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Arkivoc **2022**, part v, 0-0
to be inserted by editorial office

Organoselenium compounds as antioxidants

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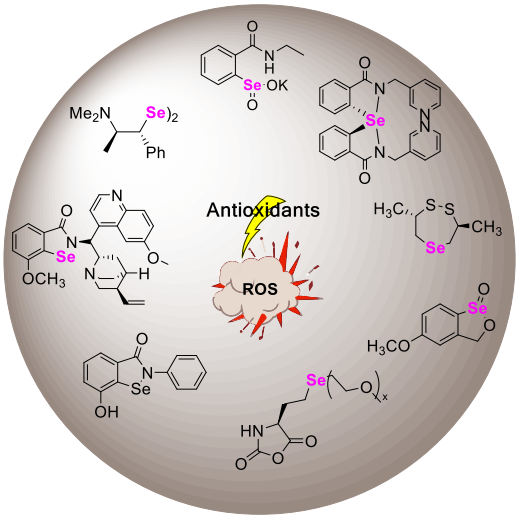
Dedicated to Prof. Józef Drabowicz on the occasion of his 76th anniversary

Received 10-14-2022 **Accepted** 11-17-2022 **Published on line** 12-01-2022

Abstract

Reactive oxygen species (ROS) are responsible for many of civilization's diseases, including cancer, diabetes, and Alzheimer's disease, decomposition of products in the food industry, and deterioration of physicochemical properties of polymers and nanomaterials. In recent years, several organoselenium compounds have been synthesized and used as peroxide scavengers, which are the source of many antioxidant substances. This review aims to collect and divide the organoselenium compounds obtained in the last twelve years with antioxidant activity, which can prove helpful in a) medicine as supplements preventing diseases caused by oxidative stress, b) as food additives preventing oxidation, or c) in the materials industry as Se-containing nanoparticles and polymers. In addition, the most common methods for determining GPx-like antioxidant activity are presented.



Keywords: GPx mimics, organoselenium compounds, antioxidants

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1. Introduction

The formation of reactive oxygen species (ROS) in living organisms is related to many basic biological processes, such as the respiratory chain, metabolism of purine nucleotides, microsomal hydroxylation cycle, and reactions involving oxidoreductases. The products of these reactions, which include the superoxide anion radical ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2), should be reduced in subsequent biochemical reactions and safely removed from the body. However, may not be the case for various reasons, for example, stress, improper diet, and strenuous exercise.[1]

The imbalance between the rate of ROS formation and the efficiency of the antioxidant system is known as oxidative stress. Excessive production of ROS with the simultaneous depletion of antioxidant reserves causes the oxidation of fatty acids, proteins, and DNA. Efforts to reduce oxidative stress can be manifested in the clinical improvement of patients, while excessive production of ROS is the primary cause or secondary complication of the disease. Toxic oxidation products are the initiators of several diseases, such as atherosclerosis, hypertension, diabetes, inflammation, Alzheimer's disease, and cancer.[1]

Antioxidants are compounds that possess the ability to prevent or inhibit the oxidation of other chemicals, and among them, we find molecules of both natural and synthetic origin.[2,3] The biological systems include endogenous compounds produced by the organism, which in turn can be divided into derivatives of enzymatic (e.g., glutathione peroxidase (GPx), thioredoxin reductase (TrxR), superoxide dismutase (SOD), and catalase) and non-enzymatic (e.g., lipoic acid, glutathione, ferritin, albumin) origin. When endogenous antioxidants are unable to protect the body against the effects of ROS, there is a need for exogenous antioxidants derived from natural sources, such as plants (e.g., flavonoids, phenolic acids, carotenoids, organosulfur compounds, vitamins) or minerals (selenium, zinc, manganese) provided via appropriate diet. The second group of antioxidants is compounds of synthetic origin, delivered to organisms in the form of dietary supplements and bioequivalent to their natural forms (e.g., vitamin C compared to chemically synthesized *L*-ascorbic acid). Synthetic antioxidants are also utilized as additives to prevent the oxidation of unstable ingredients in the food, pharmaceutical,

cosmetic, and materials industries. The classifications of antioxidants, along with the most representative examples, are shown in Figure 1.[4]

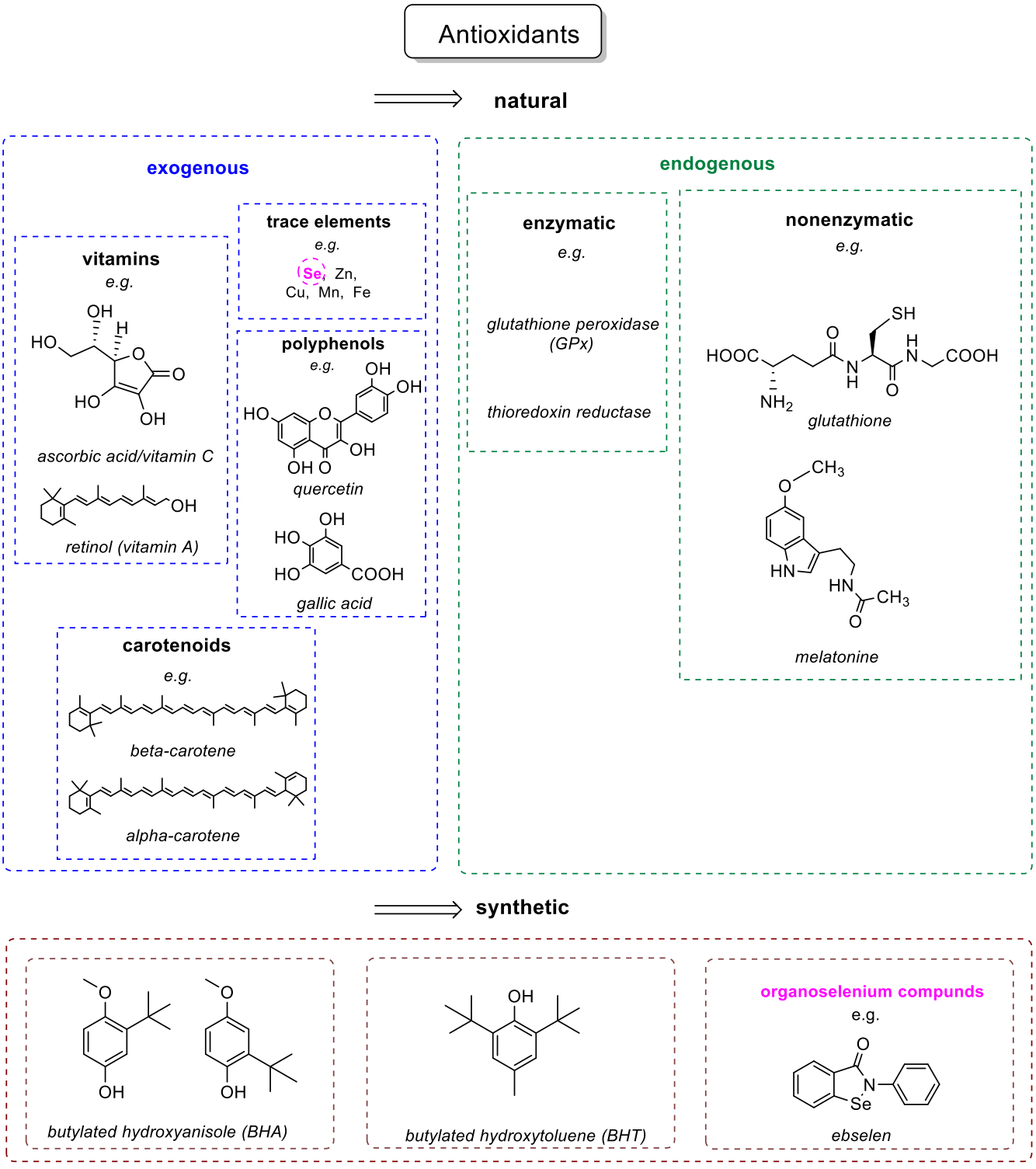


Figure 1. Antioxidants, classification with examples.

