

Review

Selenium-Based Drug Development for Antioxidant and Anticancer Activity

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Abstract: Selenium is one of the eight necessary trace elements humans require for active health balance. It contributes in several ways to the proper functioning of selenoprotein. Selenium has received enormous interest recently due to its therapeutic potential against a number of ailments. To date, numerous chemical compounds containing selenium have been investigated for the therapy of cancer and other disorders. Unifying the selenium atom into chemical components (typically organic) greatly increased their bioactivities. We foresee that the structure–property relationship of recently developed materials could significantly decrease the laborious work of background research to achieve target-oriented drug design in coming years. This review summarizes the research progress in the last 10 to 15 years and the application of selenium-containing compounds in the design and synthesis of those materials for potential antioxidant and anticancer agents.

Keywords: selenium; selenium-containing compounds; antioxidant; reactive oxygen species; cancer; antitumor activity; cancer cells



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1. Introduction

Selenium is a nonmetal/metalloid with characteristics halfway between those of sulfur and tellurium [1,2]. In the Earth's crust, it hardly ever exists in either its elemental state or as a pure ore complex. Jöns Jacob Berzelius made the discovery of selenium in 1817 and remarked that it resembled the already-known element tellurium [1]. Although minute amounts of selenium are required for normal cellular function, elemental selenium and selenium salts are hazardous in even small levels and can lead to selenosis [3]. The antioxidants glutathione peroxidase and thioredoxin reductase, as well as deiodinase enzymes, contain selenium, which is listed as an element in many multivitamins and other nutritional supplements [4,5]. Thioredoxin reductase and glutathione peroxidase catalyze processes that are necessary for shielding biological components from oxidative and free radical damage. The amount of selenium needed by different plant species varies from high levels to zero level [6]. The current recommended daily selenium allowance or recommended dietary allowances (RDA) for adult men and women is 55 micrograms [7].

Selenium-based heterocycles have made a valuable contribution in material science due to their electron-donating and electron-accepting abilities and their ability to modify electronic, structural, and morphological properties [8–11]. Selenium-based heterocycles have been utilized in small molecules, oligomers, and polymers to improve the electronic properties in an incremental direction [12–15]. Multiple selenium-containing compounds [12,16] have also been developed to improve the electronic behavior with higher mobility value in field-effect transistor (FET) devices [17]. They have also been

used as polymers in organic solar cells and organic electronic devices for better power conversion efficiency (PCE) and mobility value for implementation purposes [18].

Selenium-containing compounds have been of great significance in the domain of medicinal chemistry. Selenium and selenium-containing compounds continue to be topics of substantial interest in the fields of biochemistry, epidemiology, and pharmacology. Numerous diseases that are now known to be linked to selenium deficiency have historically affected specific groups [19,20]. When considering medicinal uses, it is vitally important to manage the right amount and the right molecular types of selenium-based pharmaceuticals. It is important to note that more than 40 years ago, the idea that selenium might have a preventive effect against human cancer was explored in mainstream scientific literature [21,22]. Cancer death rates were found to be much lower in US counties with moderate or high selenium levels, as opposed to counties with low selenium levels, which revealed an inverse relationship between selenium levels and cancer incidence [23]. Low selenium levels have been perceived in breast cancer patients and patients with pancreatic carcinomata. Selenium compounds have been shown to have antitumorigenic properties in several animal studies [24].

As a crucial trace element, selenium also performs a number of exclusive activities and has significant metabolic impacts on human health [25]. Numerous clinical studies have demonstrated that selenium deficit in the human body can lead to many significant life-threatening disorders, such as cancer, liver disease, organ failure, and cardiovascular disease [26,27]. Several studies have demonstrated that individuals with low or deficient selenium levels require an appropriate selenium supplement, which helps in boosting antioxidant activity and augmenting cellular defense capability [28]. As a result, the development of unique selenium compounds provides a desirable toolset for medical chemists in building effective pharmaceuticals. Selenium-containing compounds have been found to have antioxidants, anticancer agents, and antiparasitic, antibacterial, antiviral, antifungal, and neuroprotective properties [24,29,30]. We foresee that the structure–property relationship of recently developed materials could significantly decrease the laborious work of background research to achieve target-oriented drug design in coming years. This review summarizes the research progress that has taken place in last 10 to 15 years and the application of selenium-containing compounds from differential structural aspects, which will be helpful in increasing interest in the community in the design and synthesis of those materials for applications as potential antioxidant and anticancer agents.

