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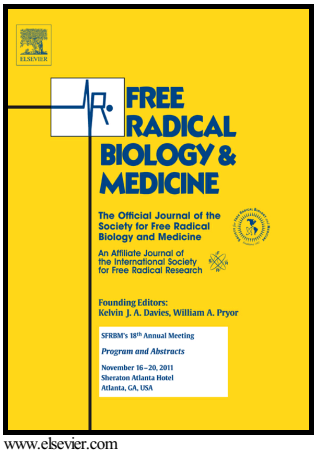

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Organic selenium compounds as potential chemotherapeutic agents for improved cancer treatment

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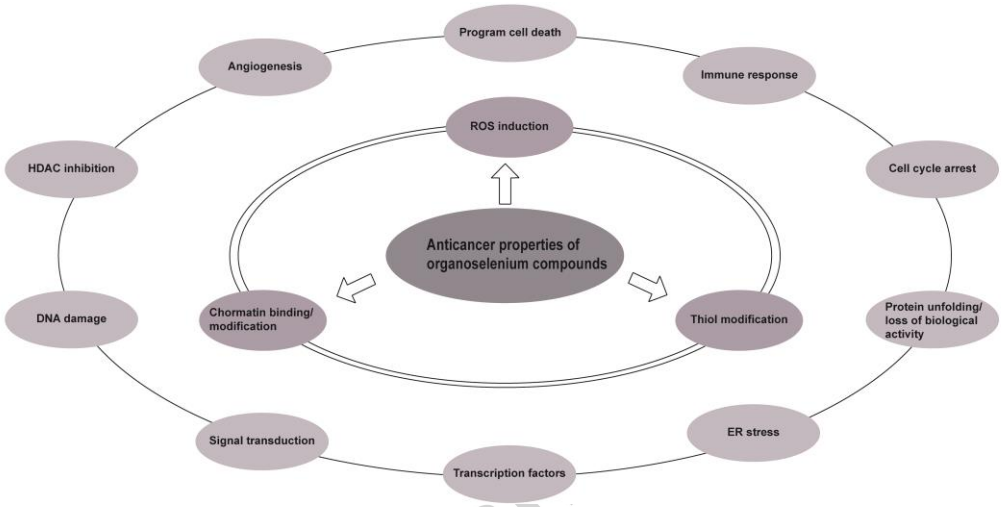
Abstract

Selenium(Se)-containing compounds have attracted a growing interest as anticancer agents over recent decades, with mounting reports demonstrating their high efficacy and selectivity against cancer cells. Typically, Se compounds exert their cytotoxic effects by acting as pro-oxidants that alter cellular redox homeostasis. However, the precise intracellular targets, signaling pathways affected and mechanisms of cell death engaged following treatment vary with the chemical properties of the selenocompound and its metabolites, as well as the cancer model that is used. Naturally occurring organic Se compounds, besides encompassing a significant antitumor activity with an apparent ability to prevent metastasis, also seem to have fewer side effects and less systemic effects as reported for many inorganic Se compounds. On this basis, many novel organoselenium compounds have also been synthesized and examined as potential chemotherapeutic agents. This review aims to summarize the most well studied natural and synthetic organoselenium compounds and provide the most recent developments in our understanding of the molecular mechanisms that underlie their potential anticancer effects.

Graphical abstract



Keywords: Organic selenium compounds Cancer therapy

Introduction:

The primary focus of selenium (Se) and cancer research over last four decades has been dedicated to the chemo-preventive effects of Se, wherein Se supplementation directly or indirectly exerts anti-oxidant functions thereby increasing the cellular defense against oxidative stress (2-5). However, during recent years, Se containing compounds have gained substantial interests as anti-cancer therapeutics, due to their pro-oxidant properties at higher levels, with evidences demonstrating their high efficacy and selectivity (1, 6). Chemical derivatives of Se include inorganic compounds like selenite and organic compounds like selenomethylselenocysteine and selenomethione. Currently, a plethora of research is dedicated towards understanding the anti-tumor potential of these compounds (7). Generally, the inorganic Se compounds exert higher genotoxic stress, which in turn,

may account for a lower therapeutic window, higher systemic toxicity and an increased risk of metastatic burden. Contrarily, organic Se compounds retain significant anti-tumor activity along with increased ability to prevent metastasis, have fewer side effects and lower systemic effects (8, 9). Organic Se compounds comprise a vast group of chemically diverse nucleophilic molecules. In order to further improve the selectivity, specificity and efficacy and, to lower the toxicity, several novel organic Se compounds have been synthesized. Taken together, due to their aforementioned characteristics, the use of organoselenium compounds has become a promising candidate in cancer therapeutics.

Rationale: Selenium as cancer therapeutic agent

All aggressive neoplastic cells exhibit a common phenotype of uncontrolled growth that might potentially metastasize leading to lethal malignancy. In order to support this relentless cell division and proliferation, cancer cells undergo aberrant metabolic adaptation that promotes their survival. Although the cellular transformation mechanisms during carcinogenesis in different cell types can occur via various pathways, the metabolic requirements of resulting cancer cells are generally very similar (10).

Equally important to the energy adaptation, acquired by the cancer cells, is their prominent feature to counteract the increased oxidized environment, which in turn is a result of an aberrant metabolism. In order to evade the ROS induced death, the cancer cells up-regulate their antioxidant scavenging molecules like glutathione peroxidase (GPx), glutathione-S-transferase (GST), glutaredoxin (Grx), thioredoxin (Trx), superoxide dismutase (SOD) and catalase (CAT) (10, 11). Several of these antioxidants rely on the reducing power of NADPH, which is also often found to be induced in cancer cells and is a key metabolite of the pentose phosphate pathway, to maintain their activity to scavenge ROS and repair ROS-induced damage. This leaves the cancer cells with very little or no room to further adapt to any additional induction of ROS, and hence, even a slight additional ROS induction, would lead to oxidative stress dependent cell death (10, 12). Contrarily, normal healthy cells generally possess relatively low steady state levels of ROS and reducing equivalents. In case of any anomaly, the elevated ROS levels in normal non-cancerous cells can therefore be

counteracted via induction of the antioxidant systems (13, 14). Hence, inducing ROS or targeting the strained antioxidant defense system to reach a threshold that is incompatible with cell viability may selectively kill the cancer cells without affecting the normal cells (12, 15, 16). Consequently, inducing oxidative stress in cancer cells using redox modulators provides an interesting therapeutic window and has been established as a mean of successful anti-cancer therapy (17).

Se compounds have been well documented to act as redox modulators and have shown higher selectivity and sensitivity in malignant cells. (1, 6, 17, 18). Hence, with respect to induction of oxidative stress using pro-oxidants as a cancer therapeutic strategy, Se compounds seem to be promising candidates. The pro-oxidant properties of Se compounds, responsible for their cytotoxicity and anti-cancer activity, can be broadly attributed to ROS generation, oxidation of protein thiols, direct or indirect DNA binding as detailed below (Figure 1).

General mechanisms of Se as anti-cancer agents

Dietary Se compounds are metabolized by several distinct pathways producing various Se metabolites, which, in turn, determine their specific biological activity. Amongst the metabolites produced, hydrogen selenide (HSe^-) and methyl selenol (CH_3Se^-) act as pro-oxidants and play a central role in redox cycling with glutathione (GSH) or the Trx/Grx systems, producing superoxides and hydrogen peroxide, further resulting in ROS generation. The increased nucleophilic nature of these redox active Se metabolites confers high reactivity and therefore an efficient anti-cancer agent (19). Moreover, metabolites of redox inactive Se compounds like methylselenocysteine are cleaved by β-lyase to the redox active intermediate CH_3Se^- which further induces ROS, DNA fragmentation and apoptosis in different cancer cells. (20, 21). Hence, the abundance of these specific metabolites governs the efficacy of Se compounds in cancer treatment (18, 22). The redox active Se metabolites through production of ROS and RNS as well as by direct interactions of thiols and DNA binding, cause single stranded/double stranded DNA breaks affecting transcription and signaling pathways (23-26).

Additionally, Se compounds can alter the intracellular redox balance by oxidation of intracellular thiols (27-29) and/or by direct oxidation of a large number of proteins and low molecular-weight compounds *via* formation of intra- or inter-molecular bonds, including selenotrisulfide bonds (S–Se–S), selenenylsulfide bonds (Se–S), and diselenide bonds (Se–Se) (30). Moreover, these compounds catalyze formation of disulfide bonds (S-S), and/or mixed disulfide bonds with glutathione (S-SG) or nitric oxide (S-NO). These oxidations may further result in numerous biological downstream effects, and directly affect the structure, biological function, or enzyme activity of proteins. Protein kinases like JNK, PKC and ASK-1, phosphatases, caspases, regulatory proteins involved in DNA repair like APE/Ref-1, NF-kB and transcription factors like Jun, AP-1, p53 and SP1 are reported to be directly modified and regulated by Se compounds through thiol oxidation (31-36). In addition, the redox modifications of specific thiol residues may also result in an altered iron–sulfur cluster biogenesis (37) as well as changes in calcium and iron homeostasis (38-40). Redox modification of thiol/disulfide exchange in proteins could ultimately lead to protein unfolding and loss of protein biological functions/activities (41, 42). More recent studies on organoselenium compounds have shown a few novel mechanisms of action like chromatin and/ histone modifications (43-47).

