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Organoselenium compounds, an overview on the biological activities beyond antioxidant properties

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ABSTRACT: *For a long period, Selenium was considered mainly a toxic element and has been the object of disputes for its controversial balance between beneficial and toxic effects. Nowadays, many evidences demonstrated its role as essential microelement in mammalian diet, having an essential role in redox homeostasis of all the living systems. Around 25 proteins were discovered to contain a selenocysteine in place of the more common sulfureted amino acid and, in this protein, selenium has the main role in the catalytic center playing a key role in several major metabolic pathways such as thyroid hormone metabolism, antioxidant defense systems, and immune functions. Many studies report that selenium has a protective effect against some forms of cancer, cardiovascular disease mortality, regulates the inflammatory mediators in asthma, maintains bone homeostasis and protects against bone loss. Antioxidant activities of organoselenium compounds has been widely studied and discussed in a number of recent review articles. In this communication, taking inspiration from a number of recent publications, we want to highlight that other biological activities can be envisioned for organoselenium compounds deriving from the peculiar reactivity of this element.*

Introduction

In the past, selenium has been the focus of disputes for its beneficial and toxic effects. Nonetheless, many evidences have shown that selenium is an essential element in the mammalian diet. More recently, environmental and dietary studies of both inorganic and organic compounds containing selenium, are back interest considering also the long-term effects of selenium in the human diet (Nogueira and Rocha, 2011).
There are approximately 25 selenoproteins containing a selenocysteine at their active center. So, Se plays a key role in several major metabolic pathways such as thyroid hormone metabolism, antioxidant defense systems, and immune functions. Many studies report that selenium has a protective effect against some forms of cancer, cardiovascular disease mortality, regulates the inflammatory mediators in asthma, maintains bone homeostasis and protects against bone loss (Chua Tan et al., 2016).
Selenium is essential for humans and animals for his role as antioxidant. This aspect has been widely studied and discussed. In literature are reported extensive evidences of the antioxidant selenium activity, this is the reason why the focus of this overview is centered in other health-effects of this element.

Selenium biology and human health

Selenium was discovered in 1817 by Bezellius. In 1957, Schwarz and Foltz discovered that selenium is an essential trace element, which prevents hepatic necrosis in the rats and in 1973 it was discovered that it is present in biological systems as selenocysteine, as part of glutathione peroxidase (GPx). These findings have influenced the opinion of the scientific community and many research groups developed efficient methodologies for the preparation of selenium-containing compounds (Ferandez-Lodeiro et al., 2014).
In Nature, inorganic selenium can be found dissolved in water or soil as selenides, selenite and selenate whereas organic selenium containing compounds are generally present in the air, soil and plants as volatile derivatives: methylselenides, trimethylselenonium ions and different selenoamino acid (Pyrzynska, 2002).

Selenium enters in the food chain through plants, that are the primary source of this exential microelement for mammalian. High level of Se concentration were reported in cereals and nuts and some of their not fully purified derivatives (Pophaly et al., 2014 , Achibat et al., 2015).The intake of Se varies hugely worldwide, ranging from deficient to toxic concentrations. The reason of the intake variability is related to the Se content of the soil and others factors that determine its availability in the food chain. These factors are: Se speciation, soil pH, organic matter content and the presence of ions that can make complexes with Se (Rayman, 2012).

Selenium deficiency has been associated and proposed as cause for several human diseases such as Keshan disease and Kashin-Beck disease. Keshan disease is associated with low levels of selenium in soil and food in endemic area and has been demonstrated that the incidence of Keshan disease decreases significantly after selenium supplementation (Yakubov et al., 2014).

The assimilation of selenium can be increased by some diet rich in low molecular weight proteins and some vitamins (especially vitamins B, C and D). The recommended intake of selenium varies depending on geographical regions. In consideration of the low selenium daily intake for some populations there is a supplementation of fertilizers with inorganic selenate.