2. Antioxidant Activity

Selenocysteine can substitute the effect of cysteine and shield healthy cells from the adverse effects of reactive oxygen species (ROS); in other ways, specific selenium compounds (Figure 1) are classified as antioxidant agents that preserve the redox environment in healthy cells [31]. In contrast, oxidation occurs at advanced levels in cancer cells and affects various aspects of their activity with ineffective antioxidant mechanisms [32]. Selenium can be administered in its elemental form or after combining it with other inorganic or organic compounds, where low doses promote cell development and high levels exhibit a cytotoxic impact [32].

The excellent antioxidant and glutathione-peroxidase-like properties of diphenyl diselenide **1** help to defend macrophages from atherogenic signaling. Pretreating J774A.1 macrophages with **1** substantially reduced the formation of ROS driven by oxidized low-density lipoprotein (oxLDL) [33]. Without affecting by inherent cytotoxicity, **1** was able to prevent breast cancer (MCF-7) cells from oxidative damage imposed by tamoxifen [34]. Cyclic diselenide, compound **2**, outperformed in terms of anti-lipid peroxidation activity ($IC_{50} = 10.7 \mu M$) [35]. In actuality, the coexistence of dithiothreitol [$Se^- Se^-$] caused by the diselenide (Se-Se) bond reduction resulted in highly active [Se^- , Se^-] that helped to convert H_2O_2 to H_2O and reintroduce the original Se-Se form [36]. Moreover, Se-Se directly converted the lipid peroxide to the respective alcohol and inhibited the chain reaction of

free radicals as an antioxidant in the process of lipid peroxidation of lecithin/cholesterol liposomes caused by 2,2'-azobis (2-aminopropane) dihydrochloride (AAPH).

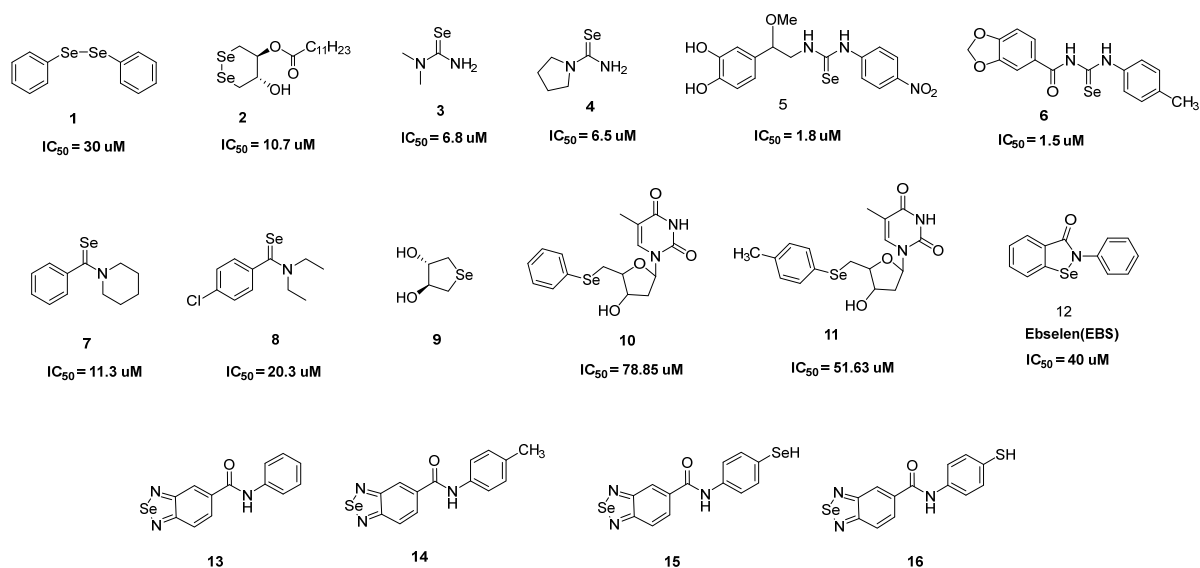


Figure 1. Selenium-containing compounds with antioxidant activity [31–43].

Dimethylselenourea **3** and its pyrrolidine analog **4** with IC_{50} values of 6.8 and 6.5 μM , respectively, showed antioxidant behavior and rapidly scavenged O_2^- produced by polymorphonuclear leukocyte (PMNs). Selenoureas appeared to readily scavenge O_2^- and generate O_2 , with little to no NADPH oxidase activity inhibition. Selenourea analog **5** also showed excellent anti-free radical properties and acted as a biomimetic catalyst for glutathione peroxidase to scavenge H_2O_2 (IC_{50} value of 3.76 μM on HeLa cells) [37]. Similarly, selenourea-based compound **6** demonstrated strong radical scavenging activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis-(3-ethylenebenzothiazoline)-6-sulfonic acid (ABTS) assays and had a preventive role on cells against oxidative stress [38]. Phenyl-ring-containing selenamides **7** and **8**, with IC_{50} values of 11.3 and 20.3 μM , respectively, efficiently scavenged O_2^- from PMNs [39].