Specificity of Se compounds towards cancer cells

Apart from ROS generation, the specificity of Se compounds is conferred by their selective uptake, localization and accumulation in cancer cells. The use of ^{75}Se-sodium selenite and ^{75}Se-selenomethionine (SeMet) as radiotrackers in diagnosis of tumors in humans' dates back to the 1960's. It was shown that ^{75}Se displayed high accuracy in localizing intracranial tumors as well as thoracic and abdominal neoplasms (48-50). However, the uptake mechanism varies between different Se compounds, and is not clearly elucidated. Due to their high reactivity, deducing the exact transport mechanism for each Se compound remains a challenge. One of the important determining factors of Se uptake is the intra- as well as extracellular redox status. It was well demonstrated that the addition of reduced extracellular thiols facilitated selenite uptake in the keratinocyte model- HaCaT cells. The authors showed that reduction of selenite with dithiothreitol (DTT) to, presumably,

selenide resulted in a significant stimulation of Se uptake and that this uptake was mediated by a membrane associated ATP-dependent transporter (51). Later studies, in a variety of cell lines, confirmed that a strong reductive microenvironment, achieved by production of extracellular thiols by cells is required for an efficient selenite uptake (52). It was demonstrated that the overexpression of the cysteine/glutamate antiporter xCT in cancer cells generated a more reducing extracellular microenvironment, leading to the reduction of selenite to selenide, thus facilitating Se uptake. Moreover, addition of an xCT inhibitor (monosodium glutamate) and a thiol scavenger (DTNB) decreased the cytotoxicity of selenodiglutathione and selenocystine in non-small cell lung carcinoma, suggesting that reduction of these compounds is required for their uptake (52). Additionally, the selective uptake of Se by cancer cells has been attributed to their aberrant metabolism, which requires an increased amount of Se, generally being rate limiting for its incorporation into central selenoproteins such as GPx and thioredoxinreductase (TrxR), which are key antioxidants enzymes in upholding the redox homeostasis (53).

Naturally Occurring Organoselenium Compounds

In recent decades, the anticancer properties of organoselenium compounds have been thoroughly investigated. Naturally occurring organoselenium compounds comprise a large group of chemically diverse molecules, which are primarily acquired through the diet and, in general, can be classified as selenides/diselenides, selenoamino acid derivatives, seleninic acids or metabolites of inorganic Se (Figure 2). While the specific metabolic pathway engaged differs from one chemical species to another, most naturally occurring organoselenium compounds typically undergo enzymatic transformation into intermediary methylselenol (CH_3Se^-), prior to a demethylation reaction into biologically available selenide (HSe^-). Our understanding of the metabolism and active forms, as well as the anticancer activity of several promising natural organoselenium compounds are discussed below.

Se-methylselenocysteine (MSC)

Se-methylselenocysteine (MSC, **1**) is a monomethylated seleno-aminoacid derivative that is converted into CH_3Se^- by selenocysteine Se-conjugated β-lyases (54). Given the high volatility and reactivity of CH_3Se^-, it has not been possible to directly identify and measure the metabolism of MSC into CH_3Se^- in cell or animal models; however, β-lyase activity has been indirectly monitored in rat liver supernatant using labelled Se-containing selenoamino acids (55). In the same study, CH_3Se^- was shown to be demethylated via a hydrolysis reaction into HSe^-. The *in vitro* cytotoxicity of MSC has been determined in the micromolar range for various human cancer cell lines including colon, breast, lung and oral squamous cells (56, 57). Additionally, MSC treatment has also been shown to reduce vascular endothelial growth factor (VEGF) expression *in vitro* (56) . Moreover, investigations into the mechanisms of cell death associated with MSC treatment have supported a role for caspase-dependent apoptosis, while the involvement and extent of mitochondrial signaling in this process still remains unclear (58-60). Another important consideration for the use of MSC is that its efficacy is completely dependent upon the production of the active metabolite, CH_3Se^-, by β-lyase activity, which varies across cells, tissues and organs (61). This could partly explain, why the promising findings in *in vivo* studies, discussed below, are not as apparent in *in vitro* studies.

The *in vivo* anticancer potential of MSC has been investigated primarily in combination therapy with traditional chemotherapy drugs. In particular, MSC has gained attention for its capacity to modulate a wide range of cellular and physiological processes that underpin metastasis, as well as for its potential to act synergistically with a wide range of anticancer compounds. In mice bearing FaDu human head and neck squamous cell carcinoma xenografts, treatment with MSC resulted in a series of promising antiangiogenic effects, ultimately resulting in tumor growth inhibition and enhanced doxorubicin delivery associated with decreased microvessel density, increased vascular maturation, improved vessel functionality and reduced vascular permeability (62). Importantly, these outcomes were more pronounced in a histologically identifiable subset of tumors that displayed fewer or no hypoxic regions and were uniform in structure. Similarly, in a mouse xenograft model of MCF-7 breast cancer, a synergistic effect of MSC and tamoxifen was observed on tumor growth inhibition (63). Likewise, in mouse xenograft models of colon carcinoma and

squamous cell carcinoma of the head and neck, a synergistic effect of MSC and irinotecan was observed; moreover, this chemotherapeutic synergy effects was evident in both sensitive (HCT-8 and FaDu) and drug-resistant (HT-29 and A253) xenografts (64). Perhaps even more promisingly, not only has MSC been shown to synergistically enhance the efficacy of chemotherapeutic drugs, it has also displayed a capacity to protect against their toxicity in animal models. Specifically, these effects have been observed in combination therapy of MSC with the aforementioned tamoxifen and irinotecan, as well as with cisplatin and oxaliplatin (63-66).

Selenocystine (SeCys)

Selenocystine (SeCys, **2**) is a diselenide oxidation product of the amino acid selenocysteine (Sec). It is highly redox active, being efficiently reduced to Sec by both low-molecular weight thiols and disulfide reductases. In turn, Sec, given its low pKa value, is highly nucleophilic, rendering it highly unstable and reactive. The capacity of SeCys to modulate redox homeostasis has made it an interesting candidate as a pro-oxidant for cancer therapy. The cytotoxic effects of SeCys have been determined in the low to medium micromolar range across lung, breast, cervical and liver cancer cells, as well as in melanoma cells (67-71). Moreover, across a broad panel of cancer cells, SeCys has been repeatedly shown to act by increasing ROS production and, subsequently, inducing DNA damage, leading to mitochondrial-mediated apoptosis associated with p53 phosphorylation. These effects have also been observed by combining SeCys with 5-FU treatment, additionally highlighting a role for ERK and AKT inactivation (72). Perhaps unsurprisingly, SeCys has been shown to potentiate the cytotoxicity of auranofin, a potent TrxR inhibitor, and TrxR knockdown primarily by enhancing intracellular ROS accumulation (70, 73, 74). Hence, SeCys can enhance oxidative stress associated with the inhibition or consumption of intracellular antioxidants.

In addition to the accumulation of intracellular ROS, other pathways are affected by SeCys treatment in cancer cells. For example, apoptotic cell death via the extrinsic/death-receptor pathway has been observed in melanoma cells following treatment with SeCys (67). More recently, SeCys treatment in cervical cancer cells has been associated with two different

types of cell death, depending on the stage of the cell cycle during treatment. Both apoptotic cell death and a paraptotic-like cell death associated with ER stress and induction of the unfolded protein response (UPR) were observed (71). Interestingly, in triple-negative breast cancer cells, apoptotic cell death has been linked more specifically with S-phase cell cycle arrest (75). Hence, the mechanism of cell death associated with SeCys appears to vary across cell types.

Despite its promise as an anticancer agent, there has been limited investigation *in vivo* into the effects of SeCys, most likely owing to its poor stability and solubility. Nevertheless, in a mouse xenograft model of melanoma, SeCys inhibited tumor growth with no signs of systemic toxicity (67). Further, in a mouse xenograft model of lung cancer, SeCys and auranofin exhibited a synergistic effect on inducing apoptosis in tumors (73). Interestingly, SeCys has been administered in humans for the treatment of acute and chronic myeloid leukemia, where it elicited a noteworthy activity, being particularly effective against immature leucocytes with respect to mature leucocytes, without inducing any significant effect on the bone marrow (76). Hence, further investigation into the potential of SeCys as an anticancer agent is warranted.

Selenomethionine (SeMet)

Selenomethionine (SeMet, **3**) is a naturally occurring amino acid that contains a sulfur (S)-to-Se modification. In humans, SeMet is usually incorporated into proteins non-specifically in place of methionine (Met). Although the anticancer mechanisms of action of SeMet have been explored, there is limited work examining its anticancer potential. SeMet has displayed notable cytotoxicity toward several cancer cells, including lung, breast, colorectal, prostate and melanoma, among others (56, 77-79). While these cytotoxic effects have been achieved at higher concentrations (medium to high micromolar range) than those observed for commonly studied redox-active Se compounds, a strong selectivity toward cancer cells over normal cells has still been realized (78). However, the redox potential of SeMet in cancer therapy has been brought into question since, in rat liver lysates, neither γ-lyase cleavage of SeMet to CH_3Se^- nor its subsequent demethylation to HSe^- was detected (55). Nevertheless, several other pathways have been implicated in SeMet-induced apoptosis,

including the activation of caspases and p53, ER stress, HDAC inhibition, altered expression of Bcl-xl, Bax, Bad and Bim, decreased cyclooxygenase-2 expression and decreased glutathione peroxidase activity (56, 77, 80, 81). Moreover, SeMet used in combination with ionizing radiation enhanced treatment selectivity toward NCI-H460 and H1299 lung cancer cells, while having little effect on WI-38 human diploid lung fibroblasts (82). Importantly, in a mouse xenograft model of colorectal carcinoma (SW480), low systemic toxicity and high tumor selectivity has been reported (81).

Selenodiglutathione/g-glutamyl-selenomethylselenocysteine (SDG)

Selenodiglutathione (SDG, **4**) is the primary metabolite produced during the reduction of selenite by glutathione. In this reaction, rather than the formation of oxidized glutathione (GSSG), a Se metabolite conjugated with two glutathione moieties, SDG (GS-Se-SG), is produced. Like inorganic Se forms such as selenate and selenite, SDG is reduced to HSe^- by GSH and by activity of the Grx and Trx systems (83, 84). Importantly, SDG has chemical properties that are very different from those of GSSG, which is not a substrate for mammalian TrxR. Moreover, the reduction of SDG by Trx is greatly altered compared to that of GSSG. SDG has exhibited cytotoxicity typically in the low micromolar range toward a panel of different cancer cells, including breast, ovarian, cervical, lymphoma, promyelotic leukemia and oral squamous (71, 85-90). In general, it has been determined as either an equally potent or more potent anticancer compound than selenite and has displayed selectively higher activity toward cancer cells than non-transformed cells. Given the similarities between the metabolism of SDG and selenite, it has long been thought that the adverse side effects associated with selenite treatment would also be associated with SDG treatment. However, more recently it has been demonstrated that despite both SDG and selenite being metabolized to HSe^-, their mechanisms of action are notably different. Specifically, SDG was shown to glutathionylate free protein thiols, which accounted for the different intracellular targets, expression patterns and, ultimately, mechanism of cell death (apoptosis-like) associated with SDG treatment compared to selenite (necroptosis-like cell death) treatment (71).