Selenium is characterized by a narrow safety range between deficiency and toxic doses and, for this reason, a deep investigation on the biological activity of the element and its organic derivatives is particularly challenging (Kieliszek and Blazejak, 2013).

There are biochemical systems in which selenium replaces the sulfur, as in the case of amino acids cysteine and methionine, giving rise to the corresponding selenomethionine and selenocysteine (Achibat et al., 2015). In addition, Selenium is involved in metabolism of lipid hydroperoxides and hydrogen peroxide. It is an integral part of some enzymes, including iodothyronine deiodinases (ID), thioredoxin reductase (TRxR) and GPx (Kieliszek and Błażejak, 2013).

GPx has a crucial role in protecting the organism against oxidative damage, in particular catalyzing the reduction of hydroperoxides using glutathione and other thiol cofactors regenerated by specific NADPH dependents reductase. After the synthesis of ebselen as lead compound endowed with GPx-like activity, numerous studies aimed to the development of small-organoselenium molecules having similar mimic action of GPx were reported. The compounds obtained for this purpose can be classified into some main categories like cyclic selenyl amides, diselenides, linear or cyclic selenides, vinyl selenides and so on. These compounds owe their activity to the reactivity of selenium-centers that is exploited in the oxidation of thiol mediated by peroxides (Bhabak and Mugesh, 2010). Mugesh and coworkers deeply investigated the GPx-like mechanism reporting a complex reaction mechanism involving ebselen and its analogues in the reduction of peroxides.

Based on the evidence of some spectroscopy-based assays several different compounds were synthetized and proposed as GPx-like candidate. As an example, recently some of us synthesized new diselenides having antioxidant properties, superior to that displayed by ebselen thus suggesting their possible application as therapeutic drugs for the treatment of oxidative stress-related diseases (Nascimento et al., 2014).

In the last years, the interest on Se supplementation in diet is increasing, consequently many food products enriched with selenium were developed. The developed functional foods are obtained by increasing the selenium concentration in soil (e.g. for for the biofortification), or using selenium as an additive. With these strategies, several selenium-enriched foods were proposed like potatoes, mushroom, onion, garlic and fermented food product. All these products respond mainly to a market request not fully supported by scientific evidences, especially in those areas, in which selenium is naturally present in the soil. Among these products probably the most interesting are those deriving from fermentation because this

process (e.g. operated by lactobacteria) offers the possibility to transform inorganic selenium to some organic forms (Pophaly et al., 2014).
The main effect of selenium on human health is the antioxidant activity. This property is reflected in the broader perspective considering that the pro-oxidant factors may favor the development of several diseases.
In addition, oxidative stress may be involved in diseases such as Parkinson, Alzheimer, diabetes and atherosclerosis. In this regard organoselenium compounds could represent a new interesting instrument to reduce, control or prevent the damage produced by the reactive species of oxygen (Nogueira and Rocha 2011).

Role of Selenium in Immune functions

Many studies shown that poor Se intake weakens immune system, as example, there are studies on relationships between dietary Selenium and viral infections. In most cases, the selenium deficiency, results in genetic mutations that increase the virulence of the virus (Huang et al., 2013).
Increased level in dietary Se in mice showed to boost signaling during T cell receptor (TCR) induced activation (Hoffmann et al., 2010). So, TCR signaling in CD4+ T-cells was enhanced with Se intake.
Selenium supplementation has pronounced immune stimulant effects, including an enhancement of proliferation of activated T cells, increased lymphocyte-mediated tumor cytotoxicity, and natural killer cell activity.
Furthermore Se promote differentiation of CD4+ T cells into T-helper-1 (Th1) rather than T-helper-2 (Th2) effector cells. This effect may reduce the Th2- type immune responses that drive asthma while boosting Th1 response which is, in turn, required for antiviral and anticancer immunity (Rayman 2012, Huang et al., 2013).
Many evidences suggest an important role of selenium in inflammatory response. Recent studies hypothesized that the supplementation may regulate inflammatory gene expression at the epigenetic level, such as the decreased acetilation of NFkB in primary and immortalized macrophages (Narayan et al., 2014).
Previous studies have demonstrated that selenoproteins in macrophages down-regulate the inducible NO synthase, a pro-inflammatory gene, while other studies demonstrated that selenium supplementation polarizes macrophages towards anti-inflammatory phenotypes (Nelson et al., 2011).

