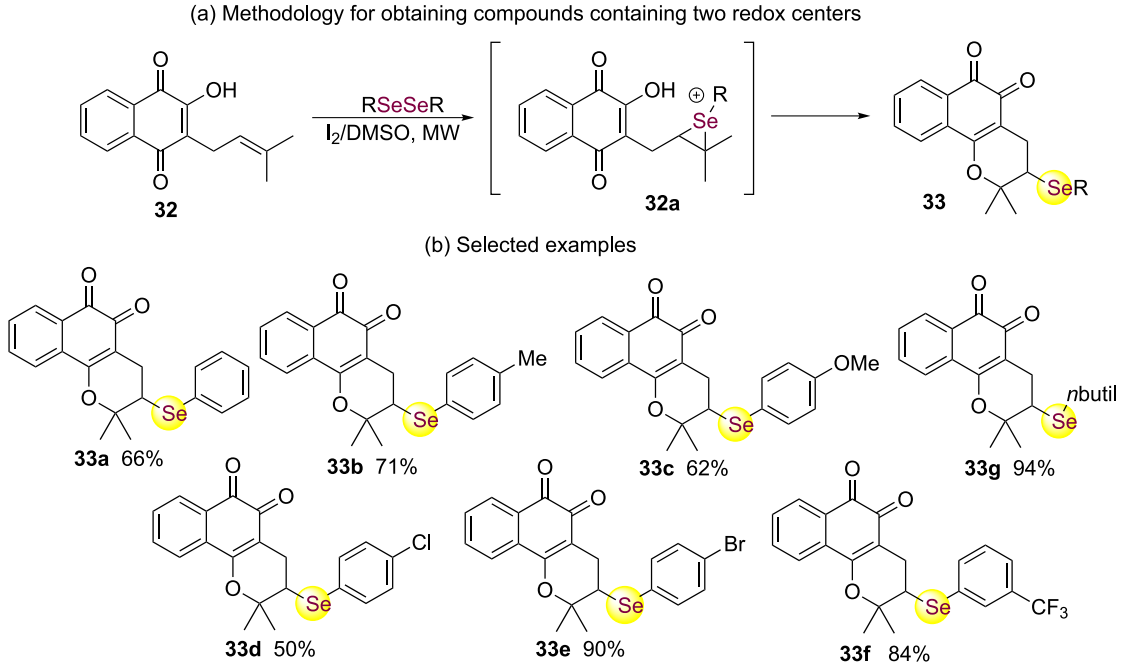
In 2015, da Silva Junior and co-workers[50] reported a fast, efficient and green methodology for obtaining compounds containing two redox centers-quinone and chalcogen. Selenium-containing β-lapachone derivatives **33** were synthesized in moderate to high yields, using I_2/DMSO as a catalytic system and microwave radiation (Scheme 15). The methodology employed allowed the preparation of the compounds from lapachol, passing through the intermediate chalcogeniranium ion **32a**, within a few minutes in a green approach. These compounds were evaluated against several human cancer cell lines (leukemia, colon carcinoma, prostate, ovary, central nervous system



68a R = R_1 = Me, R_2 = R_3 = Br
68b R = R_3 = Me, R_1 = R_2 = Br
68c R = R_1 = OMe, R_2 = R_3 = Br
68d R = R_3 = H, R_1 = CH_3, R_2 = Br

69a R = R_1 = Me, R_2 = R_3 = SePh 8%
69b R = R_3 = Me, R_1 = R_2 = SePh 23%
69c R = R_1 = OMe, R_2 = R_3 = SePh 34%
69d R = R_3 = H, R_1 = Me, R_2 = SePh 21%

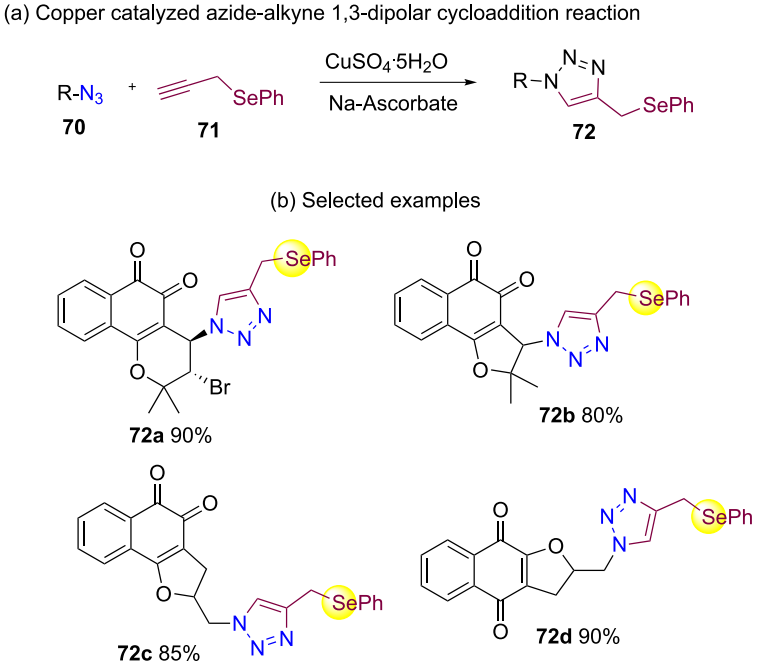
Scheme 14. Synthesis of selenobenzoquinones (adapted from reference 49).