In the biological context, selenium was considered for many years only as a poison and carcinogen.[5,6,7] A breakthrough moment that changed the perception of selenium and revealed its positive face came in the second half of the 20th century. At that time, two researchers, Schwarz and Foltz, confirmed that trace amounts

of selenium are necessary for the proper functioning of animals and human organisms.[8] Selenium biology has developed rapidly in recent decades and is now known in various forms as an essential trace element in living organisms. Nutritional functions of selenium in the human body are provided by the action of 25 selenoproteins. A key role in effectively reducing harmful peroxides is played by one, so far the best known in mammals, selenoenzyme - glutathione peroxidase (GPx). The biological activity of this protein is related to the presence of selenocysteine (Sec) in its active site.[9] Since these discoveries, the incorporation of a selenium atom in the structure of various small molecules enabled the design of many potential Se-therapeutics. Numerous publications in the field of medicinal chemistry present the significant biological potential of organoselenium compounds in diversified activity assays.[10,11,12,13]

Glutathione peroxidase (GPx) catalyzes the reduction of H_2O_2 and other organic peroxides using glutathione (GSH) as a cofactor.[14] Under physiological conditions, in the first step, active selenol (E-SeH) **1** is oxidized to selenenic acid (E-SeOH) **2**. Acid **2** reacts with glutathione (GSH) to form the selenenyl sulfide **3**. Regeneration of selenol **1** takes place as a result of the reaction of sulfide (E-Se-SG) **3** with another molecule of glutathione (GSH) and the release of its oxidized form - disulfide (GSSG). In oxidative stress conditions, when the level of hydrogen peroxide (H_2O_2) is high and glutathione (GSH) is low, over-oxidation of selenol takes place, and the formation of seleninic acid (E-SeOOH) **4** occurs (Figure 2).[15]

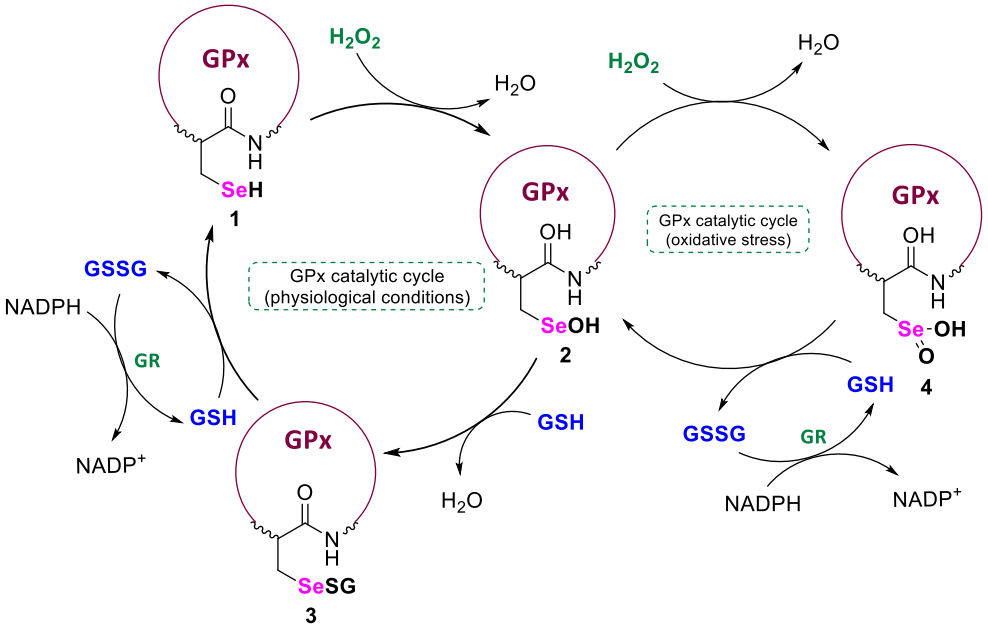


Figure 2. GPx catalytic cycle. GSH: reduced form of glutathione; GSSG: the oxidized dimeric form of glutathione; GR: glutathione reductase.

Looking at the GPx catalytic cycle, it should be noted that catalysis will be possible only if the chalcogen atom is easily reduced to the appropriate nucleophilic form and only if non-reversible overoxidation is prevented. The unique property of selenenic and seleninic species compared to sulfur analogs results from their easy oxidation-reduction reactions with the participation of thiols. The formation of sulfonic acid is irreversible[16] and sulfinic acid can be reduced only in a few cases by sulfiredoxin.[17] Therefore, an additional evolutionary benefit of using selenocysteine in the redox protein instead of cysteine is evident.[18] An in-depth analysis of the structure and understanding of the mechanism of GPx activity placed the mentioned selenoenzyme in the center of chemists' attention. Scientists are trying to synthesize organoselenium compounds that are specific mimetics of GPx and

thus possess potent antioxidant activity. In this review, we have collected information from the last twelve years on topics covering the roles of organoselenium compounds as antioxidants in a) medicine and b) in materials chemistry and the food industry.

2. Methods of Measuring GPx-like Antioxidant Activity

This section presents the most common methods of measuring antioxidant activity that has been used in the studies listed below.

Method A: GSH/GR coupled assay[19]

The glutathione reductase (GR) coupled assay was the first indirect method to evaluate GPx-mimic activity, developed by Wilson *et al.* The GR enzyme, at the expense of the cofactor NADPH (β-nicotinamide adenine dinucleotide 2′-phosphate), catalyzes the reduction of the oxidized form of glutathione (GSSG), formed during the catalytic action, back to GSH. The initial reduction rates (v_0) of NADPH are recorded by using UV spectroscopy at 340 nm. The GPx-like catalytic activity is studied using various peroxides for this reaction, e.g., hydrogen peroxide (H_2O_2), *tert*-butyl hydroperoxide (*t*-BuOOH), or cumene hydroperoxide (Cum-OOH). The half and summary equations of the involved reaction are shown below (Eqn 1,2,3).

$$2GSH + H_2O \xrightarrow[\text{peroxidase}]{GSH} GSSG + 2H_2O \quad (1)$$

$$GSSG + NADPH + H^+ \xrightarrow[\text{reductase}]{GSH} 2GSH + NADP^+ \quad (2)$$

$$H^+ + NADPH + H_2O_2 \longrightarrow NADP^+ + 2H_2O \quad (3)$$

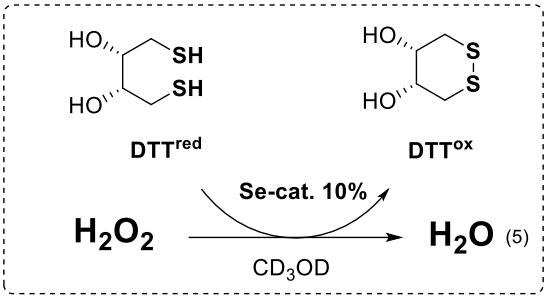
Method B: PhSH assay[20]

In this direct method developed by Tomoda *et al.*, benzenethiol (PhSH) is used as an alternative to glutathione. The reduction of hydrogen peroxide in the presence of PhSH with simultaneous formation of diphenyl disulfide (PhSSPh) is assessed using different techniques: a) spectrophotometrically through the UV absorption increase at 305 nm due to PhSSPh formation; b) using the HPLC analysis because the amount of PhSSPh formed is determined by the time required for 50% conversion of PhSH to PhSSPh ($t_{1/2}$ values) and calculated as the peak areas at different time intervals. The equation of the described reaction is shown below (Eqn 4).

$$2PhSH + H_2O_2 \xrightarrow{\text{Se-cat.}} 2H_2O + PhSSPh \quad (4)$$

Method C: DTT^{red}/ DTT^{ox} NMR assay[21,22]

The GPx-like antioxidant activity of compounds can be assessed using the test presented by Iwaoka *et al*. The organoselenium catalyst reduces hydrogen peroxide (H_2O_2) and is regenerated in the presence of dithiothreitol (DTT^{red}). The rate of the reaction is measured using ^1H NMR spectroscopy in CD_3OD[21] or D_2O.[22] The appearance of signals representing the formed disulfide (DTT^{ox}) in specific time intervals is recorded. The equation of the reaction is shown below (Eqn 5).



Method D: DPPH assay[23]

Shaaban *et al.* described another easy method to assess the radical scavenging activities of organoselenium compounds and nutritional products. The antioxidant activity of a compound is estimated by its ability to reduce stable DPPH· radical (purple color in methanol) to DPPHH (colorless) by the decrease in the absorbance at 517 nm.

Method E: ABTS assay[24]

In this method presented by Shaaban *et al.*, the antioxidant activity of organoselenium compounds is assessed by their ability to decolorize the ABTS· (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radicals and the corresponding radical-scavenging activity is estimated by the decrease in the absorbance at 734 nm.