Synthetic Organoselenium Compounds

Although the first report on the synthesis of an organoselenium compound, diethyl selenide, was back in 1836, the development of synthetic organoselenium compounds as antitumor agents is a relatively new and expanding field of research. In fact, until '90s, the chemistry of organoselenium compounds was scarcely developed in comparison with that of organosulfur compounds, mainly because of the high instability and toxicity of many Se-containing compounds. In the last three decades, on the contrary, advances in the field of synthesis and reactivity of organoselenium as well as the discovery of the fundamental role of Se and selenoproteins in cancer, has tremendously motivated an intense development of new organic Se-containing therapeutics. Below, the major and most widely studied are discussed, based on their chemical and anticancer properties.

Methylseleninic acid

Methylseleninic acid (MSA; CH_3SeO_2H), is an oxoacid Se-containing compound which has been studied since 2000 as a chemo-preventive and chemotherapeutic agents. *In vitro*, it was shown to be effective against a great variety of tumors, including human lung (91), prostate (92-95), breast (47, 96) and pancreatic (21), by acting as a pro-oxidant. In fact, in cells, similarly to selenite, it is readily metabolized to CH_3Se^-, which in turn generates superoxide upon reacting with O_2, thus leading to cell dysfunction and death. Mechanistically, MSA has been found to induce apoptotic cancer cell death in different cell lines by the activation of multiple caspases (caspase-3, -7, -8 and -9), ER stress, UPR induction, cytochrome c release and PARP cleavage (93-95, 97). In particular, MSA has been shown to induce apoptosis in both p53 wild-type, p53-mutant (94), and in p53-null cells (98), consequently demonstrating a p53-independent cancer cell death pathway. *In vivo*, MSA was shown to be effective against several models of mammary cancer cells (96, 99, 100), in colon cancer xenograft model (101), and pancreatic cancer model (21) as well as in two prostate tumor xenograft models (102). Notably, orally administered MSA was found to considerably reduce tumor growth without inducing significant systemic toxicity (92). Additionally, MSA treatment resulted in significantly less genotoxicity and higher inhibition of tumor angiogenesis compared to MSC and selenite (103) and compared to

selenomethionine (104). In combination therapy, MSA was effective in enhancing paclitaxel efficacy in the treatment of triple-negative breast cancer (105) and etoposide/paclitaxel activity in prostate cancers (106).

Recently, Cai and coworkers highlighted the potential of MSA as antiangiogenic therapeutic. In particular, they have proved that MSA inhibits angiogenesis by down-regulating the expression, and the clustering of integrin β3, which in turn, leads to the inhibition of the phosphorylation of AKT, IκBα, NFκB (107).

Selenides

Many different classes of synthetic selenides have been evaluated for their antitumor potential so far (Figure 3). Plano and coworkers synthesized and tested a series of methylimidoselenocarbamates (**5**) and demonstrated their efficacy as cytotoxic agents (at micromolar doses) against human prostate, colon and breast cancer cells. From a mechanist point of view, they showed that these compounds act as multi-kinase inhibitors, being effective in blocking PI3K/AKT/mTOR and ERK1/2, and thus leading to autophagic and apoptotic cancer cell death. In addition, a quinolone-based imidoselenocarbamate derivative was promisingly found to be effective *in vivo*, in a prostate cancer xenograft model (108-110).

The same research group also developed a series of quinazoline and pyrido[2,3-d] pyrimidine Se compounds (**6**). When tested on a panel of several human cancer cell lines (i.e. lymphocytic leukemia cells as well as colon, lung and breast cancer cells), these compounds displayed different activity profiles, depending on the position of the Se moiety (111). Another interesting class of selenides, which deserves attention, is that of quinine-based seleniocompounds (**7**). These compounds, designed by Jacob and co-workers, containing both the Se and quinone redox centers with the aim to efficiently strengthening the ROS-generating capacity of the molecule, were endowed with a noteworthy and selective antitumor activity by acting as cancer cell specific redox catalysts. Upon testing them against cells derived from the most common solid tumors (such as colorectal, lung

and breast cancer cells) as well as leukemia cells, these compounds were shown to be highly cytotoxic; however the human non-cancer cells were less affected (112-114). The same authors reported similar results obtained with peptidomimetic compounds containing Se (**8**) (115). Mechanistically, the biological activity of these compounds was consistent with a cancer specific redox modulation and a subsequent induction of apoptotic cell death.

On these bases, with the aim of developing other novel hybrid compounds with two redox centers, some Se-containing β-lapachone derivatives (**9**) were recently developed by Vieira and coworkers. When evaluated against several cancer cell lines (leukemia, human colon carcinoma, prostate, human metastatic prostate, ovarian, central nervous system and breast), these compounds showed IC_{50} values in the low and sub micromolar range whereas they were barely effective against non-cancer cells (116).

3'-Azido-3'-deoxythymidine (AZT), has for long period had a crucial role in the treatment of acquired immunodeficiency syndrome, acting as a nucleotide analog and thereby inhibiting the reverse transcriptase enzyme of the virus. In addition to its antiretroviral activity, AZT has an important role as first-line therapy in several virus-associated human cancers, including Epstein-Barr virus-associated B-cell lymphoma (117). AZT was recently recommended as first-line treatment for cases of T-cell lymphotropic virus type I (HTLV)-I–associated adult T-cell leukemia/lymphoma, stated by the therapeutic Guidelines from Brazil, (The National Committee for Health Technology Incorporation, Brazilian Ministry of Health, 2015), and currently has several ongoing clinical studies on lymphomas. Recently, Souza *et al.* synthesized and evaluated the bioactivities of a novel AZT class containing Se, S, or tellurium (Te) called chalcogenozidovudines (**10**). Among them, the prominent efficacy of three Se-derivatives as antitumor agents against human bladder carcinoma cells was highlighted (118). Se containing AZT derivatives have been evaluated for their potential toxicity and shown low toxicity against immune cells (119, 120).

Diselenides

In addition to selenides, symmetrical diselenides (Figure 4) were highly studied during the past years (121). Posser and coauthors showed for the first time that diphenyldiselenide (**11**) possess a significant cytotoxicity potential against neuroblastoma cells, and is highly effective in inducing cancer cells death through ERK1/2 mediated apoptosis (122). Subsequently, Nedel and coworkers demonstrated that substituted diaryldiselenides (3-(trifluoromethyl)-diphenyldiselenide and 4-methoxydiphenyl diselenide) have the potential to induce apoptosis in human colon cancer cells by inducing a cell-cycle arrest and activating caspase-dependent or independent pathways (123).

Recently, De Freitas and Rocha showed that diphenyldiselenide can act as a substrate for TrxR, thus laying down the basis for the development of novel diselenides as potential anticancer agents (124). In fact, different series of diselenides containing bioactive pharmacophores (e.g., naphthalene, cyclic imides) or pharmacologically relevant heterocycles (**12**) (e.g., thiazolidinone, tetrazole, pyrazole and thiazolopyrimidine) were developed, some of which were shown to exhibit cytotoxicity at sub-micromolar concentrations towards different cancer cell types (125-129). From a mechanistic point of view, these selenocompounds induced a down regulation of Bcl-2 and Ki-67 expression level and activated caspase-8, thus leading to apoptotic cancer cell death (130).

Selenocyantes

Extensive studies have shown that selenocyanate incorporation into pharmacologically relevant scaffold allows the obtainment of molecular entities with improved pharmacological potentials as compared to the original precursor compounds.

Naturally occurring and synthetic selenocyanates (Figure 5) have proven their effectiveness in the prevention and treatment of a variety of cancers, both *in vitro* and *in vivo* (131, 132). In particular, phenylalkyl selenocyanates (**13**) were shown to be effective *in vitro* towards melanoma, glioblastoma, sarcoma, prostate, breast, and colon cancer cell lines. Structure–activity relationships (SARs) evidenced that an increase in compound lipophilicity by increasing the alkyl chain length was consistent with an increase in the antitumor potential

in vitro. *In vivo*, the most promising phenylalkyl selenocyanate was able to significantly decrease tumor growth in a melanoma xenograft model, without inducing any systemic toxicity sign or by affecting blood parameters indicative of liver, kidney or cardiac related toxicity. Mechanistically, it was assessed that these compounds were able to redox cycle in the presence of GSH forming nitric oxide, superoxide and other ROS, thus affecting cancer cell redox state (133). In addition, their effects on specific phase II detoxifying and antioxidant enzymes (glutathione-S-transferase, superoxide dismutase and catalase) and, in particular, on selenoenzymes TrxR and GPx have also been reported (133-135). This, in turn, was associated in cells to a caspase-dependent apoptotic cell death through the induction of p53, Bax and suppression of Bcl-2 (136).

This class of compounds was also proven to be extremely promising in terms of combination treatments. The diphenylmethylselenocyanate and a naphthalimide based selenocyanate compound 2-[5-selenocyanato-pentyl]-7-amino benzo[de]isoquinoline-1,3-dione (**14**) were found extremely effective not only in significantly potentiating the therapeutic efficacy of classical chemotherapeutic drugs, such as cisplatin and cyclophosphamide, but also were very promising in reducing the chemotherapy-induced adverse effects and toxicity of these drugs (136-138).