Scheme 15. Synthesis of selenium-containing β-lapachone derivatives (adapted from reference 50).

and breast cancers) showing, in some cases, half-maximal inhibitory concentration (IC_{50}) values below 1 μM.

In the following year, da Cruz *et al.*[51] reported the synthesis of selenium-containing quinone-based 1,2,3-triazoles **72** using a copper catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction (Scheme 16). All compounds were evaluated for antitumor activity *in vitro* using several human cancer cell lines. The results showed most compounds to be highly active against all cancer cell lines evaluated, the *o*-quinones were more active than the *p*-quinones. In general, the most potent compounds showed IC_{50} values below 0.3 μM, being more active than the β-lapachone and doxorubicin, a standard clinical agent used against several types of cancers. Compound **72d** (*p*-quinone) showed IC_{50} values varying from 0.62 to 2.42 μM in the evaluated cancer cell lines. The most active *o*-quinones, **72a-72c**, presented IC_{50} values between 0.07 and 2.52 μM.[51]



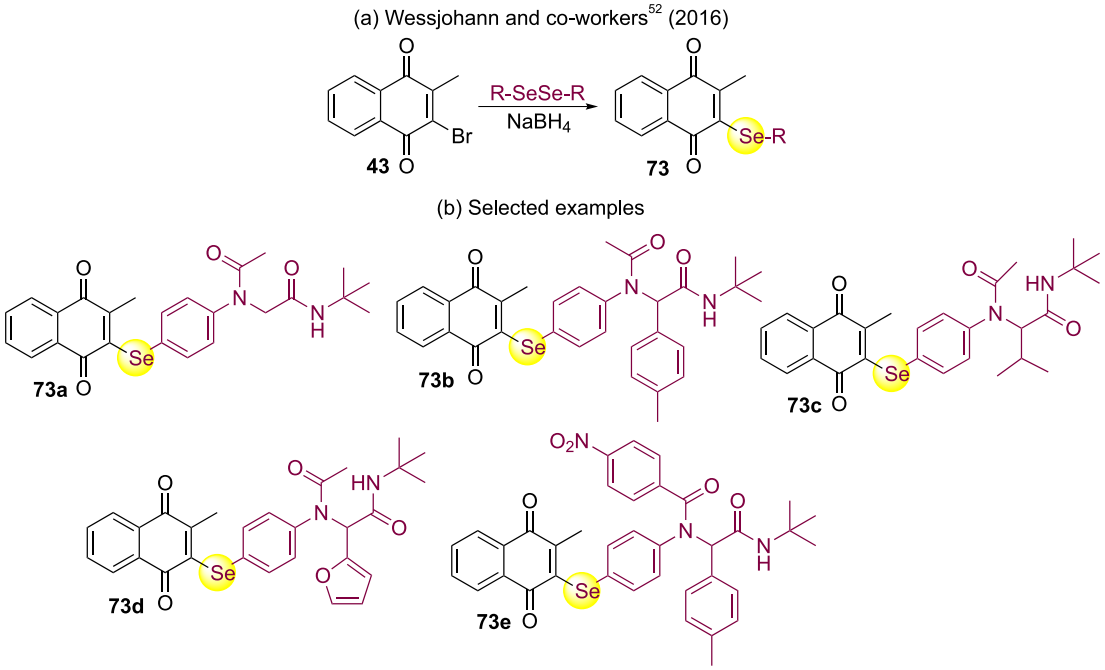
Scheme 16. Synthesis of selenium-containing quinone-based 1,2,3-triazoles (adapted from reference 51).