Antimicrobial activity of some organoselenium compounds:

During the last ten years a large variety of selenium derivatives were designed and tested as antimicrobial agents and their activity was confirmed with *in vivo* and *in vitro* assay against a broad range of microorganisms, included bacteria and fungi (Braga et al., 2010; Alberto et al., 2011; Vargas et al., 2012)
The bacterial resistance to antibiotics and the strong needs of new strategies and new drugs to contrast this world problem pushed the research to test know drugs or known biologically active compounds on new targets. An example is the idea of the repositioning of ebselen (compound **1**, **Fig 1**) and its derivative ebselen oxide (compound **2**, **Fig.1**) that demonstrated to inhibit the biofilm formation and motility in *Pseudomonas aeruginosa* (Lieberman et al., 2014).

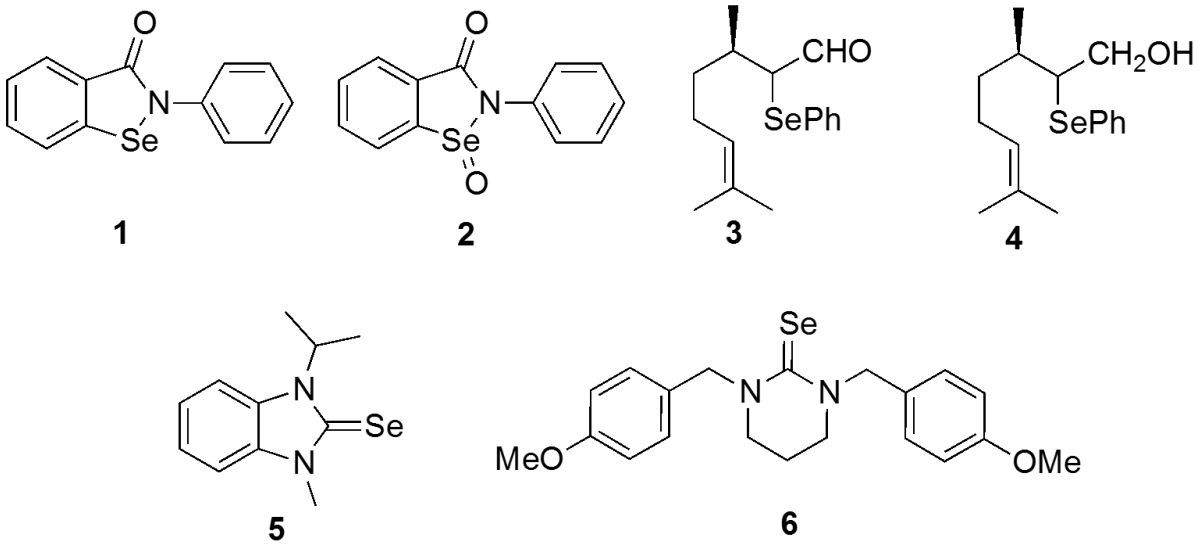


Figure 1: Structure of selenorganic compounds endowed with antimicrobial activity.