With good water solubility, cycloselenide **9** catalyzed the dielectronic reduction of H_2O_2 to H_2O and the oxidation of mercaptan (RSH) to disulfide (RSSR) through a catalytic cycle akin to the GPX [40]. The stimulation of the apoptotic signaling pathway in healthy cells was caused by a disparity in redox and immunological homeostasis initiated by the zidovudine derivatives **10** and **11** [41]. Ebselen (EBS) was demonstrated to be a glutathione peroxidase mimic and a peroxynitrite scavenger [42]. EBS pretreatments significantly reduced the amount of thiobarbituric acid-induced substance production on mouse skin. Leukocyte infiltration and activation were specifically prevented by EBS, which reduced the H_2O_2 level. Compounds **13**, **14**, and **15** were capable of neutralizing the DPPH activity by 20% at 0.25 mg/mL, whereas compound **16** scavenged the DPPH activity by >40% at 0.25 mg/mL. The result indicated that the selenadiazoles ability to scavenge free radicals was concentration-dependent [43].

3. Anticancer Activity

Cancer is one of the most serious threats to human health. It affects millions of individuals and imposes a tremendous burden on research, social life, and the economy [44]. There is a limit to current treatments' efficacy for the prevention and treatment of cancer [45,46]. The creation of novel pharmaceuticals [47,48], radiopharmaceuticals [49–51], therapeutic targets, and modified molecules with improved drug transport and efficacy have received attention in recent years [52,53].

3.1. Inorganic Se Compound

Common inorganic selenium compounds are hydrogen selenides (H_2Se), hydrogen metal selenides (HSeM), dimetal selenides (M_2Se), hydrogen diselenides (H_2Se_2), metal diselenides (M_2Se_2), metal selenocyanates (MSeCN), and metal selenosulfates (4) (SO_3SeM_2) (Table 1). Sodium selenite (Na_2SeO_3) is one of the imperative inorganic selenium salts. Na_2SeO_3 is a component of dietary supplements, such as multivitamins/minerals. The US Food and Drug Administration (FDA) approved a general form of Na_2SeO_3 as a supplement to animal diets. Cholangiocarcinoma (a type of malignancy) has been exploited to explore the effects of sodium selenite (Na_2SeO_3), primarily in preclinical models. Na_2SeO_3 , when applied to cholangiocarcinoma cells at concentrations between 1 and 10 μM , significantly reduces invasion, migration, and the epithelial-to-mesenchymal transition by causing apoptosis and downregulating N-cadherin [54]. It has been demonstrated that at the molecular level, treatment (10 μM) with Na_2SeO_3 can restrict cell proliferation in gastric cancer. At 30 μM , it caused apoptosis and elevated Se-binding protein 1 (SBP1) expression levels, which are key mediators for anticancer effects of selenium compounds. Additionally, sodium selenite reduced the levels of β -catenin, glycogen synthase kinase 3 β (GSK3 β), and nuclear factor erythroid 2-related factor 2 (NRF2) [55].

Table 1. Category of selenium-containing compounds with anticancer activity.

Compounds	Chemical Functionality	Activity
Inorganic Se Compound	Hydrogen selenides (H_2Se), hydrogen metal selenides (HSeM), Sodium selenite (Na_2SeO_3), etc.	Inhibits cholangiocarcinoma and gastric cancer.
Peptides	Organic Se-based peptide molecules	Inhibits melanoma, nasopharyngeal carcinoma, acute myeloid leukemia, colorectal adenocarcinoma, breast adenocarcinoma, and hepatocellular carcinoma.
Ebselen (EBS)	1,2-benzoselenazol-3-one carrying an additional phenyl substituent at position 2	Anti-inflammatory, antioxidant, and cytoprotective; scavenges hydrogen peroxide and peroxynitrite in human cells by acting as a Glutathione (GSH) peroxidase mimic.
Seleninic Acid	Methylseleninic acid ($\text{CH}_3\text{SeO}_2\text{H}$)	Inhibits human pancreatic (PANC-1 cells) and breast prostate cancer cells.
Selenides	R-Se-R, selenoethers, selenium equivalents of ethers and sulfides	Antioxidant (redox-modulating, antioxidant, and chemopreventive chemicals) and anti-tumoral (antiproliferative, cytotoxic, and apoptotic).
Diselenides	R-Se-Se-R, two covalently linked selenium atoms in the same molecular construct	Cytotoxicity on neuroblastoma; activates caspase-dependent and independent pathways to cause apoptosis and hinder the growth of human breast cancer.
Selenocyanates	SeCN present	Cytotoxic against breast cancer, melanoma, and T-lymphoblastic leukemia.
Selenoureas	Se instead of an O in the urea group	Reactive oxygen species scavenger; inhibits colon cancer cells; potent antiproliferative, glutathione peroxidase-like, and antiradical properties.
Selenazoles	Se-containing compound in the series of heterocyclic 5-membered ring azoles with nitrogen heteroatoms	Antitumor activity against mouse melanoma; antitumor activity for breast (MDA-MB-231) and human prostate (PC3) cancer cells.