The synthesis of selenonaphthoquinone pseudopeptides was described in 2016 by Wessjohann and co-workers.[52] Initially, the diselenides were reduced *in situ* to give the corresponding sodium selenolate upon treatment with $NaBH_4$. The attack of nucleophilic selenolate on 2-bromo-3-methyl-1,4-naphthoquinone (**43**) resulted in selenium-based quinone-peptidomimetics **73** with excellent yields (up to 93%, Scheme 17). The cytotoxic activity of these compounds was evaluated in hepatocellular carcinoma (HepG2) and breast adenocarcinoma (MCF-7) cell lines, with **73a** and **73c** being the most potent compounds and with the more pronounced cytotoxicity in the case of MCF-7 compared to HepG2cells, with IC_{50} values of 6 and 7 μM, respectively. Of the tested compounds, selenium-based quinones **73a**, **73b** and **73c** were among the most active, exhibiting good free radical scavenging activity. In addition, compounds **73b** and **73c** exhibited equipotent activity to ampicillin, an antibiotic used in clinical medicine against a range of bacterial infections. On the other hand, compound **73e** showed moderate activity: 68% of that of ampicillin.

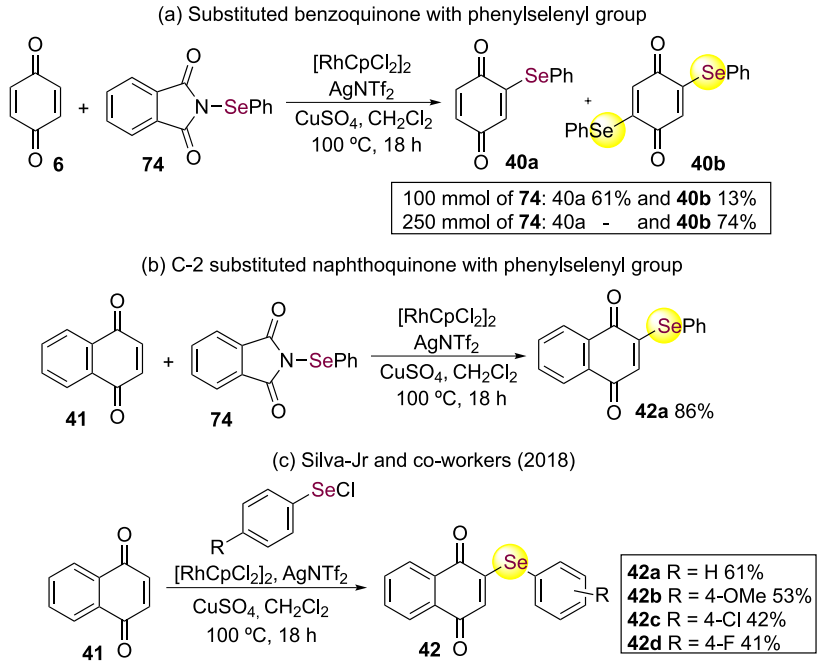
In 2017, selenoquinones were first tested against *Trypanosoma cruzi*, a protozoan that causes Chagas disease. da Silva Junior and co-workers[53] reported the synthesis of selenium-containing quinones by activating the rhodium-catalyzed C–H bond, using species with the electrophilic nature of chalcogen. Reaction of benzoquinone (**6**) with 150 mol% *N*-(phenylseleno)phthalimide (**74**) produced a mixture of **40a** and the bisquinone **40b**. However, using 100 mol% of **74**, **40a** was obtained in good yield and high selectivity. Compound **40b** could be accessed in 74% yield by using a large excess (250 mol%) of **74** (Scheme 18a). Application of the C–H functionalization conditions under Rh-catalysis to 1,4-naphthoquinone provided **42a** in 86% yields (Scheme 18b). Taking advantage of the success of the previously established methodology, other selenium-quinone hybrid compounds with potential antitumor activity were also obtained via Rh-catalyzed C–H bond activation (Scheme 18c).[54] Among these compounds, the naphthoquinone substituted at C-2 with selenium (**42a**, IC_{50} 1.13 μM, selectivity index (SI) 11.2) was 8.5-fold more active than benznidazole, often the first-line treatment for Chagas disease in most countries.[53]

In the following year, the same group demonstrated,[55] the efficient use of stable phenyl selenolate as a nucleophilic reagent in various organic transformations. For example, the A-ring selenylation of naphthoquinones and anthraquinones using copper catalysts (Scheme 19a). The reaction between iodo-quinone **75** and ArSeCl in presence of zinc, copper(I) thiophene-2-carboxylate (CuTC) and dimethylacetamide (DMAc), provided **76a-76j** in yields varying from 42 to 81% (Scheme 19b). Copper complexes and carbon nanotube-copper ferrite in the presence of RSeAg salts efficiently catalyze the reaction and provide the products in high yield (Schemes 19c and 19d). All compounds were evaluated against *T. cruzi*, with **76c** (IC_{50} 13,3 μM) and **76d** (IC_{50} 13,4 μM) being the most potent, about eight-fold more active than benznidazole, a positive control and one of the medicines used against *T. cruzi*.[55]