3. Antioxidants in Medicine

3.1. Ebselen and its derivatives

Ebselen (*N*-phenylbenzisoselenazol-3(2*H*)-one) **5** is one of the first synthetic glutathione peroxidase (GPx) mimetics to catalyze essential reactions involved in protecting cells from oxidative damage and free radicals.[25,26,27] Currently, it is in the second and third phases of clinical trials as a therapeutic in treating diseases caused mainly by oxidative stress (Figure 3).[28] This section presents recent advances in synthesis of new ebselen analogs with enhanced GPx-like activity. Modifications of the ebselen **5** structure mainly include the replacement or substitution of the phenyl group on the nitrogen atom (ring B) or the connection of various substituents on the benzamide ring A.

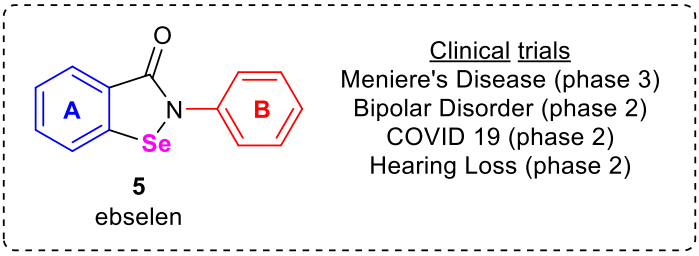


Figure 3. Structure of ebselen.

3.1.1. Modification of ebselen rings A and B. A series of benzisoselenazolones with additional substituents on the benzamide ring was examined in terms of antioxidant activity by Kumar *et al.* (2014) utilizing Method B.[20] The high GPx-like activity of benzisoselenazolone **6** (Figure 4), which forms selenol intermediate **8**, suggests the presence of the bulky *N*-quininamine substituent and the *ortho*-CH_3 benzamide substituent stabilizes compound

8, which regenerates benzisoselenazolone **6** through its reaction with H_2O_2 (Figure 4). Compound **6** showed a much higher antioxidant activity than other benzisoselenazolones presented in this article and is 10^3-fold more active than ebselen **5**.[29]

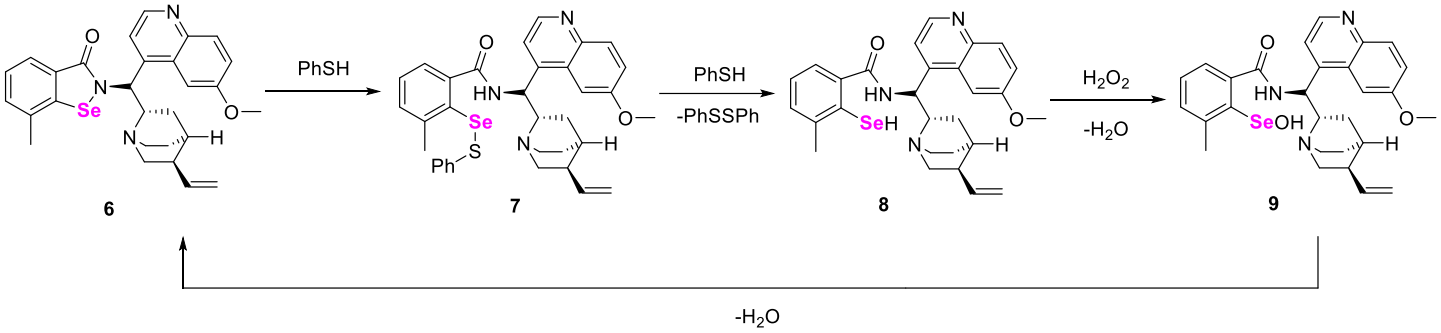


Figure 4. The high GPx-like activity of benzisoselenazolone **6** and generation of selenol **8.**

The GPx-like activity of the ebselenol series was also described by Kumar *et al.* in 2016 and compared with ebselen **5** using GSH/H_2O_2 and GSH/*t*-BuOOH assays (Method A).[19] All obtained compounds possessed antioxidant activity higher than ebselen **5**. Moreover, all derivatives were more active when the oxidant was H_2O_2. The compounds were also assessed as GPx-mimics using Method B.[20] Ebselenol **10** (Figure 5) was a 15-fold more active catalyst than ebselen **5**. The authors suggest that such high activity of compound **10** was most likely a result of the hydroxyl group and the selenium center proximity.[30] In 2021, Kumar *et al.* synthesized *N*-methyl ebselenamine compounds and then assessed their antioxidant activity (Method A),[19] noting that the excellent GPx-like activity of the obtained derivatives may be related to the close proximity of the -NHMe group and the selenium atom. Of all the compounds, derivative **11** showed the highest antioxidant activity (2.5-fold more active than ebselen **5** and 5-fold more active than α-tocopherol).[31]

In 2014, a group of Chinese researchers obtained a new series of multi-target directed ligands derived from ebselen **5** and tested them for catalytic reduction of H_2O_2 using Method A[19]. The results indicated that compound **12** (Figure 5) exhibited about 1.5-fold higher antioxidant activity than ebselen **5.**[32]

3.1.2. Modification of ebselen ring B. In 2011, a series of di- and tripeptide-based ebselen analogs was synthesized by Satheeshkumar and Mugesh. The GPx-like antioxidant activity was studied using Method A.[19] The antioxidant activity of these compounds depends significantly on the nature of the peptide moiety attached to the nitrogen atom of the selenazole ring. Compound **13** (Figure 5), which possesses a Val-Ala peptide, showed the highest antioxidant activity in all three peroxide assays (about 2-fold higher than ebselen **5**). The authors suggest that the (Val-Ala) dipeptide facilitates the formation of active selenol, which is directly involved in the scavenging of peroxides (See Figure 2).[33]

In 2014, in Wirth's research group, a series of new *N*-chiral benzisoselenazolones was synthesized. The GPx-like activity of all derivatives was determined by Method B[20] (using a high-performance liquid chromatography (HPLC) assay) and by Method A[19] (by the UV–Vis assay), each with two different peroxides, H_2O_2 and CumOOH as the substrates. Most of the obtained derivatives showed GPx-like activity similar to that of ebselen **5**. In contrast, the highest antioxidant activity was observed for the derivative **14** (Figure 5) with the hydroxyl group (about two-fold higher than that of ebselen **5** in Method A[19]).[34]

In the last seven years, several *N*-alkyl,[35] *N*-aryl,[36] and chiral benzisoselenazolones[37,38,39] were obtained by Ścianowski *et al*. The evaluation of the antioxidant activity was based on Method C.[21] The compounds **15-23** that exhibited the highest antioxidant activity in each of the mentioned groups are presented in Figure 5. In the

same research group, the oxygen atom of the carbonyl group was replaced with a sulphur atom by synthesizing the benzisoselenazothiones, and the obtained derivatives were assessed in terms of their GPx-like antioxidant activity (Method C[21]). The best peroxide scavenger was *N*-propyl benzisoselenazole-3(2*H*)-thione (2-fold more active than ebselen **5**).[40]