3.2. Peptides

The majority of inorganic Se compounds are poisonous and the minimum lethal dose is relatively low. Therefore, the ideal characteristics of these supplements include organic Se molecules with high biological activity, low toxicity, and few adverse effects. In addition, food proteolysis byproducts have been found to contain peptides with phys-

ologically active properties, including the capacity to chelate minerals. Selenocystine (SeCys, **17**), a diselenide product of selenocysteine (Figure 2) and nutritionally available selenoamino acid, displayed a significant cytotoxic effect against melanoma (A375 cells), nasopharyngeal carcinoma (CNE2 cells), acute myeloid leukemia (HL60 cells) cells and colorectal adenocarcinoma (SW620 and Colo201 cells), breast adenocarcinoma (MCF7 and MDA-MB-231 cells), and hepatocellular carcinoma (HepG2 cells) cancer cells with the IC₅₀ values of 3.6, 5.6, 34.5, 7.3, 16.2, and 17.5 μ M, respectively [56–58]. A monomethylated derivative of selenocysteine, Se-methylselenocysteine (MeSeCys, **18**), might be converted into methylselenol by selenocysteine-conjugated β -lyase [59]. The intensity of the active metabolite methylselenol is the only factor affecting the potency of MeSeCys. In the micromolar range, MeSeCys showed cytotoxic effects against many human cancer cell lines, including melanoma (A375 cells), nasopharyngeal carcinoma (CNE2 cells), acute myeloid leukemia (HL60 cells), colorectal adenocarcinoma (SW620 cells), and breast adenocarcinoma (MCF7 and MDA-MB-231 cells) cancer cells (IC₅₀ = 54, 138.7, 459.0, 632.8, 193, and 255.8 μ M, respectively) [56]. Selenomethionine (SeMet, **19**) demonstrated significant cytotoxicity against melanoma (UACC-375 cells), lung cancer (A-549 cells), breast cancer (MCF-7/S cells), colon cancer (HT-29 cells), prostate cancer (DU-145 cells), and other cancer cells (IC₅₀ = 50, 65, 45, 130, and 40 μ M, respectively) [60].

3.3. Ebselen (EBS)

Numerous organoselenium compounds have been produced and studied for various pharmacological applications since 1984, when ebselen **12** (Figure 1) was evaluated as a mimic of the important antioxidant enzyme glutathione peroxidase (GPx) [3]. Since then, the wide range of uses for ebselen's anti-inflammatory, antioxidant, and cytoprotective effects when administered orally or by subcutaneous injection has been investigated in various studies and clinical trials. Ebselen scavenges hydrogen peroxide and peroxynitrite in human cells by acting as a GSH peroxidase mimic and primarily as a peroxiredoxin mimic through thioredoxin (Trx) and thioredoxin reductase (TrxR) [61]. Ebselen inhibits TrxR in prokaryotic cells, which increases reactive oxygen species (ROS). Ebselen has been developed as a possible antibiotic in recent experiments using the distinction, particularly when combined with silver, that allows ebselen to kill multi-drug-resistant Gram-negative bacteria [61]. An analog of ebselen, called ethaselen **20** (Figure 2), can specifically inhibit TrxR activities, which reduces nuclear factor κ B (NF- κ B) activities and causes the overexpression of Bax protein and the downregulation of Bcl-2 protein [62]. It is often delivered orally or by intravenous injection. In K562/CDDP cells, the elevated Bax/Bcl-2 ratio subsequently causes a cytochrome *c* release from mitochondria to cytosol and Caspase-3 activation. Numerous cancer cell lines that have TrxR inactivation experience cell death through apoptosis commencing 24 h after treatment, particularly at ebselen concentrations between 20 and 40 μ M [62]. In a phase II clinical trial for the treatment of non-small-cell lung tumors overexpressing TrxR, ethaselen was the second organoselenium to have achieved this milestone (Ethaselen for the Treatment of Thioredoxin Reductase High Expression Advanced Non-small Cell Lung Cancers. Available online: <https://clinicaltrials.gov/ct2/show/NCT02166242> (accessed on 16 March 2022)).