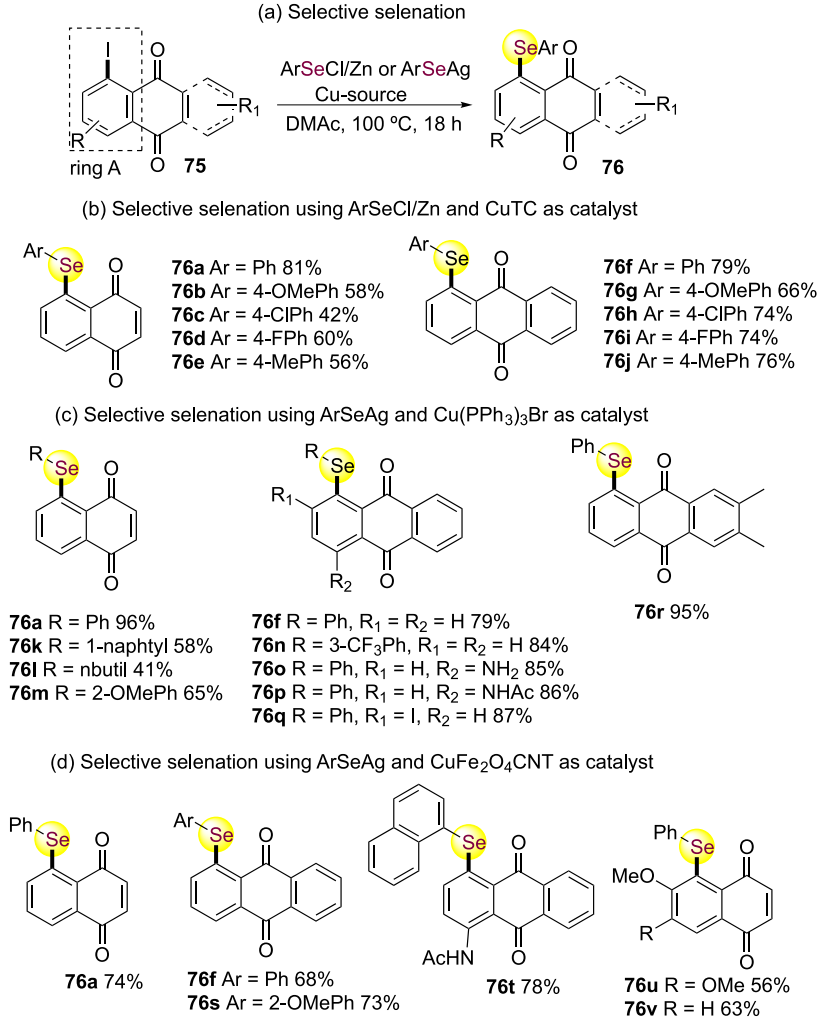
The use of electrochemistry in the synthesis of selenium-containing quinone hybrid molecules has been



Scheme 17. Synthesis of selenium-based quinone-peptidomimetics (adapted from reference 52).



Scheme 18. Functionalization of naphthoquinone via Rh-catalyzed C–H activation (adapted from reference 54).