Some studies evidenced that the mechanism of action could be correlated to the reactivity of ebselen analogous towards the thiol group of some proteins, such as the thioredoxin reductase of bacteria. The inhibition of TrxR causes cell death in pathogenic bacterial lacking a GSH system such as *H.pylori*, *S.aureus* and *M.tuberculosis* (Lu et al., 2013).
In a different work it was demonstrated that Ebselen inhibits mycobacterial growth by targetin the antigen 85 (Ag85) complex. The mechanism proposed involved the interaction with the free thiol group of a cysteine residue of this protein, after the scission of the Se-N bond of ebselen (Favrot et al., 2013).
A new organoselenium compound was synthesized starting from (R)-citronellal, the major constituent of the essential oil of citronella (Cymbopogon nardus (L) Rendle). 2-phenylseleno citronellal (compound **3**, **Fig 1**) showed interesting antimicrobial activity as well as its reduced analogous phenylseleno citronellol (compound **4**, **Fig 1**). These compounds are developed to protect foodborne against pathogenic bacteria: *Listeria monocytogenes*, *Staphylococcus aureus* and *Salmonella Typhimurium* (Victoria et a.,2012).
Two structures having a selenone group embedded in a 5 and 6 membered ring (compound **5** and **6**, **Fig 1**) showed antibacterial activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, as well as antifungal properties toward *Candida albicans* and *Candida tropicalis* (Talas et al., 2015).
Some diselenides as well as selenium nanoparticles very recently showed an anteresting antibiofilm activity highlighting how promising the use of Se is in medical application or in prolonging the shelf life of food products (Shakibaie et al., 2015).

Anticancer and cancer prevention effect:

From an epidemiological perspective, studies have shown that people in areas with soil characterized by low content of selenium (lower than 0.05 ppm) and people with decreased plasma selenium levels (below 128 ng/mL) have higher cancer incidence and/or cancer mortality, while high levels of selenium in the blood (~154 µg/mL) have been correlated with a reduced number of cancers, including pancreatic, gastric, lung, nasopharyngeal, breast, uterine, respiratory, digestive, hematological and gynecological (Tran et Webster, 2011).
Cancer cells are characterized by an increasing production of reactive oxygen species (ROS) that produce a constant state of oxidative stress. Consequently, the studies focused

on the anticancer activity of selenium containing compounds were mainly based on the evaluation of their antioxidant properties.
Both inorganic forms and organic selenocompounds were reported to exert anticancer activity. An example of inorganic selenium compound with anticancer activity is sodium selenite (**Na_2SeO_3**) that exert cytotoxic effects by means of the generation of reactive oxygen species (Weekley et al., 2014). The anticancer effect of sodium selenite was also tested toward different tumoral cells lines (Fernandes and Gandin., 2015). The same authors prepared a series of diselenides endowed with anticancer activity (compounds **7-9**, **Fig 2**).

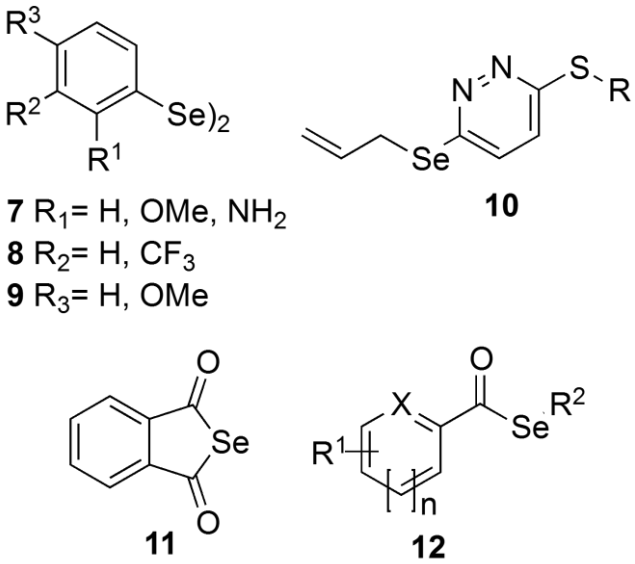


Figure 2: Structure of selenorganic compounds endowed with anticancer activity.