3.4. Seleninic Acid

Methylseleninic acid (CH₃SeO₂H) is an organoselenium compound with one carbon atom derived from seleninic acid, wherein the hydrogen atom next to selenium was swapped by a methyl functionality. It functions as a histone deacetylase inhibitor, an anti-neoplastic agent, and a human xenobiotic metabolite. Methylseleninic acid showed inhibition potency for human pancreatic (PANC-1 cells), breast (MCF-7 cells), and prostate (PC-3 cells) cancer cells with IC₅₀ values on MCF-7 cells of 2.6, 2.0, and 8.4 μ M, respectively [63]. According to the mechanisms, CH₃SeO₂H suppressed several cancer cells by triggering numerous caspase pathways, inducing the unfolded protein response (UPR), cytochrome C release, and cleaving poly (ADP-ribose) polymerase (PARP) [64].

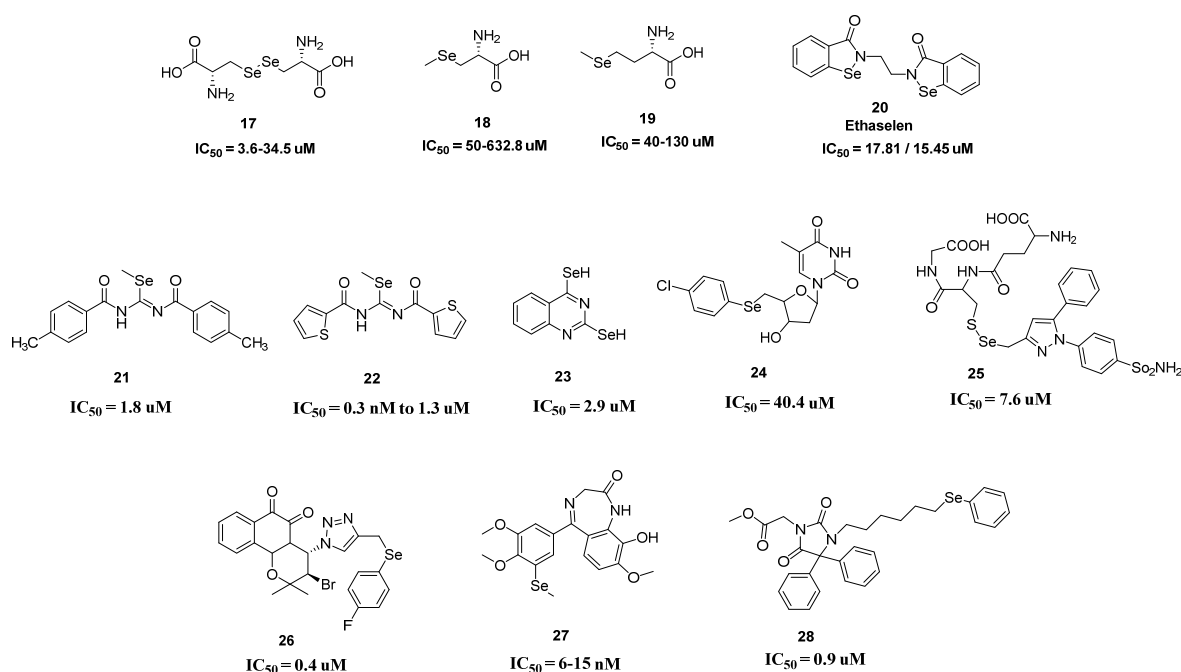


Figure 2. Structural representation of peptide-based selenium-containing compounds (17–19) [56–60], ethaselen (20) [62], and selenides (21–28) [65–72] for anticancer activity and corresponding IC_{50} values.