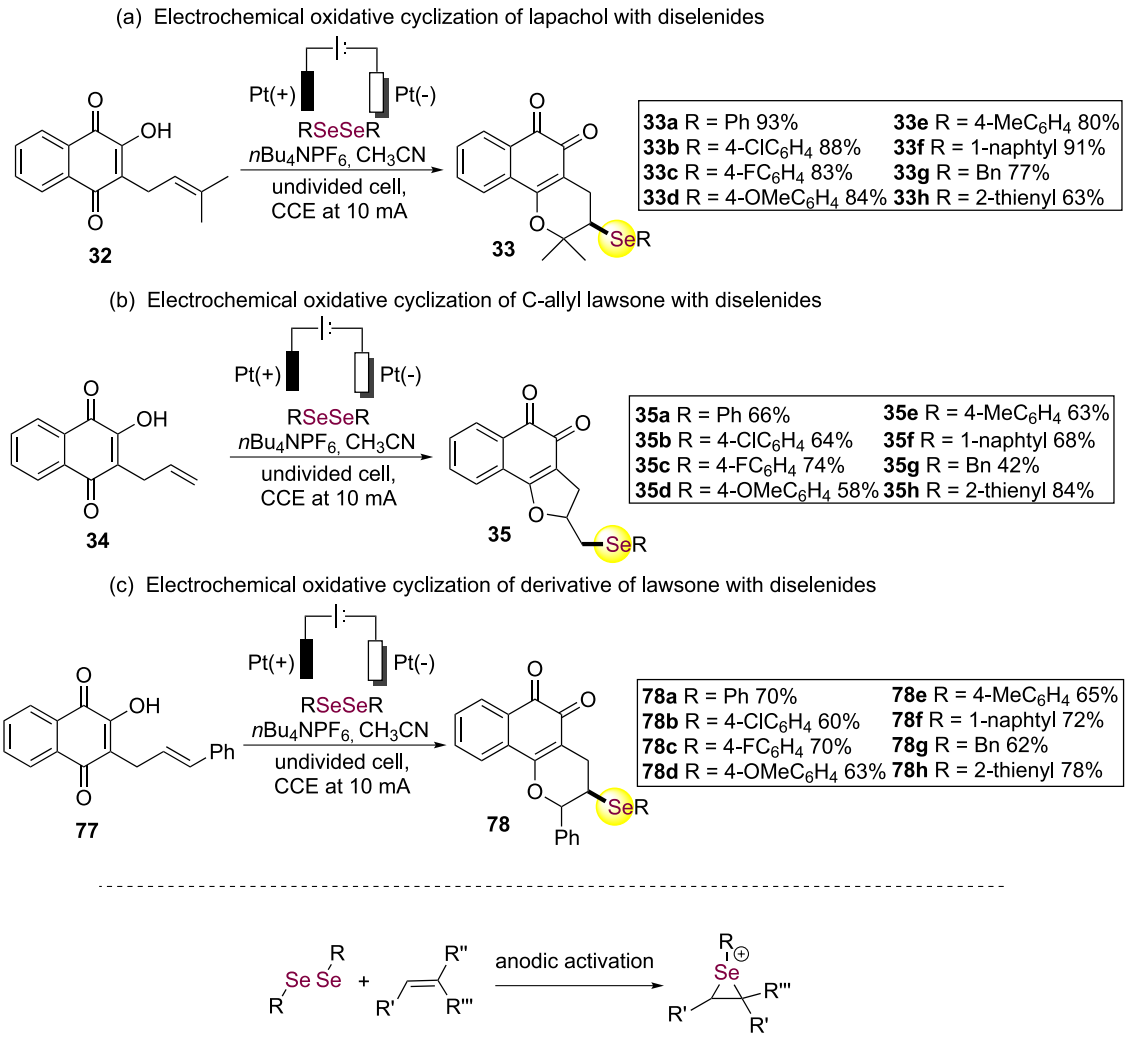


Scheme 19. Selenylation involving naphthoquinones and anthraquinones using a Cu-source as the catalyst (adapted from reference 55).

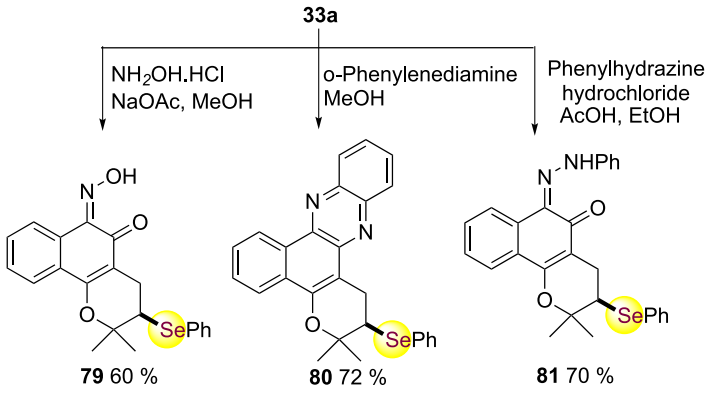
widely explored by several research groups, offering an efficient, ecological, fast and reliable methodology that avoids the use of chemical oxidants. The reactivity of lapachol **32** toward electrophilic selenated species has been described previously[50] in an I_2/DMSO oxidative system. However, this type of oxidative cyclization is also possible in an electrochemical cell. Thus, da Silva Junior and co-workers,[56] motivated by the positive results of previous studies, described a range of selenium-functionalized quinones using electrochemical selenylation. They also analyzed the reaction through cyclic voltammetry to investigate the mechanism, and it was possible to confirm the formation of the cationic intermediate, coming from an electrophilic addition of selenium, followed by a nucleophilic cyclization (Scheme 20). Some of the compounds produced exhibited considerable biological activity against five cancer cell lines and *T. cruzi*, such as **33c**, which is active against HCT-116 and B16F10 cancer cells with IC_{50} values of 0.95 and 0.98 μM, respectively (doxorubicin: IC_{50} values of 0.19 and 1.34 μM, respectively), and against *T. cruzi* with an IC_{50} of 38.3 μM (benznidazole: IC_{50} of 103.6 μM).[56]