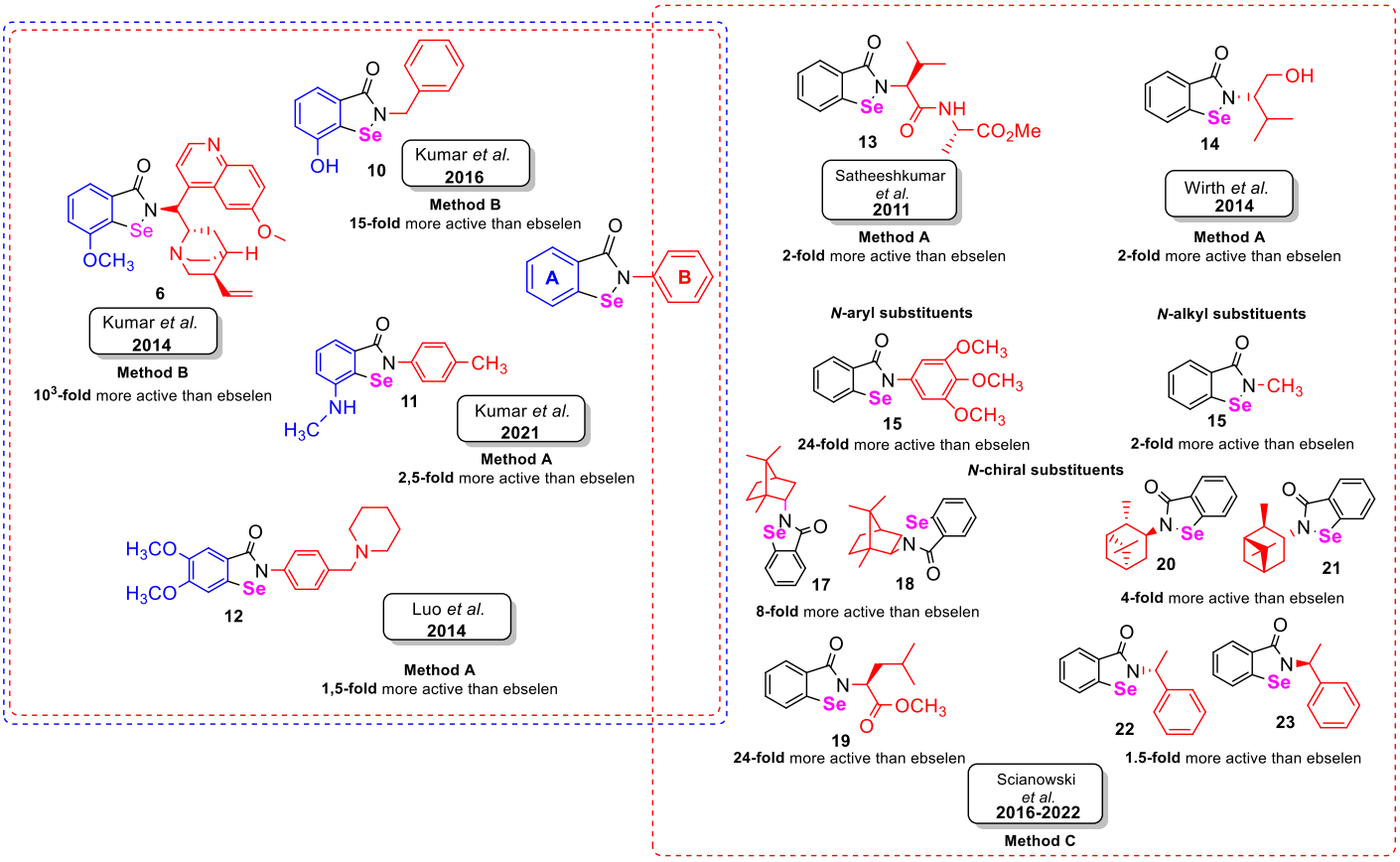


Figure 5. Ebselen analogs **6-23** with potential GPx-like activity.

3.2. Diselenides and their derivatives

In addition to benzisoselenazolones, diselenides constitute the second significant group of compounds with potential antioxidant activity similar to GPx. Diphenyl diselenide $(PhSe)_2$ is the simplest compound among diselenides exhibiting antioxidant potential higher than ebselen, probably because of intramolecular interactions that stabilize its selenylsulfide intermediate, preventing the reduction of H_2O_2. In the recent years, a number of diselenides have been synthesized and evaluated *in vitro* for GPx-like antioxidant activity by several leading research groups.

3.2.1. Diselenides obtained by Braga *et al.* and Rocha *et al.* Chiral diselenides and their derivatives from (-)-ephedrine were prepared and monitored as GPx mimetics by Braga *et al.* (2012). Diselenide **24** and derivative **25** showed catalytic performance 11.5- and 4-fold higher, respectively, compared to the standard $(PhSe)_2$.[41] By combining the structures of ebselen **5** and derivative **24** (the highest antioxidant activity in the previous work), Braga and co-workers obtained amido-based diselenide **26**, which was 9- and 3-times more active than the standard benzisoselenazolone **5** and $(PhSe)_2$.[42] The same research group confirmed that alkyl diselenide **27** containing a cholesterol unit in its structure possessed an antioxidant effect 3-fold higher than ebselen **5.**[43] Aniline-based diselenide **28** substituted with the *p*-CF_3 group was 5- and 2-times more active than ebselen **5** and $(PhSe)_2$, respectively. The obtained results showed that the catalytic efficiency increased with the electron-withdrawing capacity of the substituent in the *para* position. The amino group participates in stabilizing the selenolate intermediate through a hydrogen bond with the selenium atom, creating a zwitterionic form.[44]

In 2012, Braga, in cooperation Hassan and Rocha, obtained β-amino-based diselenides and disulfides. Diselenide **29** showed a very significant antioxidant potential (5-times higher than $(PhSe)_2$) and non-toxic effect.[45] The same scientists continued the idea of synthesizing organoselenium compounds with a heteroatom close to the selenium atom, noting the interesting GPx-like activity of this type of derivative. In 2015, they presented the synthesis of aliphatic and aromatic 2-picolylamide-based diselenides with proximal non-bonding Se--O interactions. The aromatic compound **30** possessed about 5-times higher antioxidant potential than $(PhSe)_2$.[46] Three years later (2018), Braga and Rocha conducted the synthesis of a new class of chiral diselenoamino acid derivatives from phenylalanine and valine. Diselenide **31** showed antioxidant activity similar to $(PhSe)_2$. The obtained results suggested that the catalytic activity of the GPx mimetics presented in this paper depends on the steric effects that can be influenced by the number of carbon atoms between the selenium atom and the amino acid residue and/or by the amino acid lateral residue.[47]

In 2014, Ibrahim, Rocha *et al.* revealed that an amino group in amino diselenides drastically enhances their GPx-like catalytic activities by synthesizing 1-(2-(2-(2-(1-aminoethyl)phenyl)diselanyl)phenyl)ethanamine **32** and comparing the results obtained with activity observed for $(PhSe)_2$ (two times higher activity than $(PhSe)_2$).[48] In 2019, the same compound **32** was tested *in vitro* and *in vivo* in mice, showing no acute toxicity.[49]

The GPx-like activity for all the diselenides and their derivatives **24-32** was evaluated according to Method B.[20] The relative activity observed for the individual derivatives **24-32** and their structures are summarized in Figure 6.