Recently, Kim and coworkers prepared a series of Se-pyridazines (compound **10**, **Fig 2**), which showed a pronounced anti-proliferative activity against breast cancer (Kim et al., 2014).
A widespread strategy to develop organoselenium compounds with anticancer activity is based on the modification of privileged structures inserting the selenium in key position of know anticancer agents. In this context the isosteric substitution of sulfur with selenium is worth to be mentioned (Zhao et al., 2012 ; da Cruz et al., 2016).
Very recently, some authors reported the development of compounds able to reverse the multidrug resistance of some cancer cells. For instance Dominguez-Alvarez et al. demonstrate that selenoanhydride and some selenoesters (compounds **11** and **12** respectively, **Fig 2**) have such ability (Dominguez-Alvarez et al., 2016).

Anti-inflammatory and antinociceptive effects:
The organoselenium compound most studied for its anti-inflammatory and antinociceptive activity is diphenyl diselenide (compound **13**, **Fig 3**). The effects of diphenyl diselenide have been widely studied *in vivo* and *in vitro* (Nogueira et al., 2003; Chagas et al., 2013). The mechanisms behind its antinociceptive effects are the modulation of serotonergic, nitrergic, glutamatergic and GABAergic pathways (Zasso et al., 2005; Savegnago et al., 2007; Pinto et al.,2008).
The anti-inflammatory effect of diphenyl diselenide was recently recognized as a consequent of the ability to inhibit the production of NO and to modulate macrophage activation (Rupil et al., 2012).

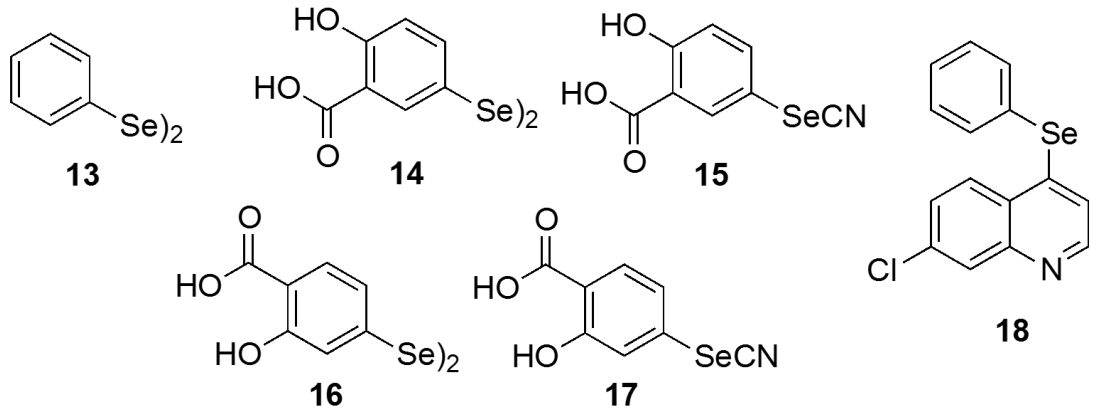


Figure 3: Structure of selenorganic compounds endowed with antiinflammatory activity.

Recently a series of selenium containing salicylic acid and quinoline derivates (compounds **14-17** and **18** respectively, **Fig 3**) were prepared and tested as potential anti-inflammatory and antinociceptive compounds (Chagas et al., 2014 ; Pinz et al., 2016).
Their anti-inflammatory activity is due to the ability of selenium containing compounds to down-regulate pro-inflammatory mediators through inactivation of signal transduction pathways, included COX-2 expression (Zhang et al., 2014).
In the same way, inorganic Se supplementation, as selenite, shift the COX pathway towards the production of anti-inflammatory prostaglandins and promotes the differentiation of macrophages in anti-inflammatory phenotypes. (Narayan et al., 2015). Selenites inhibit also the expression of adhesion proteins and NFkB, reducing the production of ROS (Pfister et al., 2016).