Derivatizations of **33a** were also investigated to demonstrate the usefulness of the selenated naphthoquinones. Reaction of **33a** with hydroxylamine hydrochloride, *o*-phenylenediamine and phenylhydrazine hydrochloride provided **79**, **80** and **81** in yields of 60, 72 and 70%, respectively (Scheme 21). Lapachone derivatives have several applications, such as fluorescent sensors for images of living cells and lipid droplets and for imaging of NQO1 activity in tumor tissues.[56]

Recently, Nascimento and co-workers[57] developed a series of seleno-1,4-naphthoquinones **84** against *Mycobacterium tuberculosis* H37Rv, a bacterium that causes tuberculosis. Seleno-functionalization of menadione was performed rapidly and economically. The synthetic approach used to obtain selenium-containing menadione derivatives was based on a two-step pathway



Scheme 20. Electrochemical selenylation/cyclization employing a quinone component (adapted from reference 56).



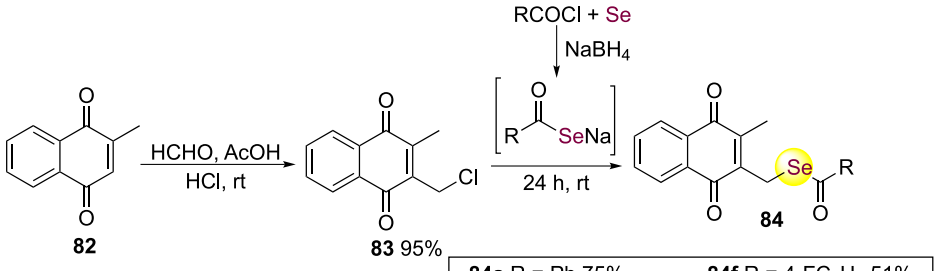
Scheme 21. Synthesis of lapachone derivatives (adapted from reference 56).

entailing the use of commercial menadione **82**. First was the insertion of the $-CH_2Cl$ group into menadione in excellent yield (95%) followed by the seleno-functionalization of **83** by means of a reaction with the respective selenocarboxylate generated *in situ*, obtaining the compounds in yields varying from 24 to 75% (Scheme 22). All compounds were evaluated against *M. tuberculosis* H37Rv, with **84a**, **84c** and **84f** showing the best minimum inhibitory concentration (MIC) values 2.1, 8.0 and 8.1 μM, respectively. These compounds were also tested *in vitro* against multidrug-resistant clinical isolates (CDCT-16 and CDCT-27) and showed remarkable values from 0.8 to 3.1 μM. A final analysis was carried out exploring its toxicity against the Vero cell lines, where **84a** and **84f** proved to be non-toxic. Therefore, the new selenium-menadione conjugates were shown to be a promising class of anti-tuberculosis agents, mainly in combating the multidrug-resistant event.