The synthetic compound 1,4-phenylenebis(methylene)selenocyanate (p-XSC, **15**) has also been proven to be effective *in vitro*, at low micromolar concentrations, against androgen responsive and androgen unresponsive human prostate cancers by inducing cell cycle arrest in the G1 phase and activating JNK, p38, ERKs 1&2 and Akt cancer cell signaling (139-141), and by inhibiting the m-TOR downstream effectors (142).

As for selenides, some multi-target selenocyanate compounds were recently developed. By combining an indoleheterocycle microtubule inhibitor with a selenocyanate moiety, Krishnegowda and coworkers developed a series of selenocyanate derivatives (**16**) endowed with a very promising *in vitro* antitumor activity (in the low micromolar range) against colon, breast and lung cancers and against melanoma. The conjugation of the indoleheterocycle and the selenocyanate moieties in the same molecular entity yield to

selenoisatin-analogs was able to induce cancer cell death through a mechanism encompassing both microtubule and Akt inhibition (143).

In addition, selenocyanate containing triterpenes based on homobetulin scaffold (**17**) were recently developed and tested for their *in vitro* antitumor potential. These compounds exhibited an antiproliferative activity in the low micromolar range and were barely effective against non-tumor cells (144).

Selenoesters

Initially, selenoesters (Figure 6) were developed based on the rationale that they may undergo hydrolysis or enzymatic reduction in cells, thus generating *in situ* redox active compounds (145). These redox active metabolites, being ionic species of Se (such as selenol), could readily participate in cellular redox processes, ultimately triggering cancer cell death. Many alkyl and aryl selenoesters (**18**) showed a prominent cytotoxic activity (at nanomolar ranges) against prostate, breast, lung and colon cancer cell lines (145). In addition, some selenoesters with ketone terminal fragments were effective in reversing the multidrug resistance (MDR) phenomenon in mouse MDR T-lymphoma cells and in human colon cancer cells. owing to their ability to act as strong inhibitor of cellular efflux pump P-gp (146, 147).

Among sugar-based selenoesters, both xylitolselenious ester (xylitol-Se, **19**) and sucrose selenious ester (sucrose-Se, **20**) have been synthesized. While barely characterized, the xylitol-Se compound has shown selective cytostatic effects on human hepatoma cells, in a dose-dependent manner, by acting as GSH depleting agents (148, 149). Interestingly, this cytotostatic effect was not detected in normal human hepatic cells. Similarly, the Sucrose-Se was selectivity inhibited the proliferation of several cancer cell lines in a dose-dependent manner without affecting the proliferation of non-cancer human liver cells. Additionally, in an acute toxicity test in mice, the sucrose-Se showed a very high median lethal dose compared to sodium selenite (290.0 and 13.1 ppm, respectively), thus laying down the basis for a further preclinical development of this type of selenocompounds (150).

Ethaselen

Ethaselen (1,2-[bis(1,2-benzisoselenazolone-3(2H)-ketone)]ethane, Figure 7, **21**), also known as BBSKE, has been synthesized and extensively studied by Zeng and co-workers in a number of cell lines (151). They have found that it targets and inhibits thioredoxin reductase (TrxR), a central antioxidant and redox regulatory enzyme, which has been proposed as a promising target for anticancer drugs (152). Ethaselen, via its TrxR inhibitory effect, has also been shown to inhibit the proliferation of tumor cells through S phase arrest (153). More detailed studies revealed that TrxR inhibition by ethaselen occurs through targeting of the C-termina,l but not the N-terminal active site of the enzyme, and that it does not inhibit thioredoxin or glutathione reductase. The same study showed that downstream effects of ethaselen caused oxidation of Trx and increased the levels of ROS (154). Concomitantly, *in vivo* experiments have also shown promising results with ethaselen, with tumor inhibitory effects in the range of 40-80% in prostate, tongue and liver cancer models (155-157). The metabolism and secretion of ethaselen has further been suggested to occur via oxidation, methylation and glucoronidation (158). Ethaselen has also been tested *in vivo* in several combination therapies. One study used ethaselen in combination with cisplatin (cis-diaminedichloroplatinum II, DDP) in a lung xenograft mouse model. Compared to single drug administration, the combination treatment showed significant synergistic reduction of tumor size, with no evident signs of systemic or organ toxicity (159). In a leukemic cisplatin resistant cell line, similar findings were observed, with significant synergistic effects of cisplatin and Ethaselen (48). In the resistant cell line, cisplatin alone was unable to induce ROS and the Bax to Bcl-2 ratio, while Ethaselen still able to induce ROS via the inhibition of TrxR and the suppression of NF-κB. Co-treatment of ethaselen with Sunitinib, a multitargeted tyrosine kinase inhibitor, has similarly displayed synergistic effects against proliferation of colorectal cancer cells (160). In accordance with other studies (27) showing that the inhibition of TrxR sensitizes cancer cells to radiotherapy, Whang and co-workers showed that ethaselen enhances the efficacy of radiation therapy *in vitro* and *in vivo* without causing any signs of toxicity (161). Despite the promising activity of ethaselen, the solubility in physiological media is not optimal, thus precluding its application without a

suitable formulation. The formulation as copolymer micelles lately reported by Liu *et al.* allowed for an increased water solubility and ultimately led to an enhanced antitumor activity, which was attributed to a massive accumulation at the tumor site (162). Ethaselen has reached Phase I clinical trials in patients with non-small cell carcinoma. In the Ia/b phase, 1200 mg/day was found to be a safe and tolerable dose (ClinicalTrials.gov identifier: NCT02166242).

More recently, novel benzisoselenazolone derivatives (**22**) have been synthesized and evaluated for their antiproliferative properties compared to ethaselen. Among the new compounds, some showed a superior antitumor activity compared to ethaselen, and they retained a good selectivity toward cancer cells, with only weak cytotoxic effects against non-cancerous cells (163-165). Notably, Ye and coworkers have lately synthesized some ethaselen derivatives by linking it to a carmustine-based moiety. These combination molecules were shown to possess an improved solubility, a low toxicity profile and a very efficient antitumor activity in several cancer cell lines (166). The authors also established a SAR model relevant to further structural modification. Overall, their results have highlighted the potential of ethaselen-based combination molecules for the development of novel antitumor agents.

Ebselen

Ebselen (Figure 7, **23**), a structurally related compound to ethaselen, has mainly been considered as a glutathione peroxidase mimic and hence, also, as a strong antioxidant. In comparison to ethaselen, ebselen is an efficient substrate for TrxR, and the reaction is known to be stimulated by Trx, leading to a rapid oxidation of Trx (167). The antioxidative properties of ebselen has been widely studied, but a few studies have also suggested that ebselen might possess antiproliferative and anticancer properties via ROS production (168). In addition, ebselen has been proposed to alter the mitochondrial function, including Bax activation (168). These anticancer properties have also been suggested to be via the inhibition of Quiescin sulfhydryl oxidase 1, an enzyme that promotes the growth and invasion of tumor cells and alters the extracellular matrix composition. In the same study,

the authors described that a daily oral treatment with ebselen resulted in a 58% reduction in tumor growth in mice bearing human pancreatic tumor xenografts (169). By combining ebselen with gamma radiation, a major antitumor efficiency was accomplished, by both inducing apoptosis and inhibiting cancer progression, as well as by modulating the response of pro- and anti-inflamatory cytokines (170).

New chiral ebselen analogues have been synthesized by Pacuala *et al.,* but they only exhibited moderate cytotoxic properties (171). A series of benzoselenazole-stilebene hybrids (**24**) have been synthesized by combining reservatrol and ebselen, with the aim to create compounds that possess the pharmacological activity of both compounds simultaneously. These compounds were found to possess antiproliferative properties, causing cell cycle arrest and programed cell death in the low micromolar range, as well as significantly inducing ROS formation (172). Ebselen has been shown to comprise weak histone deacetylace (HDAC) inhibitory activity, and the development of new ebselen and ebsulfur analogs increased these features further, with the ebsulfur analog reaching nanomolar potency (173).

Selenium-containing 5-membered rings

Se-containing 5-membered ring compounds (selenophenes, selenazoles and selenadiazoles, see Figure 8) have been prepared and evaluated for their pharmacological potential as anticancer agents.

Selenophene

Among compounds endowed with antitumor potential, one of the most promising derivatives is selenophene, D-501036, 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-N-methylpyrrole (**25**), which was identified as a potent antineoplastic agent with a broad spectrum of activity against human cancer cell lines. It elicited IC_{50} values in the low micromolar range, being highly selective against cancer cells compared to normal cells and highly effective against multi drug resistant (MDR) cancer cells. Furthermore, D-501036 exhibited strong antitumor activity *in vivo*, in a mouse xenograft

model of human renal carcinoma. Concerning its mechanism of action, it was found to induce cell death through a p-53 and mitochondrial mediated apoptotic pathway (174-176). Selenopheno quinolinones and coumarins were also shown to promote cancer cell death. Depending on the analog examined, they affected different antioxidant defense enzymes (i.e. SOD, GPx and TrxR) and activated caspase-7 (177).

Selenadiazoles

Selenadiazoles have also attracted attention in the past years owing to their potential as anticancer agents. Initially, a series of 4-methyl-1,2,3-selenadiazole-5-carboxylic acid amides were synthesized and characterized for their antitumor potential *in vitro* and *in vivo* against murine cancers (178). Later, a series of 20 selenadiazole derivatives were designed and synthesized, with 1,2,5-selenadiazolo-[3,4-d]pyrimidine-5,7-(4H,6H)-dione (**26**) being the most promising derivative. This compound was found to be cytotoxic toward different human cancer cells, namely melanoma, hepatoma and breast cancer cells (179). This compound was able to kill cells through the induction of both extrinsic and intrinsic caspase-dependent apoptosis. Mechanistically, an overproduction of ROS and depletion of mitochondrial membrane potential, through regulation of the expression of pro-survival and pro-apoptotic Bcl-2 family members, contribute to cancer cell death induction.