Antiviral activity
Many evidences highlighted how the Se deficiency could enhance viral infection by weakening immune system (Beck et al.,2003) while it is proven that selenium can reduce HIV infection and suppressing AIDS (Soriano-Garcia 2004; Stone et al., 2010). In the search of anti-HIV compounds, Sancineto at al. recently developed a series of diselenides (compound **19**, **Fig 4**) capable of potently and selectively inhibit HIV-1 and HIV-2 replication in cellular assays. Beside the broad antiviral activity, the diselenide showed an interesting ability in inhibiting the viral replication of clinical isolates as well as strains resistant to the marketed drugs (Sancineto et al. 2016).
The ability of ebselen to react with free cysteines initially pinpointed by Xu et al. in 2010 (Xu et al., 2010), was recently exploited to explain its anti-HCV activity (Mukherjee et al., 2014; Chockalingam et al., 2010). Indeed ebselen, thanks to the reaction with a cysteine located in the active site, is able to covalently inhibit the viral helicase, which is a key enzyme for HCV replication.
Recently diphenyl diselenide (compound **13**, **Fig 3**) showed antiviral activity against herpes simplex virus 2 (Sartori et al., 2016). Herpes simplex virus 1 was recently targeted by selenium containing nucleosides such as selenophenfurin (compound **20**, **Fig 4**) (Arote et al 2013). This compound was previously reported for its antiproliferative properties (Franchetti et al., 1997).

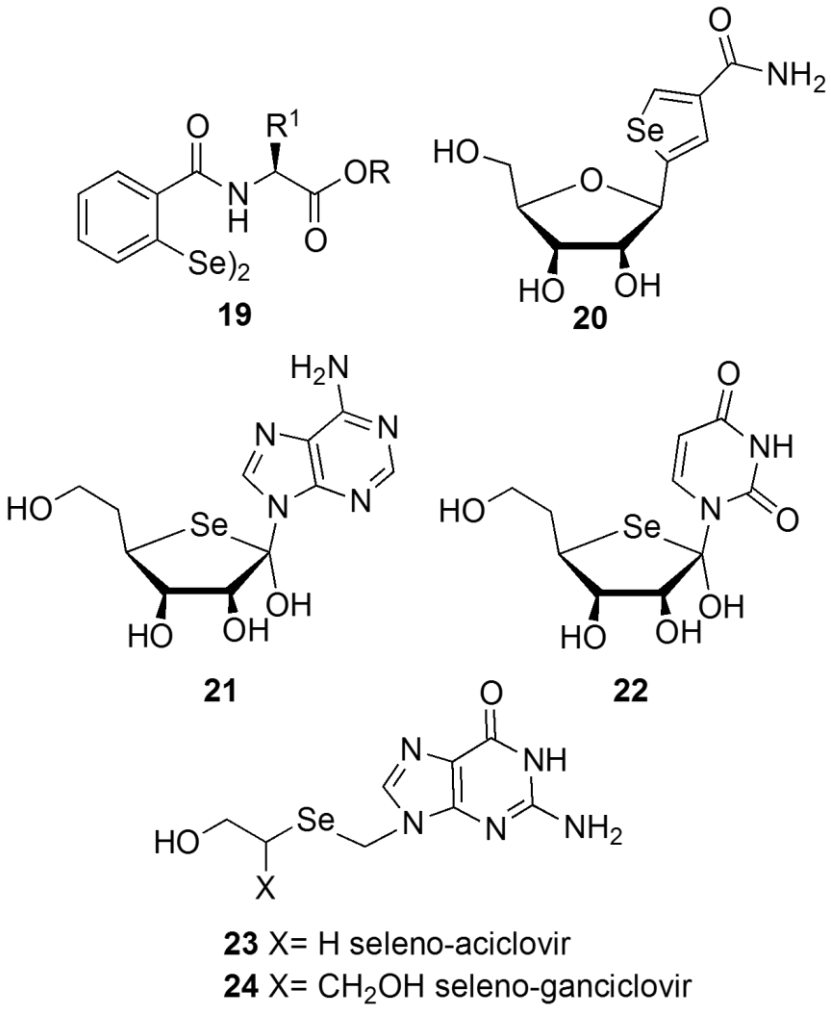


Figure 4: Structure of selenorganic compounds endowed with antiviral activity.