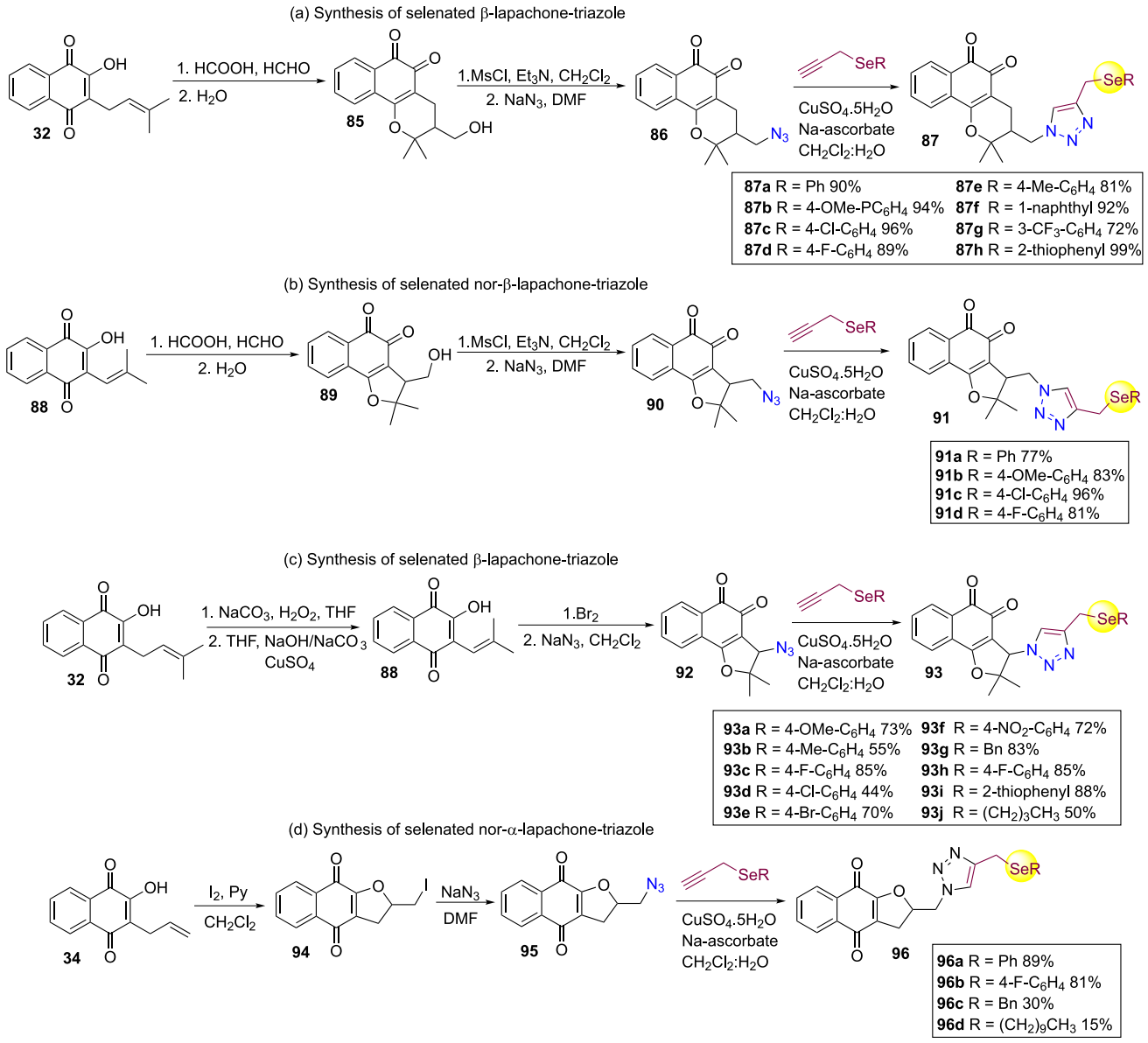
In the same year, da Silva Junior and co-workers[58] published the synthesis and biological evaluation against several cancer cell lines of 48 new compounds containing two redox centers (combinations of selenium and naphthoquinones) linked by a triazole ring. The authors reported that selenonaphthoquinones **87a-87h**, **91a-91h**, **93a-93j** and **96a-96d**, were synthesized by an accessible synthetic approach, making it possible to obtain selenated beta-lapachone-triazoles and selenated nor-beta-lapachone-triazoles (Schemes 23a and 23b) containing a spacer between the redox centers, and selenated β-lapachone-triazoles and selenated nor-α-lapachone-triazoles (Schemes 23c and 23d) without this space. Furthermore, it was reported that the antitumor activity of these compounds was generally satisfactory with IC_{50} values below 0.5 μM, significantly lower cytotoxicity in the L929 control cell line and good selectivity index. Thus, the wide range of compounds synthesized, in addition to showing good initial results, serves as an inspiration for the discovery of new antitumor drugs.[58]

3. Final Remarks

In recent decades the scientific community has devoted its efforts to the study of tellurium- and selenium-containing quinones, which is an important class of compounds with different relevant biological properties. A selenium or tellurium atom can be introduced into quinones as an electrophile, using an appropriate nucleophilic carbon such as double bond, and dichalcogenides or arylchalcogenyl halides. On the other hand, chalcogen-containing quinones can also be prepared through the



Scheme 22. Seleno-functionalization of menadione (adapted from reference 57).



Scheme 23. Synthesis of selenated lapachone-triazole (adapted from reference 58).

reaction of quinones containing electrophiles with different nucleophilic selenium or tellurium species generated through diverse methodologies. The choice of method is guided by the structure of the quinone derivatives that react with the chalcogen source. Due to the high potential of quinones containing an organochalcogen moiety as bioactive structures, we believe that new investigations into the design, synthesis and biological evaluation of these molecules can lead to new biochemical tools and consequent new successes in drug development. We visualize that this review and perspectives described herein will stimulate further efforts from researchers across the quinone and organochalcogen community.