The same authors later developed the anthrax[1,2-c][1,2,5]selenadiazolo-6,11-dione (**27**) and highlighted its efficacy in inducing a time- and dose-dependent cell death in human breast carcinoma cells (180). Similarly to the previous selenadiazole derivative, the authors showed that the cell death pathway was driven by depletion of the mitochondrial membrane potential, up-regulation of Bax, Bad and PUMA expression, and down-regulation of Bcl-xl expression. However, the caspase-dependent cell death was, in this case, not mediated by ROS production.

In 2014, Zhang and coworkers developed a new selenodiazole compound, 4-(benzo[c][1,2,5]selenadiazol-6-yl) benzene-1,2-diamine (**28**), and tested it against different human cancer cell lines (181). Remarkably, this compound was effective (at micromolar doses) against all tested cell lines, while barely affecting non-tumor cells. From mechanistic investigation in glioma cells, the authors showed that the selenodiazole derivative induced

a caspase-dependent mitochondrial mediated apoptotic cell death as consequence of AKT dephosphorylation and p53 activation. New Se-NHC adducts have also been synthesized from mono- and bis-benzimidazolium salts. The benzyl substituted benzimidazolium salt and respective Se-NHC adduct was proven to be, by far, the most efficient when tested in a colorectal cancer cell line (HCT 116), and were found to induce apoptosis via the intrinsic pathway (182).

Selenazofurin

Selenazofurin (2-β-d-ribofuranosylselenazole-4-carboxamide, **29**), the Se analogue of tiazofurin synthesized in 1983 by Sivastava and Robins (183), was initially shown to possess a pronounced antitumor activity against murine melanoma cancers both *in vitro* and in animal models, as well as against human promyelocytic leukemia cells *in vitro* at nanomolar levels (184, 185). Similar results were reported by Gebeyehu *et al.* with a series of selenazofurin dinucleotides, whereby the latter dinucleotide analogues were more effective than the mononucleotide precursor (186). Mechanistically, selenazofurin and its derivatives are metabolized to the corresponding selenazole-4-carboxamide-adenine dinucleotides and act as potent noncompetitive inhibitors of inosine monophosphate dehydrogenase (IMPD), a rate-limiting enzyme of *de novo* guanine nucleotide biosynthesis. Based on these interesting and promising results, in the 90's, Franchetti and coworkers developed a new analog, selenophenfurin (**29**), in which the selenazole ring was replaced into a selenophene heterocycle (187). This compound was shown to be effective against leukemia, lymphoma, and solid tumor cell lines at concentrations similar to those of selenazofurin.

Se-containing 6-membered rings

Very few Se-containing 6-membered rings (Figure 8) have been developed for the use as anticancer agents. Among the 6-membered ring-based compounds, Koketsu and coworkers developed a series of 1,3-selenazine-based compounds (**30**) and demonstrated their antiproliferative effects against fibrosarcoma and gastric cancer cells via the induction of apoptotic cell death (188, 189). Later, they also developed some 1,4-osxaselenins (**31**) and

demonstrated their inhibitory effect on the proliferation of human ovarian and cervical cancer cells by inducing apoptosis (190).

Selenium-nonsteroidal anti-inflammatory drug (Se-NSAID).

A few years back, a study performed by Bi *et al.* presented evidence for a synergistic effect between a nonsteroidal anti-inflammatory drug (NSAID), sulindac, and Se (191). In this study, a non-toxic dose of sulindac was used in combination with Se, which significantly inhibited intestinal tumorigenesis, determined by reduced incidences of tumors (52%) and tumor multiplicities (80%). The results were linked to a significant induction of the expression of p27 and p53 as well as JNK1 phosphorylation. Recently, a Se-containing selenocoxib derivative (Figure 9, **32**) was developed and the authors highlighted the ability of this compound to decrease melanoma cell growth by arresting cells in the G0-G1 phase of the cell cycle, promoting apoptosis and inhibiting cellular proliferation (192). Mechanistically, the Se-containing selenocoxib derivative retains COX-2 inhibitory activity and PI3K/Akt inhibitory activity. Similarly, Plano and coworkers later incorporated Se into NSAIDs, generating Se-NSAID hybrids (**33**) (193). The most effective was a SeCN-aspirin analogue, which was shown to be extremely selectivity toward cancer cells and was found to cause cell cycle arrest in G1 and G2/M phases and induce apoptosis by activating caspase 3/7 and PARP cleavage in colorectal cancer cells.

Se containing histone deacetylase inhibitors

Histone deacetylases (HDACs) are involved in the epigenetic regulation of gene expression by the remodeling of chromatin through their deacetylase activity. Inhibition of HDACs has emerged as a target for specific epigenetic changes associated with cancer and other diseases. The use of HDAC Inhibitors is therefore believed to be an attractive therapeutic strategy against cancer. Se containing derivatives of the FDA approved HDAC inhibitor suberoylanilide hydroxamic acid (SAHA, **34**) have been synthesized and studied in melanoma and lung cancer cell lines. Both of the reported compounds, bis(5-phenylcarbamoylpentyl) diselenide and 5-phenylcarbamoylpentyl selenocyanide were able

to inhibit HDAC activity and were also found to possess PI3 kinase pathway inhibitory properties. More importantly, both were significantly more effective in inducing cytotoxicity towards different cancer cell lines compared to SAHA (194-196).

HDAC inhibition has also been reported for MSC and SeMet, which are transaminase substrates of glutamine transaminase K (GTK) and L-amino acid oxidase (197). GTK and L-amino acid oxidase are able to convert MSC to the corresponding alpha-keto acid, β-methylselenopyruvate (MSP), while L-amino acid oxidase converts selenomethionine to its corresponding alpha-keto acid, alpha-keto-gamma-methylselenobutyrate (KMSB). These metabolites structurally resemble the known HDAC inhibitor, butyrate, and both MSP and KMSB have been shown to inhibited HDAC activity (43).

Selenium containing nanoparticles in the treatment of cancer

Nanoparticles (NPs), both metallic and non-metallic (polymers, oxides and semi-conductors), are highly emerging and substantial alternatives for oncotherapy due to their excellent bioavailability, biological activity and low toxicity (71). Se containing nanoparticles (SeNPs), have recently gained interest as potential novel therapeutic agents, due to their high biocompatibility, stability and pronounced selectivity (119, 182). During the last decade, a surplus of SeNPs have been synthesized using distinct and novel strategies for therapeutic purposes. Primarily the colloidal SeNPs can be synthesized using different precursor materials, like sodium selenite, sodium dioxide and selenicious acid, using physical, chemical or biological methods (74). Chemical synthesis involves reduction of ions, which is then followed by physical synthesis where bulk material is converted to smaller units, microwave synthesis, laser ablation and gamma irradiation (74). The biological synthesis of SeNPs uses living organisms like plants, phytocompounds and microorganisms to reduce Se salt to elemental Se (73, 75, 173, 177). SeNPs have been used to target cancer cells both by indirectly functioning as drug delivery vehicles and also directly by taking advantage of the anticancerogenic properties of Se. Although the vast majority of the research to date has been emphasized on the use of SeNPs as drug delivery

payloads, recent studies have shown the direct cytotoxic effects of SeNPs selectively on cancer cells.

SeNPs as drug delivery vehicles:

One of the critical obstacles for anti-cancer therapy is the limited availability of drug delivery systems for hydrophobic anti-cancer drugs that often have low solubility in aqueous media preventing their intravenous administration. In such cases, use of NPs as a drug delivery vehicle is of prime importance. However, lack of particular targeting effects by these NPs, might inevitably cause drug cytotoxicity and undesirable side effects. Therefore cancer-targeted ligands are conjugated to surface of NPs, which leads to the preferential accumulation of NPs in tumor bearing organs, and further selective killing of cancer cells and reducing the toxicity towards normal cells. As emphasized before in this review, Se and Se containing compounds have higher selectivity towards cancer cells making them a prime candidate for SeNP drug delivery vehicle.

The strategic use of drug containing Se nanocapsules is mainly to enable the incorporation of drugs at a higher concentration than their intrinsic solubility and at the same time confer protection from degradation and systemic toxicities (170). Generally, the surface decorated SeNPs bind to the cellular receptors on the cancer cell surface, undergo cellular internalization via receptor mediated endocytosis subsequently leading to degradation of the nanoparticle and intracellular release of the drugs to achieve anticancer synergism combining with the native anticancer activity of SeNPs. Accordingly, several groups have published promising anti-cancer effects of various ligands conjugated to SeNPs. Transferrin conjugated SeNPs have been shown to enhance the uptake of doxorubicin into the mammalian breast cancer cell line MCF-7, further selectively inducing apoptosis and inhibiting cancer cell growth in *in vivo* MCF-7 mice xenograft model (198). Recently, paclitaxel loaded SeNPs have shown to induce apoptosis via oxidative stress, altered mitochondrial membrane potential and via activation of effector caspases in different

cancer cell lines (77). Jiang *et al.* developed a GE-11 peptide-conjugated SeNPs as a nanosystem targeting EGFR over-expressed cancer cells via PI3K/AKT and RAs/Raf/MEK/ERK pathways (84). In another study, apoptosis inducing aptamer – NAS-24 conjugated to SeNPs loaded with epirubicin significantly reduced viability in MCF-7 and C26 cells as well as reduced tumor growth in cancer-bearing mice as compared to EPI treatment alone (199). Mechanistic studies have shown that gold NPs (AuNPs) with Se ligands (AuNP/Se) significantly induced and enhanced the production of ROS leading to cellular apoptosis, which was initially a limitation for only AuNPs (200).