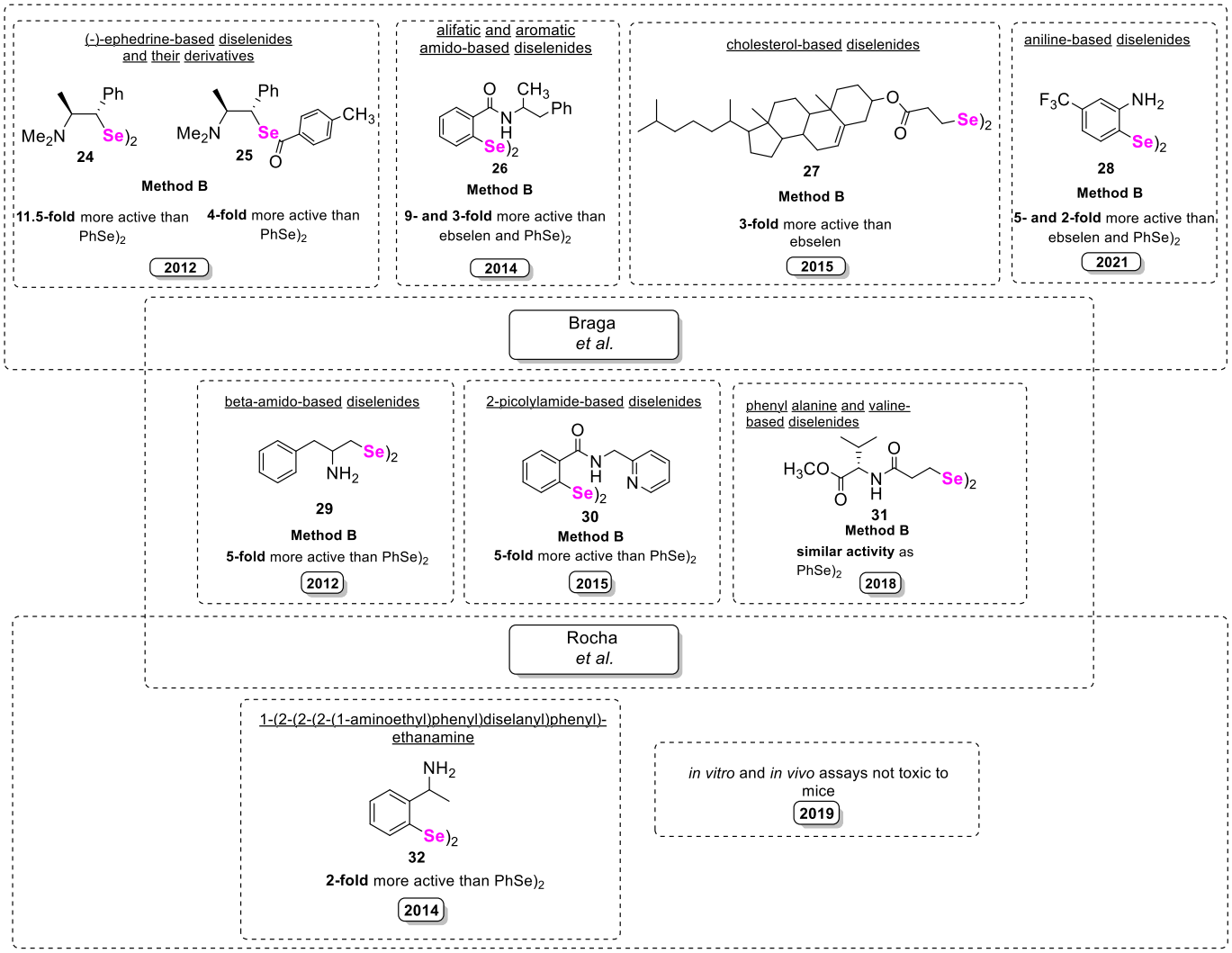


Figure 6. Diselenides and their derivatives **24-32** with potential GPx-like activity assessed by Braga, Rocha *et al*.

3.2.2. Diselenides designed by Singh *et al.* Another research group specialized in synthesizing organoselenium compounds with potential antioxidant activity is that of Singh *et al*. In 2014, they assessed the antioxidant potential of nicotinoyl-based organoselenium compound **33** (2,2'-diselenobis[3-amidopyridine]), and it was two-times more active than ebselen **5**.[50] The results obtained in this work inspired the authors to synthesize new pyridine-based GPx mimics by substituting suitable functional groups. In the same year, an article appeared about the synthesis of pyridoxine-derived diselenides and other organoselenium derivatives (selenides, selones, seleninic acids, selenosulfides) was performed. Among all derivatives, the lower potential was observed for selenide **34**, selone **35**, selenosulfide **38** and the highest for diselenide **36** (1.5-fold more active than ebselen **5**) and seleninic acid **37** (2-fold active than ebselen **5**).[51] In the next paper (2015), Singh *et al.* proposed to modify diselenide **36** by introducing a bromine atom in the 6-position of the pyridine ring. This substitution increased the antioxidant activity of derivative **39** (2-fold more active than ebselen **5**).[52] In 2021, Singh, Kumar *et al.* received a series of diselenides **40a-d**, selenazolonamines **41a-d**, selenoxides **42a-d**. They noticed that electron-donating substituents dramatically increased the antioxidant potential. Moreover, the selenoxides **42a-d** showed a GPx-like activity higher than the corresponding selenazolonamines **41a-d**. The highest antioxidant activity was observed for diselenide **40d** (2-fold more active than ebselen **5**).[53] The GPx-like activities of all

compounds **33-42** were assessed by utilizing Method A.[19] The relative activities for the individual derivatives **33-42** and their structures are summarized in Figure 7.

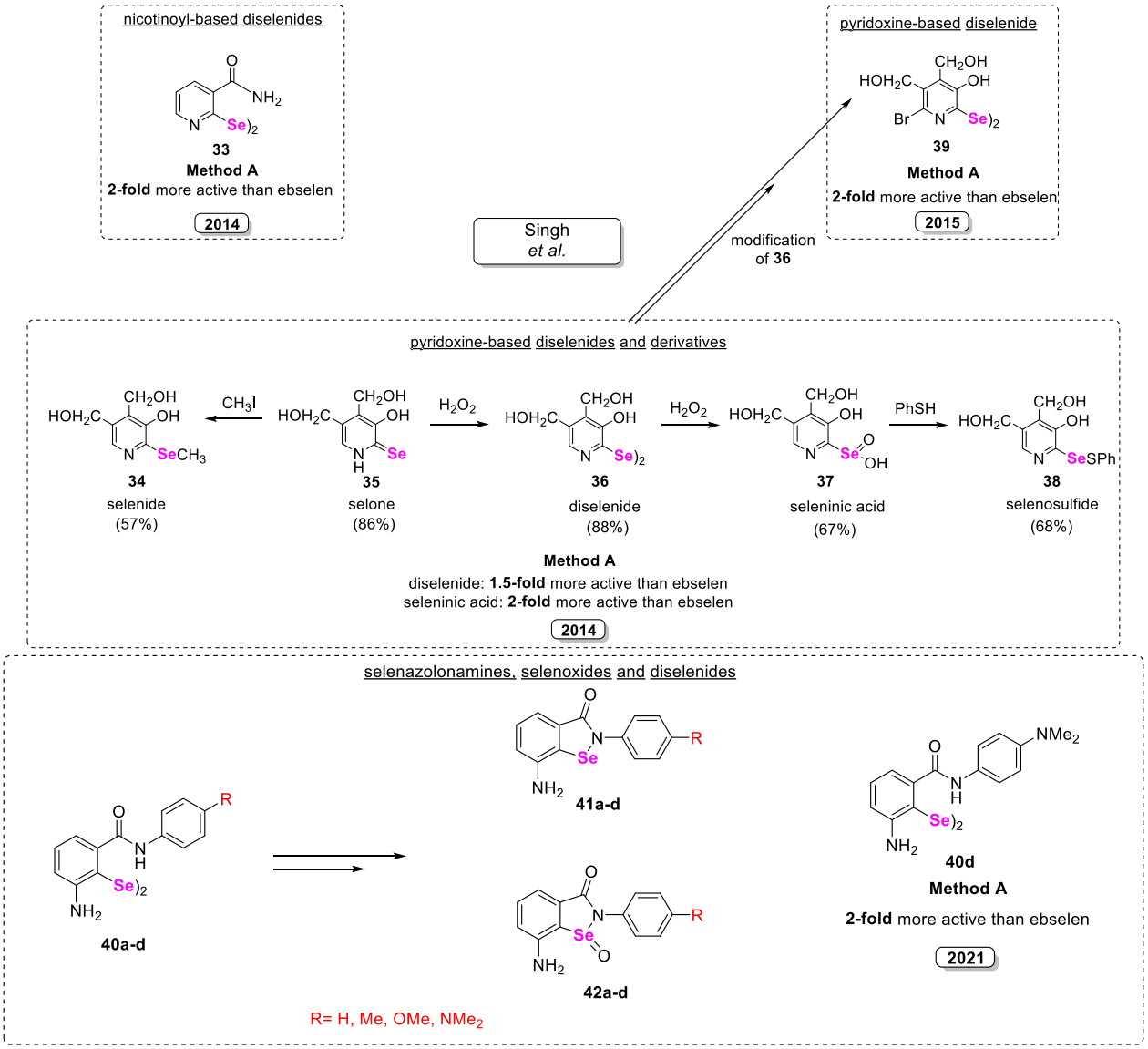


Figure 7. Diselenides and their derivatives **33-42** with potential GPx-like activity assessed by Singh *et al.*

3.2.3. Diselenides synthesized by Mugesh *et al*. As mentioned above, the high activity of amine-based diselenides is related to the presence of basic amino groups which can deprotonate the selenol to generate a more reactive selenolate in the catalytic cycle of GPx (See Figure 2). Mugesh *et al*., in various studies, assessed the antioxidant activity of *tert*- and *sec*-amine-based diselenides. Modification of the aromatic *tert*-amino diselenide **43** ring[54] by introducing a 4- or 6-methoxy group increased the antioxidant activity of the new derivatives **44** and **45**.[55] The *sec*-amino diselenides **46a-d** containing alkyl substituents turned out to be unstable and rapidly cyclized to the corresponding isoselenazolones **47a-d**. These, in turn, showed GPx-mimetic activity 2- and 3-fold higher than ebselen **5**. Stable diselenides **48a-d** presented lower antioxidant activity than isoselenazolones **47a-d** and marginally better than ebselen **5**.[56] The antioxidant activity was also assessed for diselenide **49** and compared with the derivative **44**.[57] The GPx-mimic activity for derivatives **43-48** was evaluated

using Method A[19] and for compound **49** using Method B.[20] The relative activities for the individual derivatives **43-49** and their structures are summarized in Figure 8.