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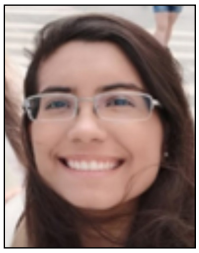
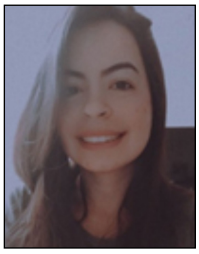
Author Contributions

Pâmella S. Cordeiro, Ingrid C. Chipoline, Ruan C. B. Ribeiro, David R. Pinho were responsible for the bibliographic search, writing original draft and drawing of the schemes; Vitor F. Ferreira, Fernando C. da Silva, Luana S. M. Forezi and Vanessa Nascimento

for investigation, project administration resources, writing original draft and writing-review and editing writing.



Pâmella S. Cordeiro *was born in Niterói-RJ in 1996. She received her Bachelor's degree in Chemistry in 2019 from Universidade Federal Fluminense. In the same year she started doctoral studies in the Postgraduate Program in Chemistry at Universidade Federal Fluminense. Her line of research is based on the green synthesis of organocompounds with biological potential.*



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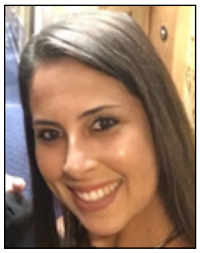
David R. Pinho *is a pharmacy student at Universidade Federal Fluminense. He is currently a scientific initiation scholarship holder in a project financed by the Carlos Chagas Filho Research Support Foundation of the State of Rio de Janeiro (FAPERJ). His work has an emphasis on the synthesis of compounds containing organochalcogen menadione hybrids with potential bioactivity, being developed at the Laboratory of Applied Organic Synthesis (LabSOA).*

Vitor F. Ferreira *received his Bachelor's degree in Chemistry in 1976 and a Master's degree in Natural Product Chemistry in 1980, both from the Federal University of Rio de Janeiro. In 1984 he finished his PhD in Organic Chemistry at the University of California, San Diego. In 1986 he became Professor of Organic Chemistry in the Organic Chemistry Department of Universidade Federal Fluminense (UFF), in Niterói-RJ, and in 1995 became full Professor. In 1998 he spent one year in postdoctoral research at the University of Oklahoma. Professor Ferreira is currently a full Professor at the Pharmaceutical Technology Department of UFF, researching the synthesis of small molecules, with a focus on the development of new methods in organic synthesis in the search for bioactive compounds and their pharmaceutical formulation. He is a full member of the Brazilian Academy of Science and was president of the Brazilian Chemical Society from 2012 to 2014. He is currently the advisor to the presidency of the "Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ)".*

Fernando C. da Silva *received his Bachelor's degree in Industrial Chemistry in 2002 and his PhD in 2007, both from Universidade Federal Fluminense. He then completed a postdoctoral stage at the University of Aveiro (Portugal) at the Laboratory of Synthesis of Porphyrin Compounds. Currently, he is an Associate Professor in the Department of Organic Chemistry of Universidade Federal Fluminense. He was an affiliate member of the Brazilian Academy of Science 2016-2020 and his research interests focus on the synthesis of quinones, 1,2,3-triazoles, coumarins, carbohydrates, diazo compounds, β-enaminones and porphyrins.*

Luana S. M. Forezi *received her Bachelor's degree in Chemistry in 2008 from the Federal University of Juiz de Fora and her MSc (2011) and PhD (2014), with a period at the University of Aveiro (Portugal), at the Laboratory of Synthesis of Porphyrin Compounds, both at Universidade Federal Fluminense. She carried out*



two postdoctoral studies: one at the Federal University of Rio de Janeiro (2015) and another at the Fluminense Federal University (2015-2020). Since 2020, she has been adjunct Professor in the Department of Organic Chemistry at Universidade Federal Fluminense. Her the research interests focus on the synthesis of coumarins, 1,2,3-triazoles and quinones.

Vanessa Nascimento *was born in Marau (RS State), Brazil. In 2009 she obtained her BSc degree in Industrial Chemistry from the Federal University of Santa Maria. She then moved to the Federal University of Santa Catarina, where she received her MSc (2011) and PhD degrees (2015) at the Selenium and Tellurium Derivatives Synthesis Laboratory and with a period at the Università degli Studi di Perugia in the Santi's group. She then completed a postdoctoral stage at UFSC (2015-2016) in the Catalysis and Interfacial Phenomena Laboratory. Since 2016 she has been adjunct Professor in the Department of Organic Chemistry at Universidade Federal Fluminense. Her research focuses mainly on the synthesis and applications of pillararenes and organochalcogenides.*

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