3.5. Selenides

In comparison with their diselenide counterparts, organic selenides (R-Se-R), commonly known as selenoethers, are the selenium equivalents of ethers and sulfides (Figure 2). Antioxidant substances (redox-modulating, antioxidant, and chemopreventive chemicals) and antitumoral substances (antiproliferative, cytotoxic, and apoptotic) are the two main categories of selenides. Methylimidoseleno carbamates **21** [65], which are multi-kinase inhibitors, blocked PI3K/Akt/mTOR and ERK1/2, simultaneously causing autophagy and death in cancer cells. They demonstrated anticancer activity against the human prostate cancer cell line PC-3 with an IC_{50} value of 1.85 mM. The similar derivative **22** [66] showed antiproliferative action against breast cancer MCF-7 ($IC_{50} = 3.4\text{ nM}$), colon cancer HT-29 ($IC_{50} = 0.3\text{ nM}$), lymphocytic leukemia K-562 ($IC_{50} = 6.1\text{ }\mu\text{M}$), hepatocarcinoma Hep-G2 ($IC_{50} = 0.6\text{ }\mu\text{M}$), and prostate cancer PC-3 ($IC_{50} = 1.3\text{ }\mu\text{M}$) cells. The Se-containing quinazoline **23** had a potent cytotoxic impact on lymphocytic leukemia (CCRF-CEM cells) and breast cancer (MCF-7 cells) with IC_{50} values of 2.99 and 2.92 μM , respectively [67]. A series of Se-containing zidovudine derivatives, **10**, **11**, and **24**, showed potential antitumor effects with IC_{50} values of 78.85, 51.63, and 40.4 μM , respectively, against human bladder cancer cell 5637 [68]. Targeting the COX-2 and PI3K/Akt signaling pathways, selecoxib-1-GSH, **25**, demonstrated increased potency against melanoma cells with an IC_{50} value of 7.66 μM , compared with celecoxib ($IC_{50} = 55.6\text{ }\mu\text{M}$), and reduced xenograft tumor formation by almost 70% with minimal toxicity [69]. The IC_{50} values for compound **26** were 0.59 μM for human promyelocytic leukemia (HL-60 cells) and 0.37 μM for human colon cancer (HCT-116 cells), respectively [70]. With IC_{50} values between 6 and 15 nM, compound **27** with a benzodiazepine scaffold showed potent cytotoxicity against five cancer cell lines: A549, MDA-MB231, HepG2, HeLa, and HCT116 [71]. Mechanistic investigations revealed that **27** interfered with intracellular microtubule organization, stopped the cell cycle at the G2/M phase, and ultimately promoted cell death. With IC_{50} values of 0.67 and 0.90 μM , respectively, compound **28** with a phenylselenide tail effectively inhibited the proliferation of both sensitive (PAR) and resistant (MDR) mouse T-lymphoma cell lines [72].

3.6. Diselenides

Organic diselenides (R–Se–Se–R) have two covalently linked selenium atoms in the same molecular construct. Numerous diselenides were produced using various synthetic techniques and demonstrated potential antitumor efficacy, Figure 3. Through ERK1/2-mediated apoptosis, diphenyl diselenide **1** demonstrated blatant cytotoxicity on neuroblastoma cell SHSY5Y ($IC_{50} = 30 \mu M$) [73]. Subsequently, it was shown that substituted diaryl diselenide, 3-(trifluoromethyl) diphenyl diselenides **29** and 4-methoxydiphenyl diselenides **30** activated caspase-dependent and independent pathways to cause apoptosis in HT-29 cells [74]. One of the earliest examples of a diselenide that showed synergistic potency when paired with well-known antitumor medications was diphenyl diselenide **31**, which had a significant effect on MCF-7 cells ($IC_{50} = 15 \mu M$) [75]. Diselenide **32**, which has a pyridazine scaffold, significantly inhibited the growth of human breast cancer cells MCF-7 ($IC_{50} = 10.3 \mu M$) [76]. Aggregation induced emission (AIE) properties were visible in the fluorescent 9,10-distyrylanthracene (DSA) derivative **33** that contains a diselenide group [77]. SeDSA-SePTX-Co-NPs (Co-NPs), which provided improved advantages in cell imaging and antitumor activity with strong selectivity between tumor and normal cells, were produced by the combination of **33** and a paclitaxel analog. With IC_{50} values of 3.9 (Caco2 cells), 8.3 (BGC-823 cells), 6.8 (MCF-7 cells), and 6.6 (PC-3 cells), μM compound **34** showed powerful anticancer properties [78]. Diselenide **35**, which has a lengthy selenide chain, demonstrated effective early melanocytic lesion prevention and showed reduced HDAC activity and controlled Akt activity [79].