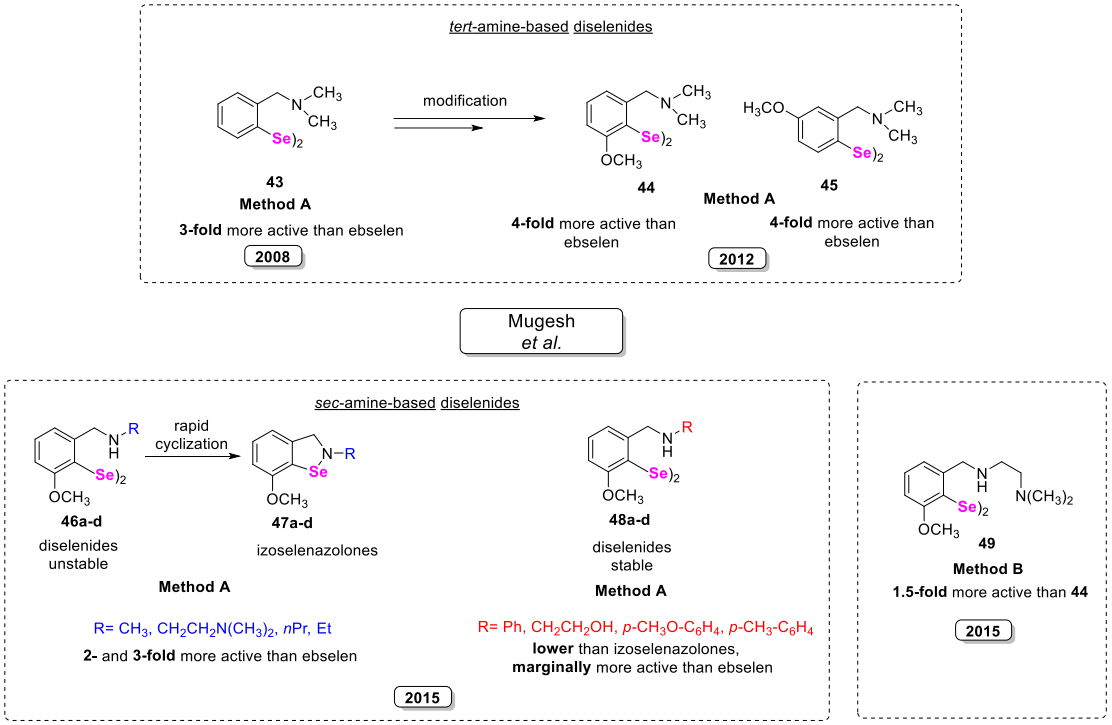


Figure 8. Diselenides and their derivatives **43-49** with potential GPx-like activity assessed by Mugesh *et al*.

3.2.4. Diselenides designed by Ścianowski *et al*. *N*-alkyl,[35] *N*-aryl,[36] and *N*-chiral[37,39] amido-based diselenides were synthesized in the Ścianowski research group. A significant increase in the antioxidant potential was observed for appropriate diselenide derivatives: *N*-alkyl selenenic acids **52a-f** and water-soluble potassium salts of these acids **53a-f.**[58] The salts **53a-f** showed the highest GPx-mimetic activity among all compounds presented by the Ścianowski group. Additionally, the solubility of these salts **53a-f** in water gives them great potential in pharmacology. The GPx-mimic activity for all derivatives **50-57** was assessed using Method C.[21,22] The relative activities for the individual derivatives **50-57** and their structures are summarized in Figure 9.

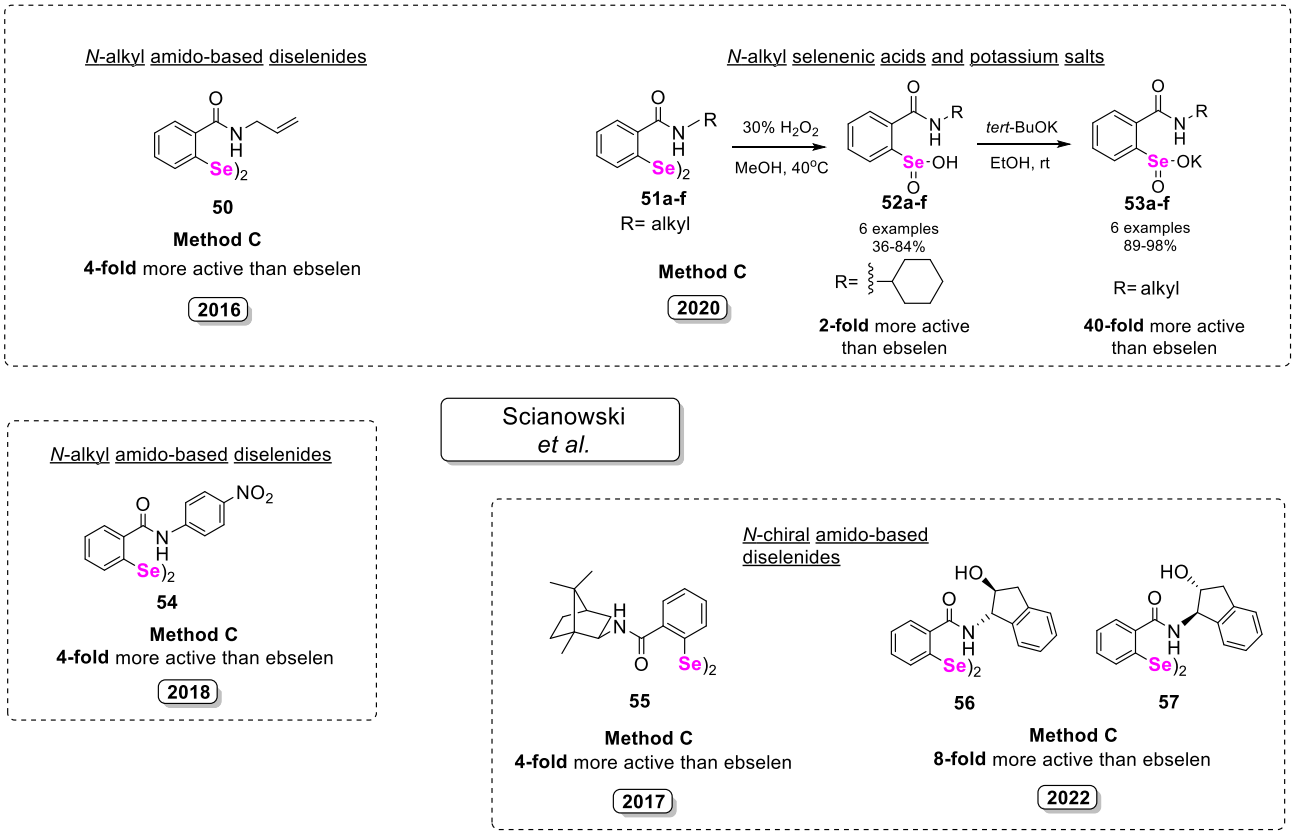


Figure 9. Diselenides and their derivatives **50-57** with potential GPx-like activity assessed by Ścianowski *et al.*

3.3. Other organoselenium compounds as antioxidants

Braga *et al.* (2012) assessed the GPx-like catalytic activity of selenides and selenoxides using Method B.[20] The selenoxide **58** with an amino chelating group showed 3-fold higher activity than ebselen **5**. Selenide **59** was a poorer catalyst than selenoxide **58**, but showed catalytic activity comparable to ebselen **5**.[59] In 2016, Manichetti and Braga synthesized different benzo[*b*][1,4]selenazines. The best antioxidant potential tested using Method C[21] was observed for benzoselenazine **60** which was lower than that of diphenyldiselenide.[60]

The antioxidant activity of dithiaselenepanes was assessed using Method C[21] by Capperucci *et al.* (2016). According to this assay 3,7-dimethyl-1,2,5-dithiaselenepane **61** was more active than $(PhSe)_2$. Intriguingly, the more hindered dithiaselenepane **62** showed lower catalytic efficiency than **61**.[61] In 2019, a series of cyclic and open-chain selenides was obtained within the same research group. They suggested that the nature of the functional groups close to the selenium atom strongly influenced the catalytic antioxidant properties of organoselenides. β-Seleno nitriles **63** and **64** and 2-oxo-1,4-oxaselenane **65** were the best catalysts according to Methods A[19] and **C**.[21] As in the previous report,[61] also, in this case, a higher GPx-like activity of cyclic selenides compared to acyclic analogs was observed.[62] In the same research group (2015), resveratrol-based benzoselenophenes **66-68** were obtained, for which the antioxidant activity was assessed using Method D.[23] All the selenophene derivatives **66-68** were more efficient than resveratrol (about 1.5-fold more active) when tested under the same conditions.[63]