SeNPs as direct anti-cancer agents:

Non-functionalized SeNPs, synthesized by different green chemical and biotechnological process have been shown to be efficient against a variety of different cancer cell lines like HeLa and MDA-MB-231 in a time and dose dependent manner (54, 55). However, SeNPs are prone to aggregation in aqueous medium and therefore synthesis of surface decorated SeNPs have gained particular interests, wherein by means of functionalization with variety of different agents, the physiochemical properties and *in vivo* pharmacokinetic and biodistribution profiles of these SeNPs are enhanced. Surface decoration of SeNPs allows the decorating ligand to target membrane receptors or transporters that are overexpressed on the cancer cell plasma membrane, thus facilitating the uptake and improved antiproliferative efficacy as compared to the elemental nude SeNPs. To date several surface decorating ligands for SeNPs like ATP (201), Spirulina (59) or Undaria pinnatifida (202) polysaccharides, transferrin (198), sialic acid (89), chitosan (88, 203), and folate (78) have been developed. These decorated SeNPs have shown anti-cancer properties by various mechanisms like ROS induction, depletion of mitochondrial potential, cell cycle arrest and apoptosis. Recently, biogenic SeNPs have been shown to induce cell death in human prostate adenocarcinoma cell line by ROS mediated activating of necroptosis (90). In brief, several studies on SeNPs targeting the cancer cells *in vitro* and *in vivo* seem promising. However, the exact mechanism of action and/or synergism that Se imparts to other

canonical drugs is yet to be understood and needs to be studied further, and novel more sophisticated compounds are warranted.

Conclusion

Many different classes of naturally and synthetic organoselenium compounds have been explored as antiproliferative agents, and the field is constantly emerging, with several compounds demonstrating pronounced cytotoxic activity against cancer cells compared to non-transformed ones. The current knowledge of their dose efficacy range, target cancers and mode of cell death are summarized in Table 1. Coherently, *in vivo* experiments clearly confirm their scarce systemic toxicity and enhanced tolerability, both when used as monotherapy and, strikingly also when administered in combination with conventional chemotherapeutic agents. In combination with other treatments, Se compounds not only increase the therapeutic potential, but they also seem to protect against unwanted side effects. With this said, more profound *in vivo* experiments are required for many of these compounds to elucidate their specific anticancer properties. However, what seems to be clear is that organoselenium compounds are more efficient, selective, and well-tolerated than the corresponding non-chalcogenated molecules, thus illustrating the importance of further exploiting the potential of novel orgnoselenium compounds and SeNP for the development of novel cancer-specific anticancer agents.

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Figure legends

Figure 1. Schematic representation of general mechanisms of action of Se compounds. Se compounds exert their anti-cancer activity by targeting one or more metabolic processes mainly by induction of ROS, thiol modification and/or chromatin binding/modification, which further leads to selective killing of cancer cells.

Figure 2. Naturally occurring organoselenium compounds 1-4.

Figure 3. Selenides 5-10.

Figure 4. Diselenides 11-12.

Figure 5. Selenocyanates 13-17.

Figure 6. Selenoesters 18-20.

Figure 7. Benzisoselenazolone derivatives 21-22, Ebselen and corresponding derivatives 22-24,

Figure 8. Se-containing 5-membered rings 25-29, and Se-containing 6-membered rings 30-31.

Figure 9. Se-containing cox inhibitors 32, Se-NSAID hybrids 33, and Se containing HDAC inhibitors 34.

Table 1 Summary of the anticarcinogenic properties of organoselenium compounds

Compound	**Target Cancers**	**Effective Dose *in vitro* (48-72 hour IC_{50})** Very low (0.1-2 µM) Low (1-20 µM) Medium (10-100 µM) High (100+ µM)	**Mechanism of Cell Death**
Selenocystine (SeCys)	Acute promyelocytic leukemia	Medium (Chen & Wong 2009b)	**Apoptosis** mediated by caspases, mitochondrial dysfunction/signalling and PARP cleavage.(Chen & Wong 2008; Chen & Wong 2009b; Chen & Wong 2009a; Poerschke & Moos 2011) **Paraptotic-like** mediated by ER stress and UPR (Wallenberg et al. 2014)
	Breast	Low-medium (Chen & Wong 2009b)	
	Colon	Low-medium (Chen & Wong 2009b)	
	Cervical	High (Wallenberg et al. 2014)	
	Melanoma	Low (Chen & Wong 2008)	
	Nasopharyngeal	Low (Chen & Wong 2009b)	
	Liver	Low (Chen & Wong 2009b)	
	Lung	Low (Poerschke & Moos 2011)	
Selenomethionine (SeMet)	Breast	Medium-high (Redman et al. 1998) to >1000µM (Suzuki et al. 2010)	**Apoptosis** mediated by caspases and ER stress (Suzuki et al. 2010; Redman et al. 1998; Yang et al. 2009) Involvement of decreased COX-2 expression (Baines et al. 2002)
	Colon	High (Baines et al. 2002)	
	Lung	>1000µM (Suzuki et al. 2010)	
	Prostate	Medium-high (Redman et al. 1998; Sinha et al. 2008)	
	Melanoma	Medium-high (Redman et al. 1998)	
	Oral Squamous	>1000µM (Suzuki et al. 2010)	
Se-methylselenocysteine (MSC)	Breast	High (Suzuki et al. 2010)	**Apoptosis** mediated by caspases, ER stress, mitochondrial dysfunction/signalling and PARP cleavage (Suzuki et al. 2010; Jang et al. 2003; Kim et al. 2001; Yeo et al. 2002)
	Colon	Medium-high (Schröterová et al. 2009)	

	Lung	>1000µM (Suzuki et al. 2010)	
	Oral Squamous	Medium-high (Suzuki et al. 2010)	
Selenodiglutathione (SDG)	Acute myeloid leukaemia	Low (Cho et al. 1999)	**Apoptosis** associated with ROS production and oxidative damage (Cho et al. 1999; Wallenberg et al. 2014; Ghose et al. 2001; Last et al. 2006; Tobe et al. 2015)
	Breast	Low (Tobe et al. 2015)	
	Cervical	Low (Wallenberg et al. 2014)	
	Lymphoma	Low (Last et al. 2006)	
	Oral	Very low-low (Ghose et al. 2001)	
Methylseleninic Acid (MSA)	Breast/ Mammary	Low *in vitro* (de Miranda et al. 2014). Also determined *in vivo* (Wu et al. 2012; Sundaram & Yan 2017)	**Apoptosis** mediated by caspases, ER stress, UPR, mitochondrial dysfunction/signalling and PARP cleavage (Poerschke & Moos 2011; Wang et al. 2014; Shigemi et al. 2017; Hu et al. 2005; Jiang et al. 2002) **Anoikis**, whereby cell detachment is a prerequisite for caspase activation and PARP cleavage (Jiang et al. 2001)
	Colon	Only *In Vivo* data (Zeng & Wu 2015)	
	Lung	Medium (Poerschke & Moos 2011)	
	Lymphoma	Low-Medium (Shigemi et al. 2017)	
	Pancreatic	Very low- Low (Wang et al. 2014)	
	Prostate	Low *in vitro*. Also determined *In Vivo* (Jiang et al. 2002; Singh et al. 2014)	
Methylimidoselenocarbamates & Quinolone-based imidoselenocarbamates	Breast, Colon, Liver, Lymphocytic Leukemia, Prostate	Very low-medium (Ibáñez et al. 2012; Plano et al. 2007; Ibáñez et al. 2011)	**Apoptotis** and **autophagy** caused by multiple kinase inhibition. Specifically, inhibition of the PI3K/AKT/mTOR and ERK1/2 pathways (Ibáñez et al. 2012; Ibáñez et al. 2011)
Quinazoline and Pyrido[2,3-d]pyrimidine selenocompounds	Breast, Colon, Lung, Lymphocytic Leukemia	Low-medium (Moreno et al. 2012)	Apoptosis associated with DNA degradation/ fragmentation (Moreno et al. 2012)
Quinine-based selenocompounds with multiple redox centres	Breast	Very low (Doering et al. 2010)	Probable ROS-mediated mechanism (Doering et al. 2010)
	Colon	Very low-Low (Doering et al. 2010; Jardim et al. 2018)	
	Gliomal	Very low-Low (Jardim et al. 2018)	