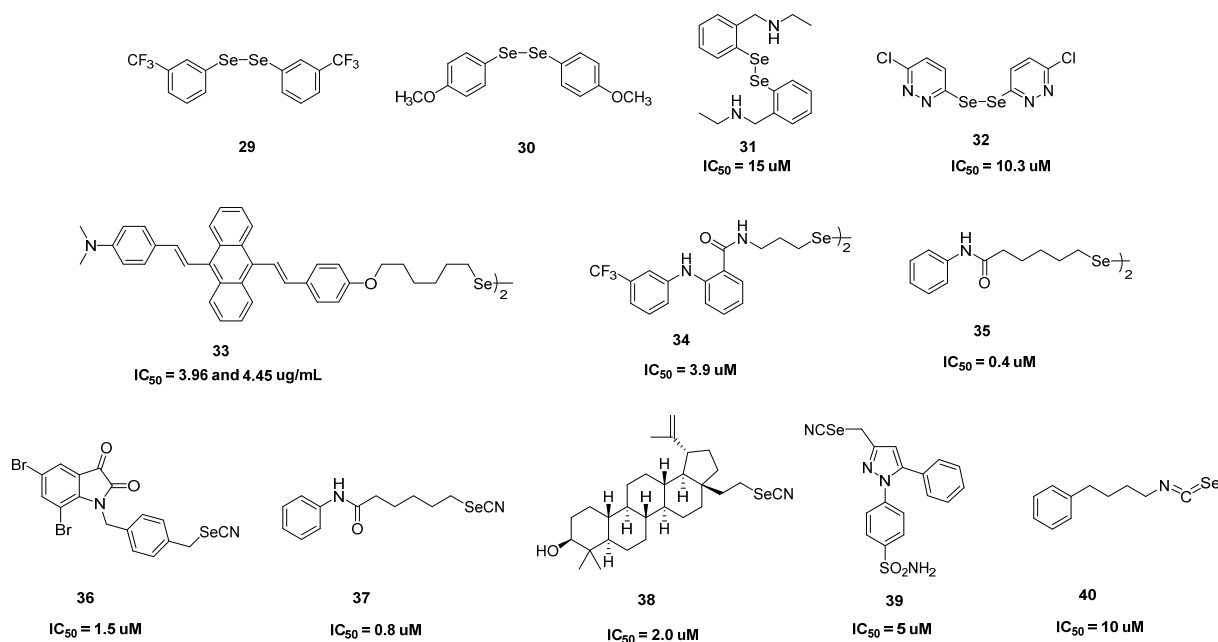


Figure 3. Structural representation of diselenides (29–35) [73–79] and selenocyanates (36–40) [79–83] for anticancer activity.

3.7. Selenocyanates

Selenocyanate (SeCN) (Figure 3) has been demonstrated to be a crucial pharmacophore for drugs that enhance anticancer activity through synergistic effects brought on by the combination of both functions (Se and CN). SeCN compounds like *p*-xylene selenocyanate and benzyl selenocyanate have been investigated for their anticancer properties for a very long time and numerous new active selenocyanate compounds with strong cytotoxic properties have been found in recent years. The tubulin polymerization and Akt phosphorylation were inhibited by compound **36**, a benzyl selenocyanate derivative that exhibited cytotoxicity against the MCF-7 breast cancer cell line with an IC_{50} value of $1.5 \mu M$ [80]. Compound **37** was an SeCN-containing derivative of vorinostat (an FDA-approved drug)

that demonstrated cytotoxicity against melanoma cell line WM115 with an IC_{50} value of $0.8 \mu M$ [79]. It was also utilized to stop the onset of early melanocytopathy. Without compromising the development of human fibroblasts, selenium-containing triterpenoids **38** demonstrated low micromolar cytotoxic action with an IC_{50} value of $2 \mu M$ against T-lymphoblastic leukemia [81]. Selenocyanate analog selncoxib-1 **39** inhibited the development of the prostate cancer cells PAIII and PC-3M with low IC_{50} values ($5 \mu M$ for each) by downregulating the levels of p-AKT, COX-2, and HIF-1a [82]. Phenylalkyl isoselenocyanates (ISCS), which were discovered to be effective antitumor drugs, are isoselenium analogs of phenylalkyl isothiocyanates (ITCs). Phenylbutyl isoselenocyanate **40** exhibited strong anti-proliferative activity against the cell lines of fibrosarcoma HT-1080 ($IC_{50} = 11 \mu M$), melanoma UACC 903 ($IC_{50} = 10 \mu M$), fibrosarcoma HT-1080 ($IC_{50} = 11 \mu M$), glioblastoma T98G ($IC_{50} = 27 \mu M$), prostate cancer PC-3 ($IC_{50} = 19 \mu M$), fibrosarcoma HT-1080 ($IC_{50} = 11 \mu M$), and colon cancer Caco-2 ($IC_{50} = 12 \mu M$) [83].

3.8. Selenoureas

Seleniourea, a functional group containing a Se instead of an O in the urea group, has been reported to have antitumor potential (Figure 4). As a mimic of glutathione peroxidase, compound **41** with an N-phenylselenourea group is an efficient reactive oxygen species scavenger [84]. On HeLa cells, it had a potent antiproliferative impact ($IC_{50} = 1.9\text{--}11.8 \mu M$). Low IC_{50} values ($0.7\text{--}6.6 \mu M$) for compound **42** with two selenourea groups were perceived in a number of cancer cell lines, including HCT116, A549, 1205Lu, DU145, and PANC-1 [85]. With IC_{50} values ranging from 0.7 to $2.5 \mu M$, **42** effectively lowered the viability of three colon cancer cell lines (HCT116, HT29, and RKO). Selenourea **43** exhibited potent antiproliferative, glutathione peroxidase-like, and antiradical properties when used against HeLa cancer cells [37].