Singh *et al.* (2017) prepared phenolic 2,3-dihydrobenzo[*b*]selenophene antioxidants bearing an HO-group in *ortho*, *meta* and *para* positions with respect to the Se atom. Compound **70**, carrying the phenolic group in *ortho* position, was found to be the best catalyst, three-fold more active than $(PhSe)_2$. Compound **69** (HO-group

in *para* position) was slightly more active than the reference compound.[64] The antioxidant activity was determined using Method B.[20]

Quinoline derivatives containing selenium were synthesized by Alves *et al.* in 2021. For these compounds, the antioxidant activity was assessed using Method D[23] and Method E.[24] The obtained results indicated that compounds **71** and **72** were effective DPPH and ABTS radical scavengers, respectively.[65]

Shaaban *et al.,* in their recent papers (2018, 2022),[66,67]obtained a series of selenides and determined their GPx-like antioxidant activity using Methods D[23] and **E**.[24] In the first article, the quinoid-based *N*-substituted maleanilic acid **73** and its corresponding methyl ester **74** were more active (approximately 1.5-fold) than ebselen **5**.[66] Compounds **75** and **76** showed GPx-like activity similar using Method D[23] like vitamin C.[67]

Iwaoka *et al.,* in their reports (2010, 2015, 2017),[21,68,69]assessed the antioxidant activity of water-soluble cyclic **77**, **81**, **83-86** and linear selenides **78-80**, **82** using Methods A[19] and **C**[21] in water and methanol. As a result, they managed to formulate some general characteristics of the compounds that contribute to the increased GPx-mimic activity: 1) the most preferred cyclic ring size is five, 2) generally, the reactivity of the substituents increases in the series NH_2 <HO <CO_2H in aqueous medium and *vice versa* in methanol, 3) in most cases a greater number of substituents increases the activity of the compound, 4) the stereo configuration of the substituents does not affect the activity of the compounds in water, unlike in methanol.[21,68,69]

Mugesh *et al.* (2012, 2015) tested GPx-like antioxidant activity for diaryl selenides bearing amide moieties and spirodiazaselenuranes using Method A.[19] The reactivity of the selenides **87**, **89** and the spirodiazaselenuranes **88**, **90** indicated that the substituents attached to the nitrogen atom have a significant effect on the antioxidant activity. It has been observed that the introduction of electron-withdrawing groups generally decreased, while the introduction of electron-donating groups significantly increased the GPx activity of both diaryl selenides and spirodiazaselenuranes.[70,71]

The effect of introducing the methoxy group (in proximity to the selenium atom) on GPx-like antioxidant activity was investigated in cyclic selenium esters (2014)[72] and a series of *o*-(hydroxymethyl)phenyl selenides (2016)[73] by Press and Back. In both cases, it was observed that a single electron-donating methoxy group in *para* position to selenium increased the catalytic activity. In contrast, *m*-methoxy groups have little effect, and *o*-methoxy substituents inhibit the activity. Moreover, the effects of multiple methoxy groups were not cumulative. The best peroxide scavengers (Method B[20]) were cyclic selenium ester **91** and selenide **92**.

McNeil and Back (2016) found that the dimeric form **94** acted roughly twice as fast in Method A[19] than the monomer **93** due to two redox centers in **94** instead of one in **93**. Therefore, dimeric form **94** better mimicked the multivalent selenoenzyme GPx, which possessed four redox-active selenocysteine moieties.[74]

In 2020, Ścianowski *et al.* presented a new method for the synthesis of *N*-substituted unsymmetrical phenylselenides with an *o*-amido function. The highest H_2O_2-scavenging potential (Method C[21]) was observed for the derivative **95** with *N*-(3-methylbutyl) substituent. The phenylselenide **95** showed 2-fold higher activity than ebselen **5**.[75]

The structures of all the derivatives mentioned above **58-95,** with high antioxidant activity, are summarized in Figure 10.

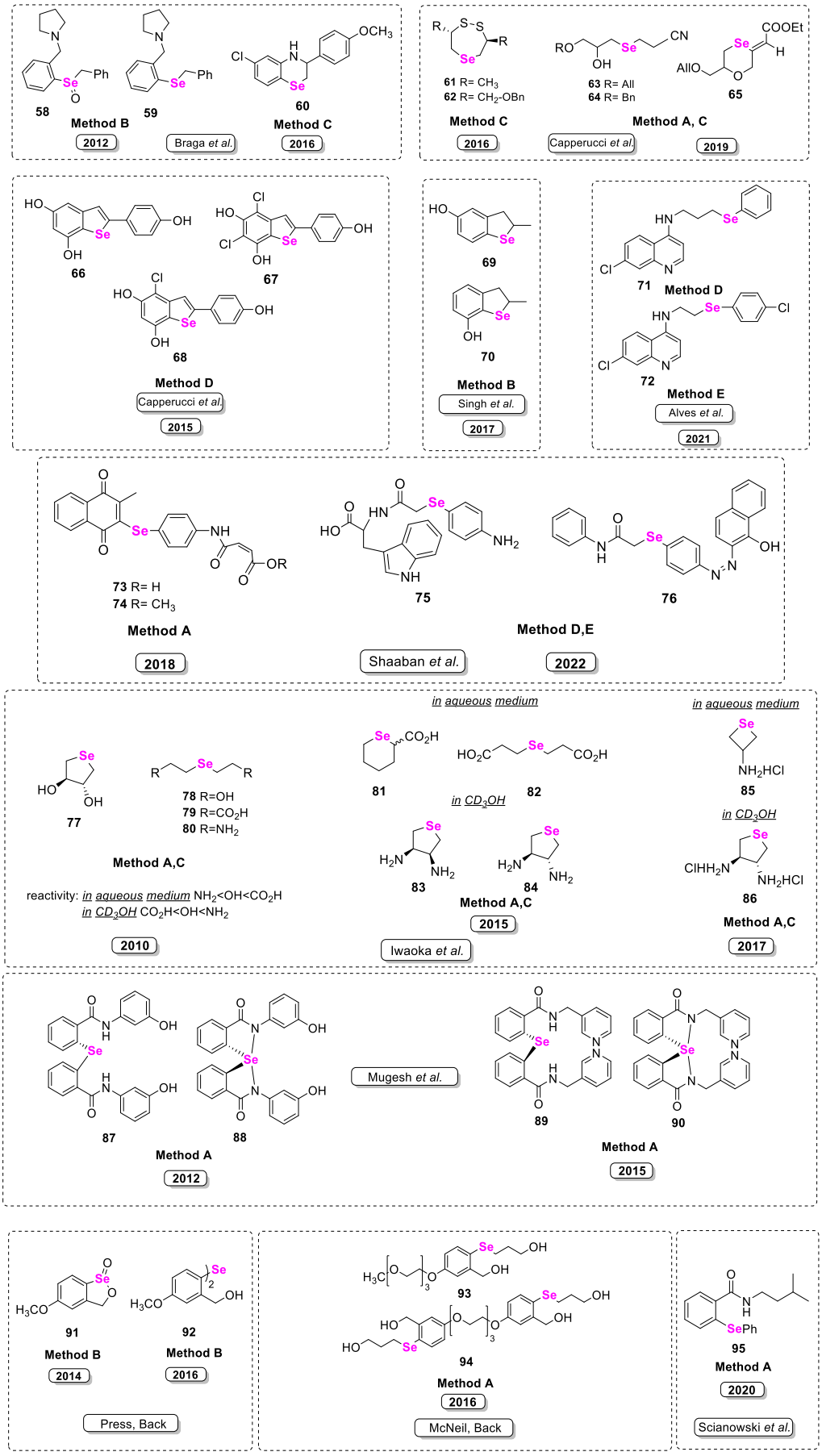


Figure 10. Other organoselenium compounds **58-95** with potential GPx-like activity.