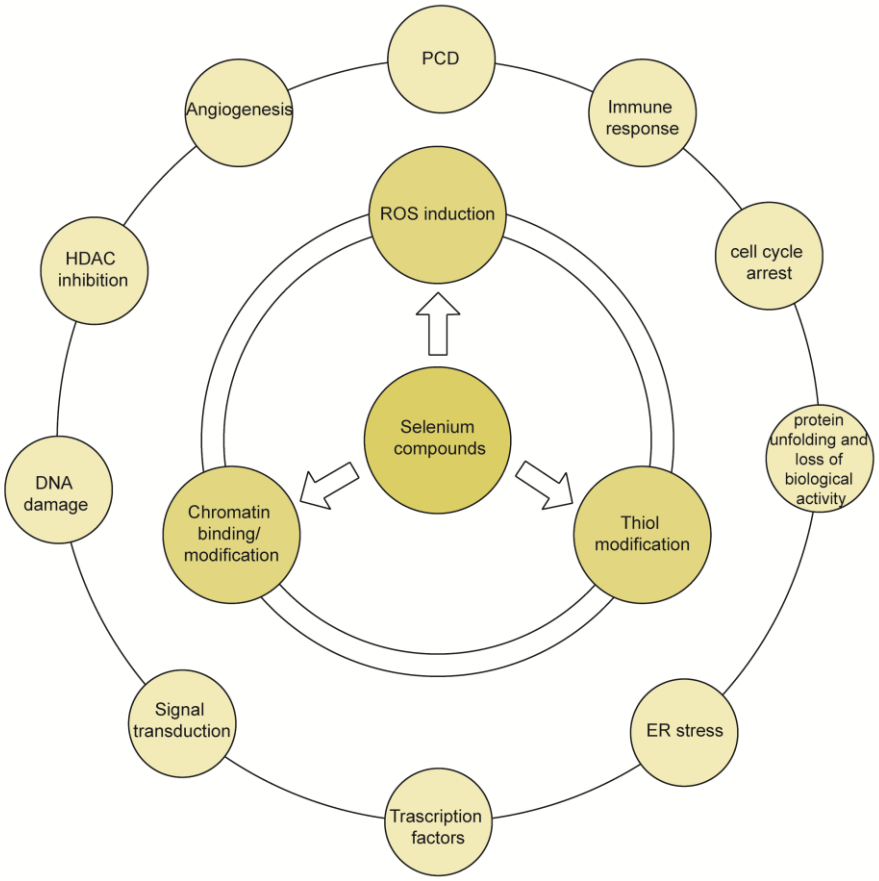
	Prostate	Very low-Low (Jardim et al. 2018)	
	Leukemia	Very low-low (Doering et al. 2010; Jardim et al. 2018)	
	Lung	Very low-low (Jardim et al. 2018)	
Peptidomimetic selenocompounds with multiple redox centres	NIH Panel of 58 cancer cell lines	GI_{50} values - very low to low (Shaaban et al. 2012)	**Apoptosis** mediated by caspases, ROS induction, ER stress and damage to the cytoskeleton (Shaaban et al. 2012)
	Breast, Melanoma and Kidney	24 hour IC_{50} values – low to high (Shaaban et al. 2012)	
β-lapachone selenoderivatives with two redox centres	Breast, Colon, CNS, ovarian, leukaemia, ovarian and prostate	Very low-low (Vieira et al. 2015)	Probable ROS mediated mechanism (Vieira et al. 2015)
Ethaselen	Cervival, Gastric, Liver, Lung,	Very low-low (Zhao et al. 2006)	**Apoptosis** mediated by thioredoxin reductase inhibition and subsequent oxidative stress (Zhao et al. 2006; Shi et al. 2003; Wang et al. 2012)
	Prostate	Low (Shi et al. 2003)	
	Tongue	Low (Xing et al. 2008)	
Benzisoselenazolone derivatives	Breast, Cervical, Liver and Lung	Low-medium (Fu et al. 2016; Luo et al. 2012; Li et al. 2016)	Not determined. Compounds are based on an Ethaselen scaffold.
Ebselen	Bone marrow/ myeloma	Medium (L. Zhang et al. 2014)	**Apoptosis** mediated by mitochondrial signalling. Acts as a substrate for thioredoxin reductase and rapidly oxidises thioredoxin, leading to oxidative stress. (L. Zhang et al. 2014; Zhao et al. 2002)
Chiral Ebselen Analogues	Breast, Liver, Promyelocytic Leukemia, Prostate	Medium-high (Pacuła et al. 2017)	Not determined. Compounds have antioxidant activity.
Benzoselenazole-stilbene hybrids	Breast, Cervical, Liver, Lung	Very low-low (Yan et al. 2015)	**Apoptosis** mediated by thioredoxin reductase inhibition and oxidative stress (Yan et al. 2015)
Selenophenes *D501036*	Breast, Cervical Colorectal, Epidermal, Kidney, Nasopharyngeal	Very Low (Juang et al. 2007)	**Apoptosis** mediated by ROS-induced DNA damage. Mitochondrial mediated, caspase dependent signalling. (Juang et al.

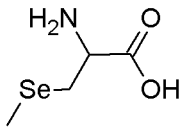
	, Liver, Lung,		2007; Shiah et al. 2007)
Selenodiazoles *1,2,5-selenadiazolo-[3,4-d]pyrimidine-5,7-(4H,6H)-dione (SPO)*	Breast, Liver, Melanoma	Medium (Chen et al. 2008)	**Apoptosis** mediated by caspase signalling, ROS production and mitochondrial dysfunction. (Chen et al. 2008; Chen et al. 2009; Y. Zhang et al. 2014)
Selenodiazoles *anthrax [1,2-c] [1,2,5] selenadiazolo-6,11-dione (ASDO)*	Breast	Medium (Chen et al. 2009)	
Selenodiazoles *4-(benzo[c][1,2,5]selenadiazol-6-yl) benzene-1,2-diamine*	CNS/Gliomal	Medium (Y. Zhang et al. 2014)	
Selenazofurin *(2-β-d-ribofuranosylselenazole-4-carboxamide)* & Selenazofurin derivatives	Bladder, Cervical, Colon, Leukemia, Lymphoma, Kidney	Very low in blood cell tumours, Low in solid tumours (Boritzki et al. 1985; Lucas et al. 1983; Gebevehu et al. 1985; Franchetti et al. 1997)	Act through non-competitive inhibition of inosine monophosphate dehydrogenase, thus limiting de novo guanine nucleotide biosynthesis. (Boritzki et al. 1985; Lucas et al. 1983; Gebevehu et al. 1985; Franchetti et al. 1997)
Selenazines *1,3-selenazine-based compounds*	Fibrosarcoma, Gastric	Low (Koketsu et al. 1999; Wu et al. 1999)	**Apoptosis** involving DNA fragmentation
Selenazines *1,4-oxaselenins*	Cervical, Ovarian	Medium-high (Koketsu et al. 2001)	
Se-NSAID hybrid compounds	Breast, Colorectal, Melanoma, Pancreatic	Low-medium (Gowda et al. 2013; Plano et al. 2016)	**Apoptosis** mediated by caspases, PARP cleavage and ROS production. Involvement of COX-2 and PI3K/AKT inhibition. (Gowda et al. 2013; Plano et al. 2016)
Se-HDAC Inhibitors	Breast, Fibrosarcoma,	Very low-low (Desai et al. 2010; Karelia et al. 2010;	**Apoptosis** mediated by caspases and PARP

Suberoylanilide hydroxamic acid (SAHA) selenoderivatives	Lung, Melanoma, Pancreatic, Prostate	Gowda et al. 2012)	cleavage. Involvement of HDAC inhibition and PI3K pathway inhibition. (Desai et al. 2010; Karelia et al. 2010; Gowda et al. 2012)
3'-Azido-3'-deoxythymidine (AZT) selenoderivatives *chalcogenozidovudines*	Bladder	Medium (De Souza et al. 2015; Ecker et al. 2017)	**Apoptosis** via oxidative stress. Production of pro-inflammatory cytokines. (De Souza et al. 2015; Ecker et al. 2017)

Highlights

- Selenium compounds have gained substantial interest as anticancer agents.
- The review covers naturally occurring and synthetic organoselenium compounds.
- Their chemical properties and main mechanisms of action are discussed herein.





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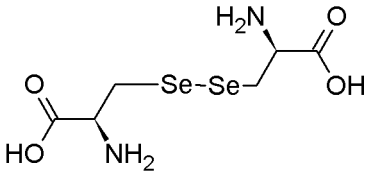

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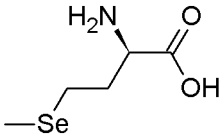

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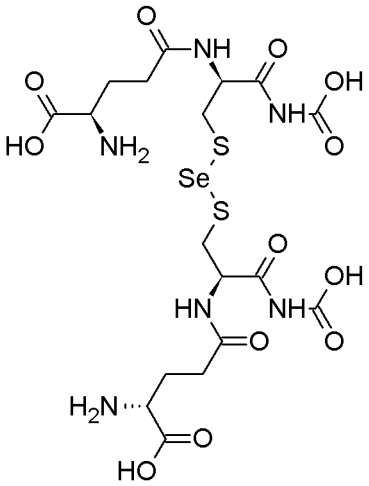

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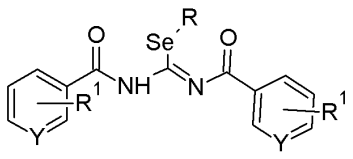
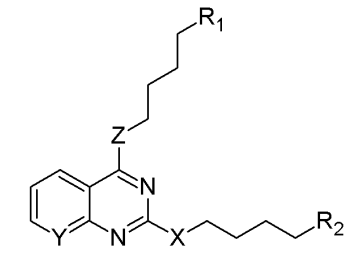