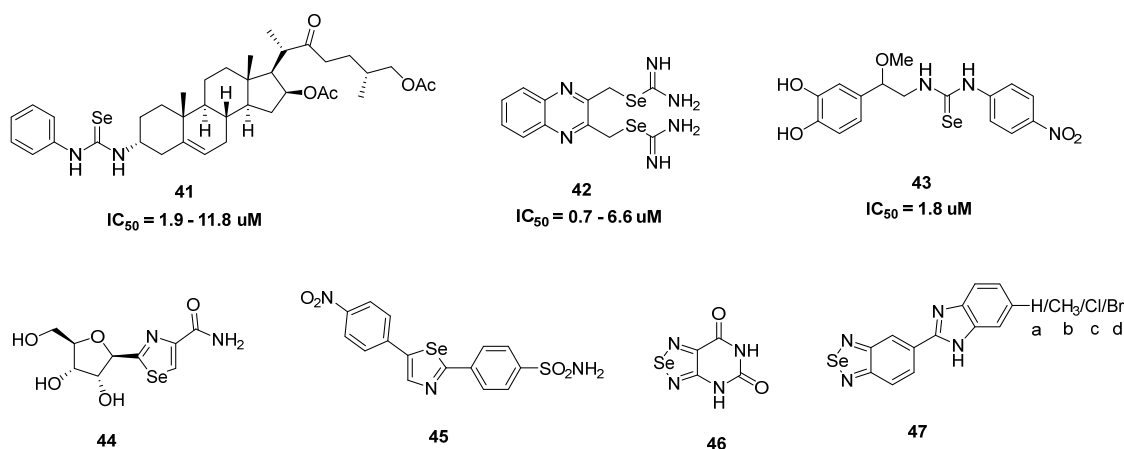


Figure 4. Structural representation of selenoureas (**41–43**) [84,85] and selenazoles (**44–47**) [86–89] for anticancer activity.

3.9. Selenazoles

Selenazoles (Figure 4) are selenium-containing compounds in the series of heterocyclic 5-membered ring azoles with nitrogen heteroatoms. Significant efforts have been made to develop selenazoles as effective cancer chemotherapeutics. In this category, compound **44** was the onset compound having substantial antitumor activity against mouse melanoma [86]. Next-generation selenazole **45** displayed effective antitumor activity for breast (MDA-MB-231) and human prostate (PC3) cancer cell lines [87]. Among the other selenazoles, compound **46** also showed potent antitumor activity against melanoma (A375 cells IC_{50} $14.3 \mu M$), breast cancer (MCF-7 cells IC_{50} $46.0 \mu M$), and liver cancer (HepG2 cells IC_{50} $19.6 \mu M$) [88]. On the other hand, compound **47** showed a practical antiproliferative effect with benzimidazole functionality [89]. Compounds **47a**, **47b**, **47c**, and **47d** displayed antiproliferative effects for MCF-7 and MDA-MB-231 cells with lower

ranges (1–26 μM) IC_{50} values. Selenium-based small molecules have been explored not only as potential antioxidant and anticancer agents but also as antimicrobial, antialzheimer, antidepressant, antidiabetic, antifibrotic, antiparasitic, antiviral, antifungal, and neuro-protective agents. Recent interest focused on selenium-based nanomedicines in confronting various diseases, especially as antitumor and antidiabetic agents. However, most of the work involving selenium compounds is still in the preclinical stage. We can expect that new selenium-based pharmaceutical compounds with therapeutic promise against human diseases will continue to be developed in coming years, because our knowledge of the biology, biochemistry, and pharmacology of selenium is quickly expanding.

4. Conclusions

Selenium-containing compounds with a variety of functional groups have been found to have antioxidant and anticancer activities. In the search for effectiveness in the prevention and treatment of cancer and other related disorders, selenocyanates, selenoureas, selenoesters, selenium-containing heterocycles, selenium nanoparticles, selenides, and diselenides have been taken into consideration. In addition to the antioxidant and anticancer activities of selenium-containing compounds, they have also been explored as antifibrotic, antiparasitic, antibacterial, antiviral, antifungal, neuroprotective, and even anti-Alzheimer agents. Although selenium in its elemental form is usually seen as a harmful element with few or no benefits, significant progress has been made when it is incorporated into bioactive compounds. However, due to the high toxicity of selenium, limited clinical exploration of selenium-based drug components has been observed. Efforts must be focused on finding the proper balance of the dose a person could receive as a drug molecule that should not exceed the safe amount of elemental selenium. The conjugation of selenium in organic or inorganic compounds under a structural modification approach or in combination with other reactive safe chemical functionalities or hybrid platforms could lead to a solution towards more clinically approved selenium-based drug molecules. As our fundamental knowledge of selenium biology, biochemistry, and pharmacology grows, it will be possible to predict future innovative approaches for the logical development of new therapeutics that are selenium-based or that target particular parts of selenium metabolism.

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