4. Antioxidants in Other Areas

In the food industry, antioxidants are considered food additives. They protect food against fatty acid oxidation (rancidity), extend the time of shelf life consumption, and prevent the loss of food value. They react with primary oxidation products (mainly fats), creating less reactive radicals. For the general population, the main source of Se in the diet are organic forms (generally greater than 80%).[76]

Ebselenols substituted with a hydroxyl group in the benzisoselenazolone ring were evaluated for their capacity to inhibit peroxidation of linoleic acid in a two-phase chlorobenzene/water system open to the atmosphere using HPLC with UV detection assay.[77,78] While ebselenols **97** inhibited peroxidation at the same time as the standard α-tocopherol, ebselenols **96** stopped this process for much longer. In the absence of a reducing agent (ascorbic acid), ebselenol **96** scavenged peroxide radicals with a stoichiometric number as high as n = 3 (for comparison, α-tocopherol is known to trap two peroxyl radicals per molecule, so the stoichiometric number is n = 2). The presented properties of ebselenols **96**, **97** (Figure 11) indicate that these compounds can be used in food technology (as antioxidants protecting food against autooxidation of fatty acids and thus prolonging the shelf time), in polymer producers, or the oil industry (as antioxidants protecting against autoxidation, which corresponds to the oxidative deterioration of organic materials).[79]

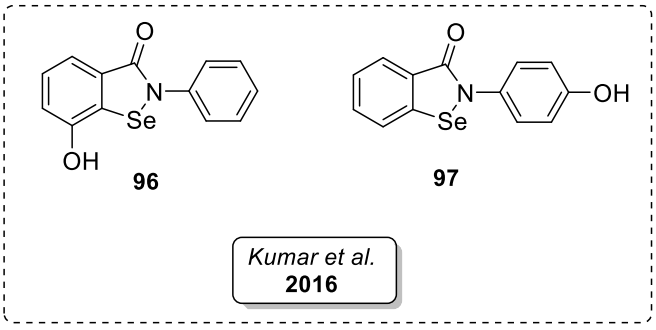


Figure 11. The structures of ebselenols **96** and **97** with high antioxidant activity.

Unique physical, chemical, and antioxidant properties have made selenium nanoparticles (SeNPs), particularly popular.[80] Additionally, SeNPs, due to their higher bioavailability and lower toxicity compared to other chemical forms of selenium, may be a promising source of selenium in the diet.[81]

In 2018, Huang *et al.* designed the first Se@pDA self-assembly nanocomposite that exhibited remarkable ROS scavenging property due to excellent GPx-mimic ability of selenium and polydopamine (pDA) reducibility (Figure 12). Compared to a single composite, the Se@pDA nanocomposite possessed exceptional multi-antioxidative capacity mimicking intracellular enzymatic and non-enzymatic antioxidants that constitute the antioxidant machinery system. Experimental data have shown that Se@pDA nanozymes can be effective in ameliorating the oxidative damage caused by ROS in lipids as well as in DNA, compared to individual Se or pDA nanoparticles.[82]

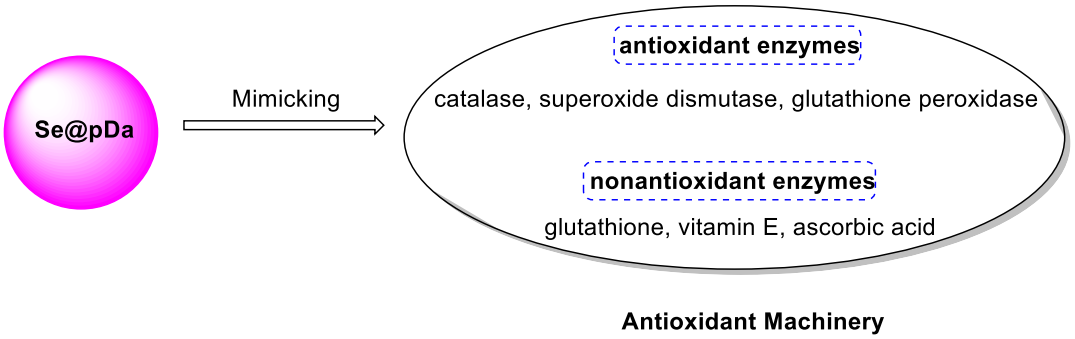


Figure 12. Illustration of Se@pDA nanozyme as a mimic of intracellular antioxidant machinery.

Selenium-containing polymers, due to the unique properties of selenium, are susceptible to various stimuli, such as light, radiation, or redox reaction. The most interesting factor, in the context of this review, is the redox (oxidative- and reductive-reactivity) stimulus.

P(EG_x-SeHC) **99**, water-soluble selenium-containing polymers, were prepared by ring-opening polymerization (ROP) of EG_x-SeHC **98** (derived from selenohomocysteine (SeHC)) and oligoethylene glycol by Lu *et al.* in 2019 (Figure 13).[83] The obtained polymer, is a promising protein mimic because of its peptide skeletons and helical conformations on the one hand, and on the other hand, due to the presence of selenocysteine, it shows redox responsivity. Compared to the oxidation of homocysteine-derived polypeptides,[84] which normally requires six hour treatment with 1% acetic acid and 300 mM of 1% H_2O_2 at 38 °C, P(EG_x-SeHC), **99** could be oxidized with 20 mM H_2O_2 in one hour in water at room temperature to obtain **100**. The presented features indicate that selenopolypeptides could find potential applications as chiral materials, stimuli-responsive carriers, autoxidation, and anti-inflammatory agents.

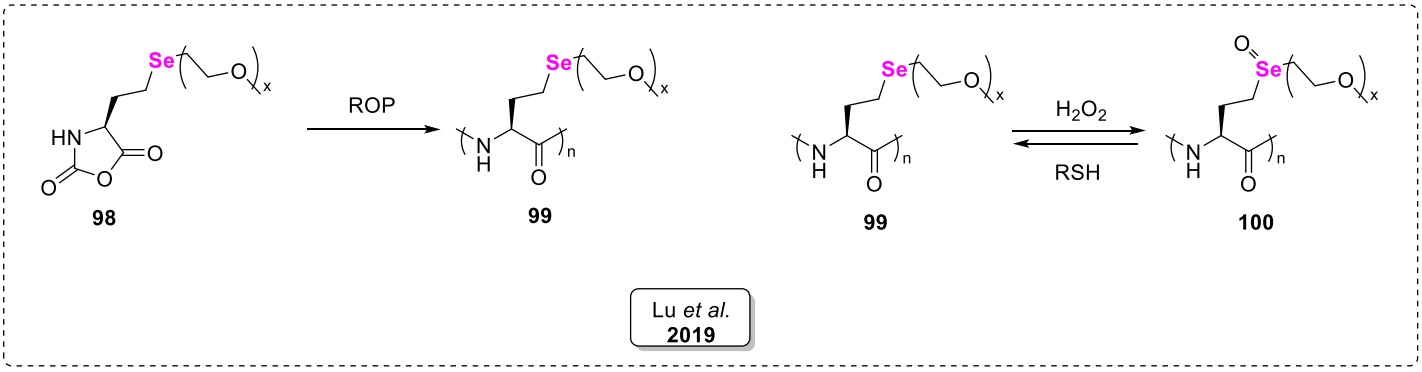


Figure 12. Preparation and oxidation of P(EG_x-SeHC) **99.**

Redox reactions play a significant role in drug delivery and the release of selenium-containing polymers. This is because selenoxide and selenone possess better hydrophilicity than selenium. Xu *et al.,* in their papers (2010, 2013),[85,86] presented amphiphilic block polymers with selenide moieties in the main chain or in the side chain. The polymers self-assembled to form micelles, and then they were structurally disrupted under the mild conditions of 0.1% H_2O_2, releasing the desired compound. X-ray photoelectron spectroscopy (XPS) and ^{77}Se NMR measurements in both cases showed that transformation from selenide to selenone is associated with the change of hydrophobic to hydrophilic character.[85,86]

5. Conclusions

Antioxidants play a significant role in protecting the body against the negative effects of ROS, excess of which is the initiator of many diseases. The development of antioxidants containing selenium in their structure is strongly related to the progress in synthesizing compounds capable of mimicking the catalytic cycle of the essential antioxidant selenoenzyme - glutathione peroxidase. Benzisoselenazolones, diselenides, selenides, selenoxides, or selenoesters are compounds that, in connection with their GPx-like activity, can be considered as potential antioxidant drugs in medicine. Ebselenols can additionally be used as diet additives in the food industry. On the other hand, the antioxidant properties of Se-containing nanoparticles and polymers provide a wide spectrum of possibilities for their use in the materials industry. This article reviews the literature from the past 12 years to 2022.

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