Sahu et al, in an attempt to develop next generation nucleosides as antiviral agents, reported 4′-selenonucleosides (compounds **20** and **21**, **Fig 4**) (Sahu et al., 2014). These compounds showed promising properties and paved the way for the development of the selenol-analogues of Acyclovir and Ganciclovir by the same authors (compounds **23** and **24**, **Fig 4**). These compounds retained the antiviral activity but showed an improved oral bioavailability if compared with the parent drugs (Shau et al., 2015).

Effects on Central Nervous System

The presence of several selenoproteins in human and rodent brains, as recently demonstrated by Yakubou et al., 2014, fueled the interest toward the development of selenium containing molecules able to exert activity in central nervous system (CNS).

Beside α-phenylseleno citronellal **3** and diphenyldiselenide **13**, in **Fig. 5** are reported the structures of synthetic and semi-synthetic selenorganic compounds that have shown antidepressant activities. These compounds have been tested *in vitro* and *in vivo* suggesting a possible implication of dopaminergic, serotonergic, noradrenergic systems for the antidepressant activity (Gerzson et al., 2012 ; Sartori Oliveira et al., 2012 ; Donato et al., 2013 ; Dias et al., 2014 ; Victoria et al., 2014 ; Quines et al., 2016).

Recently diphenyl diselenide was tested as anxiolytic agents in animal models by Rosa et al. They discovered that the selenocompound acts through the multiple modulation of

GABA-A and 5-HT receptors (Rosa et al., 2016). In addition it was recently studied as a potential anti-Alzehimer agent (Zamberlan et al., 2014).

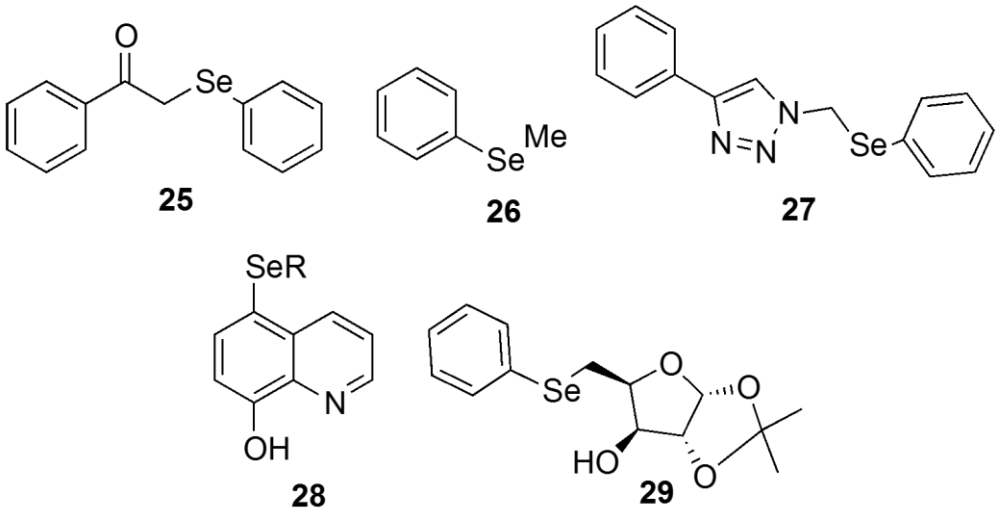


Figure 5: Chemical structures of organoselenium compounds with antidepressant-like activity.

In the search for anti-Alzehimer agents, selenium-containing clioquinol derivatives (compounds **28**, **Fig 5**) demostrated an interesting ability to reduce the metal-induced Aβ aggregation, beside showing antioxidative properties and hydrogen peroxide scavenging activity (Wang et al., 2014).