Y = C, N

R = alkyl

R^1 = H, alkyl, OCH_3, Cl, CF_3, CN, NO_2

5



Y = N, C

X = S, Se

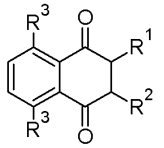
Z = NH, O, Se

R_1 = H, OH, CH_3,

R_2 = H, CH_3

R_3 = H, OCH_3, SCH_3, $SeCH_3$

6

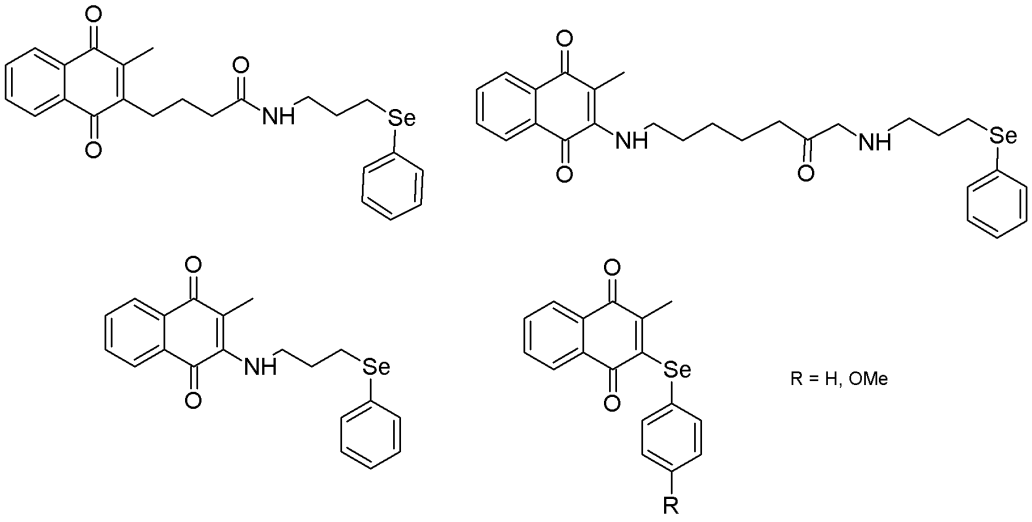


R^1 = H, Se-Ph, CH_2-$CH(OEt)_2$

R^2 = Se-Ph, CH_2-$CH(OEt)_2$

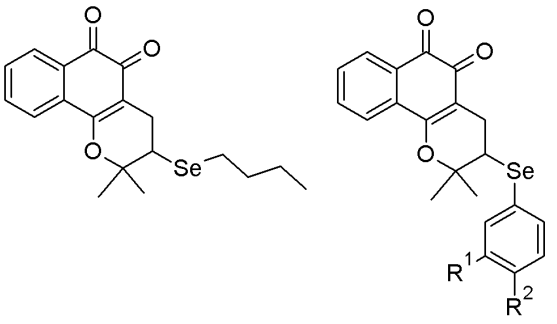
R^3 = H, OH

7



R = H, OMe

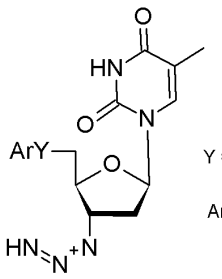
8



R^1 = H, CF_3

R^2 = H, Me, OMe, Br, Cl

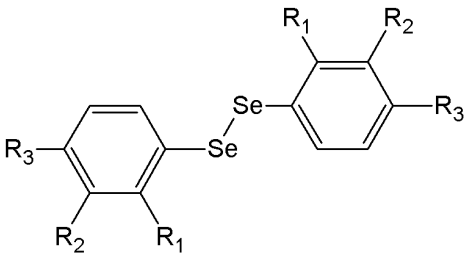
9



Y = Se, Te, S

Ar = aryl

10

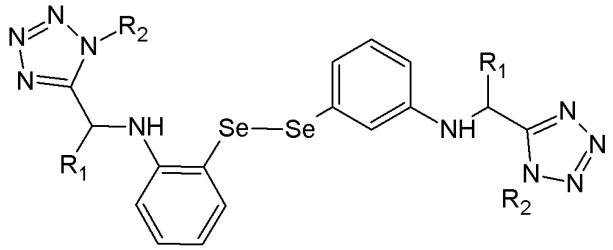


R_1 = H, OMe, NH_2

R_2 = H, CF_3

R_3 = H, OMe

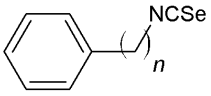
11



R_1 = H, $CH(CH_3)_2$, furan, *p*-toluene

R_2 = *tert*-buthyl-, *p*-CH_3O-Ph-, 2,4-CH_3O-Ph-, 1,1,2-trimethoxy-, cyclohexane, Ph

12



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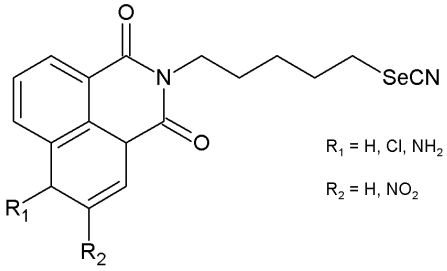
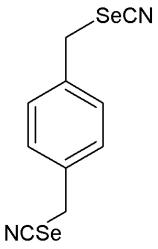


R_1 = H, Cl, NH_2

R_2 = H, NO_2

14



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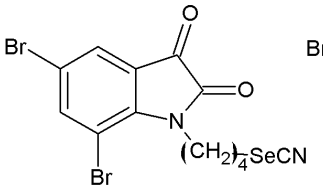

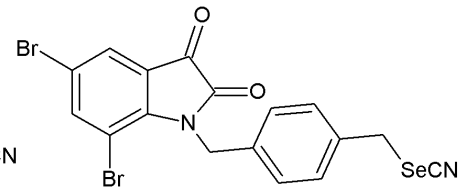

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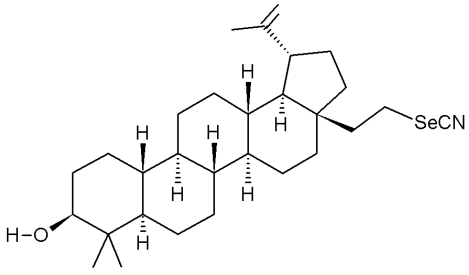

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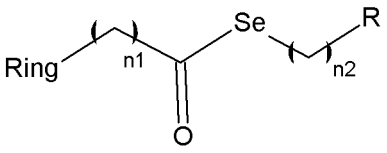
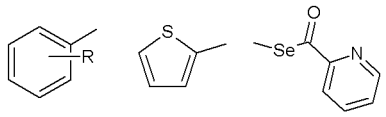


n1 = 0, 1

n2 = 0, 1, 2

R = CH_3, $COC(CH_3)_3$, $COCH_3$, $CONH_2$, $COOCH_3$, $COOC(CH_3)_3$, COOPh

Ring = 

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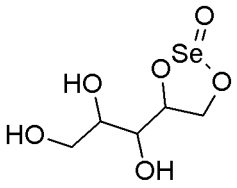

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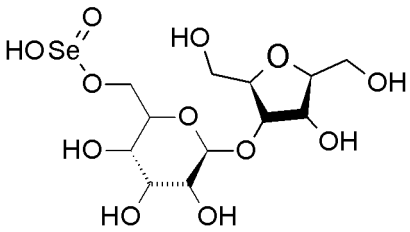

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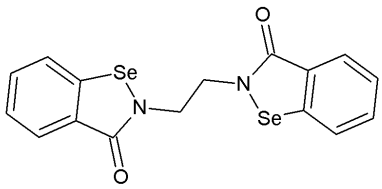

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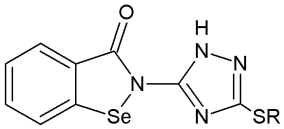
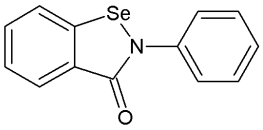


R = CH_2CH_3, $CH_2CH_2CH_3$, $CH_2(CH_3)_2$, butyl-, isobutyl-, pentyl-, hexyl-, benzyl-, *p*-F-benzyl, *p*-Cl-benzyl-, *o*-CH_3-benzyl-, *m*-CH_3-benzyl-, *p*-NO_2-benzyl-

22



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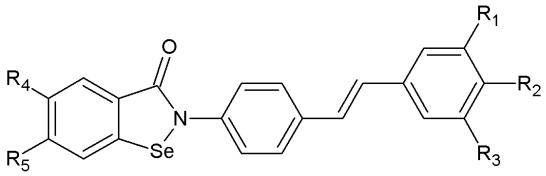
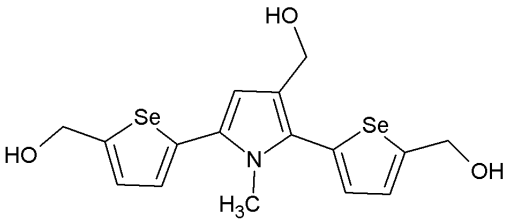


R_1, R_2, R_3 = H, OCH_3

R_4 = H, F, Cl

R_5 = H, Cl

24



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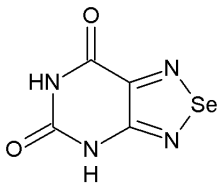

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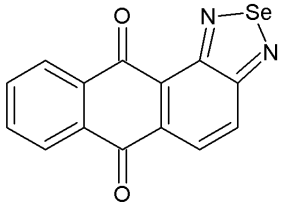

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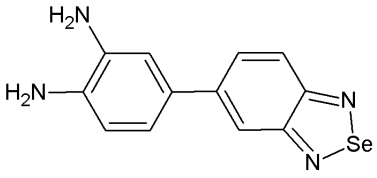

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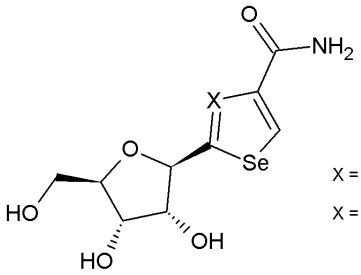
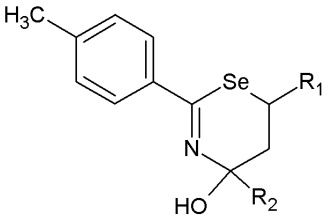


X = N (Selenazofurin)

X = CH (Selenophenfurin)

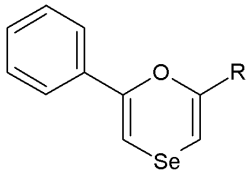
29



R_1 = H, $CH_2CH_2CH_3$, $CH(CH_3)_2$

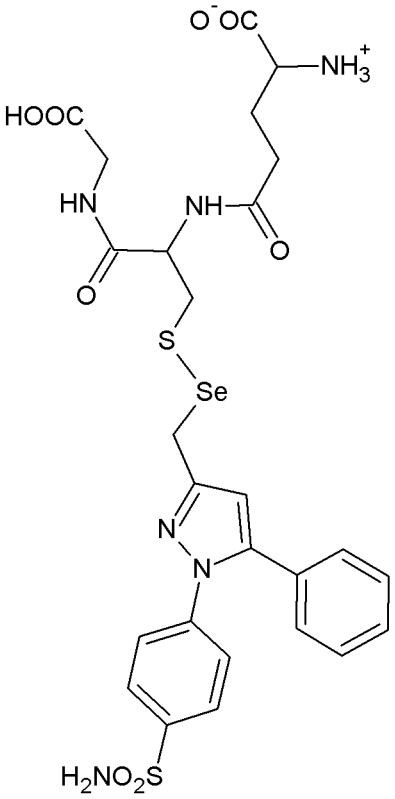
R_2 = CH_2CH_3, CH_3

30



R = Ph, *p*-CH_3O-Ph- , *p*-Cl-Ph-

31



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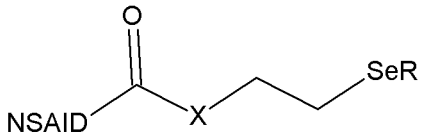
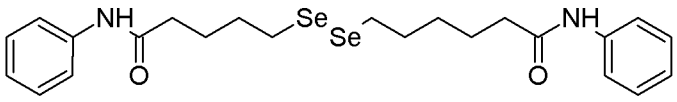
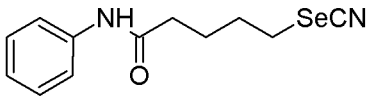


X = NH, O, Se
R = H, CH_3, CN
NSAID = Aspirin, Ibuprofen, Naproxen

33





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