Other biological effects

Chiapinotto Spiazzi et al. recently reported the discovery of the Selenofuranoside (compound **29**, **Fig 5**) which, in an animal model, is capable of reduce the memory loss through the modulation of the acetylcholine esterase (AchE) activity (Chiapinotto Spiazzi et al.,2015).

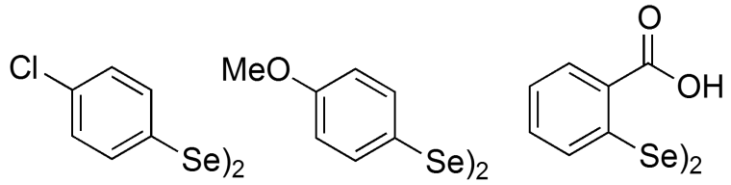
Selenium can contribute to detoxification process of heavy metals such as mercury in mammalian systems, as shown in the pioneering study reported by Cardellicchio et al in 2002. The mechanism by which selenium detoxify Hg is the HgSe (tiemannite) which is poorly soluble and thus fairly toxic (Cardellicchio et al., 2002).

The role of Selenium in the detoxification of mercury was recently confirmed in studies carried out on different mammalian cells (García-Sevillano et al., 2015 ; Gajdosechova et al., 2016).

De Farias et al, have evaluated the effects of Se supplementation on thyroid autoimmunity and the results showed the decrease of level of antibody anti-thyreoperoxidase (antiTPO) (de Farias et al., 2015). Nevertheless, there are conflicting data about the use of Se supplementation in autoimmune thyroiditis as Hashimoto's thyroiditis (van Zuuren et al., 2014).

Zhang et al, have conducted studies to understand the role of selenoproteins and selenium intake in homeostatis of bone. The results evidenced the importance of selenoproteins in maintaining bone homeostasis and protecting against bone loss. In particular, selenoproteins P which is responsible of the selenium transport to bone, resulted to be pivotal in the onset of pathologic and physiologic status of rheumatoid arthritis, osteoporosis, skeletal development and breast cancer (Zhang et a., 2014).

The selenium supplementation can also influence the glucose homeostasis. In pregnant women with gestational diabetes mellitus, selenium supplementation produces a significant reduction in fasting plasma glucose and serum insulin levels (Asemi et al., 2015).
A recent study on metabolic alteration inducted in rats, have shown that compound **30** (**Fig 6**) has a homeostatic effects on glucose metabolism and restored triglycerides, colesterol, glycemia and lactate levels (Quines et al., 2016). The effects on lipid metabolism of compound **31** (**Fig 6**), has been evaluated. Diet supplemented with this compound determined a partially protection against total cholesterol and triglycerides levels (Sartori Oliviera et al., 2016).
Some of us recently reported the ability of some diselenides to act as hormetins (a selected example is compound **32** of **Fig 6**). Cells treated with such compounds showed an improved ability to face the hydrogen peroxide mediated stress (Bartolini et al. 2015) when compared with the untreated ones.



30 **31** **32**

Figure 6: Chemical structures of organoselenium compounds endowed with other biological activities.

Toxicity:
Despite the relevance of selenium as an essential element, its toxicity is known many years before its discovery. In human, chronic Se toxicity result in Selenosis characterized by skin rush, hair loss, gastrointestinal disturbances and abnormal function of the nervous system. High levels of dietary Se have been associated with diminished thyroid hormone levels and hepatotoxicity (Huang et al., 2012). In addition, toxic concentrations of Se cause garlic breath, hair and nail loss, disorders of the nervous system and skin, poor dental health, and paralysis (Rayman., 2012).
The use of Se as fertilizers, supplements and in enriched foods, has increased considerably as result of marketing and consumer trends, forgetting that intake of selenium for therapeutic or nutritional purposes should be done under medical supervision (Stranges et al., 2010 ;Nogueira and Rocha, 2011).

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