The innovative potential of Selenium-containing agents to fight cancer and viral infections

Wesam Ali[1,2¶], Rosaria Benedetti[3], Jadwiga Handzlik[2], Clemens Zwergel[,2,3,4 ¶*], Cecilia Battistelli[5, ¶*]

[1] Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University, Medical College, Medyczna 9, PL 30-688 Kraków, Poland

[2] Division of Bioorganic Chemistry, School of Pharmacy, Saarland University, Campus B 2.1, D-66123 Saarbruecken, Germany

[3] Department of Precision Medicine, "Luigi Vanvitelli" University of Campania, Via L. De Crecchio 7, 80138 Naples, Italy

[4] Department of Drug Chemistry and Technologies, Sapienza University of Rome, "Department of Excellence 2018-2022", Piazzale Aldo Moro 5, 00185 Rome, Italy

[5] Istituto Pasteur Italia, Fondazione Cenci-Bolognetti, Department of Molecular Medicine, "Department of Excellence 2018-2022", Sapienza University of Rome, Viale Regina Elena 324, 00161, Rome, Italy

¶These authors share the senior authorship

***Correspondence:** Clemens Zwergel, clemens.zwergel@uniroma1.it; Cecilia Battistelli, cecilia.battistelli@uniroma1.it

Teaser (20-25 words)

A critical discussion of recent findings in the field of Selenium-based applications in disease treatments of cancer and viral infections.

Abstract (ca 100 words)

Selenium-containing compounds represented in the last years to be an emerging promise for the treatment of viral infections, tumor development and dissemination as well as for their role in drug delivery. Still, selenium is often considered as a toxic element with no or rather little beneficial effects. However, considerable advances in the understanding of the complex biology and chemistry related to this element and its incorporation in bioactive molecules have been made. In the present review, the recent findings in the field of Selenium-based applications in disease treatments of cancer and viral infections are summarized and critically discussed.

Introduction (about 3500 words)

Selenium (Se) and selenium-containing compounds possess a long history. Se, discovered by Jöns Jacob Berzelius in the early 19th century, is a chalcogen belonging to group 16 together with oxygen, sulfur, tellurium, and polonium [1]. Often, even sometimes until today, this element and Se-containing compounds have been considered to be highly toxic, causing various diseases such as

madness or cancer [2]. Back in the 1970s, D. Forst defined the term "Selenophobia" in his critical paper, where he analyzed the at that time confusing effects of Se in cancer biology [3].

Diametral effects of Se on organisms is not only limited to cancer as Se has been demonstrated to possess both protective and toxic effects on the nervous system as well as on the heart [2].

Many research efforts have been made since then, and nowadays it is well accepted that we need to dissect the role of Se as an essential trace element in various biological processes in oxidation-reduction reactions with potential toxic effects [2,4] but also the advantages of Se in rather safe small organic compounds useful in the treatment of various diseases [4].

From a chemistry point of view, Se has a peculiar nature with several oxidation states and can more easily be oxidized and reduced by redox agents than a sulfur (S) atom. As a result, Se can act as a nucleophilic or electrophilic reagent by doning or accepting electrons. The divalent behavior makes Se suitable for applications in chemistry and biology. is The glutathione peroxidase (GPx) [5,6] is the most studied Se-dependent enyzme with antioxidative properties, still the most explored among around 40 Se-dependent enyzme with a range of biological activities.

Selenium and specifically seleno-compounds are now considered as promised candidate drugs in the field of biology and medicinal chemistry. Different organic seleno-compounds, with various functional groups, have been described since 1980s, to display chemopreventive and antioxidant activities with numerous beneficial outcomes [7]. Thus, considerable advances in the understanding of the complex biology and chemistry related to this element and its incorporation in bioactive molecules have been developed [2].

With the present review, we would like to provide a concise overview on selenium-containing compounds, which represented in the last years an emerging field of investigation for the treatment of viral infections, tumor development and dissemination as well as for their role in drug delivery and multi drug resistance (MDR).

Selenium: the most investigated compounds in cancer therapy

Cancer is one of the most serious health assets worldwide impacting not only the wellbeing and survival of patients but also the economic as well as scientific commitment. Prevention and treatment of cancer patients is a key point in current practice and represents a limit to the effectiveness of treatments. For these reasons, despite the scientific progress, research in the last years has focused on some new approaches with ever lesser off-target effects, new compounds have been developed and tested for their effects on different cancer models, and new therapeutic targets, innovative and epigenetic drugs [8], modified molecules able to increase drug delivery and efficacy [9] and, more recently, molecular strategies impairing non-coding RNAs activity have been identified [10].
In this scenario, Selenium-containing molecules have been designed and tested for their effectiveness, especially against cancer [11] but also counteracting cardiovascular diseases, different kinds of viral and bacterial infections, and neurodegenerative diseases [2]. Tumor cells are generally more sensitive to selenium compounds compared to normal ones, and they become more susceptible to apoptosis and to the block of angiogenesis [2], two important prerequisites for tumor progression and invasion. Generally, Se-compounds are considered as antioxidant agents, maintain the redox status in healthy cells, since selenocysteine may be replaced by cysteine, and protect normal cells by the toxic effects

of reactive oxygen species (ROS) [12]. Conversely, in cancer cells, oxidation occurs at higher levels with respect to reduction and influences different aspects of cancer cells' behavior (*e.g.* cell invasion ability). Thus, their antioxidant machinery is no longer efficient [13]. Depending on the concentration of Se administrated, it can work in two opposite directions - while low doses stimulate cell growth, high doses display a cytotoxic effect [13]. Based on these abilities of Se-compounds to induce cell death, they have been tested in cancer cells to specifically induce cytotoxicity, apoptosis, or antiproliferative effects (as for the treatment with CH_3SeH) and represent a new strategy for cancer treatment [2,7].

Cholangiocarcinoma, a severe pathology which is generally treated with surgery, is one of the cancer types used to study the effects of selenium-based treatments. It has been reported that sodium selenite (Na_2SeO_3) and selenomethionine (SeMet, **1**, Figure 1) have a great efficacy by inducing apoptosis and suppressing invasion/migration and EMT (through the downregulation of N-cadherin) at 1-10 μM and 50-100 μM respectively in KKU-M213 and for KKU-M214 cholangiocarcinoma cells [14].

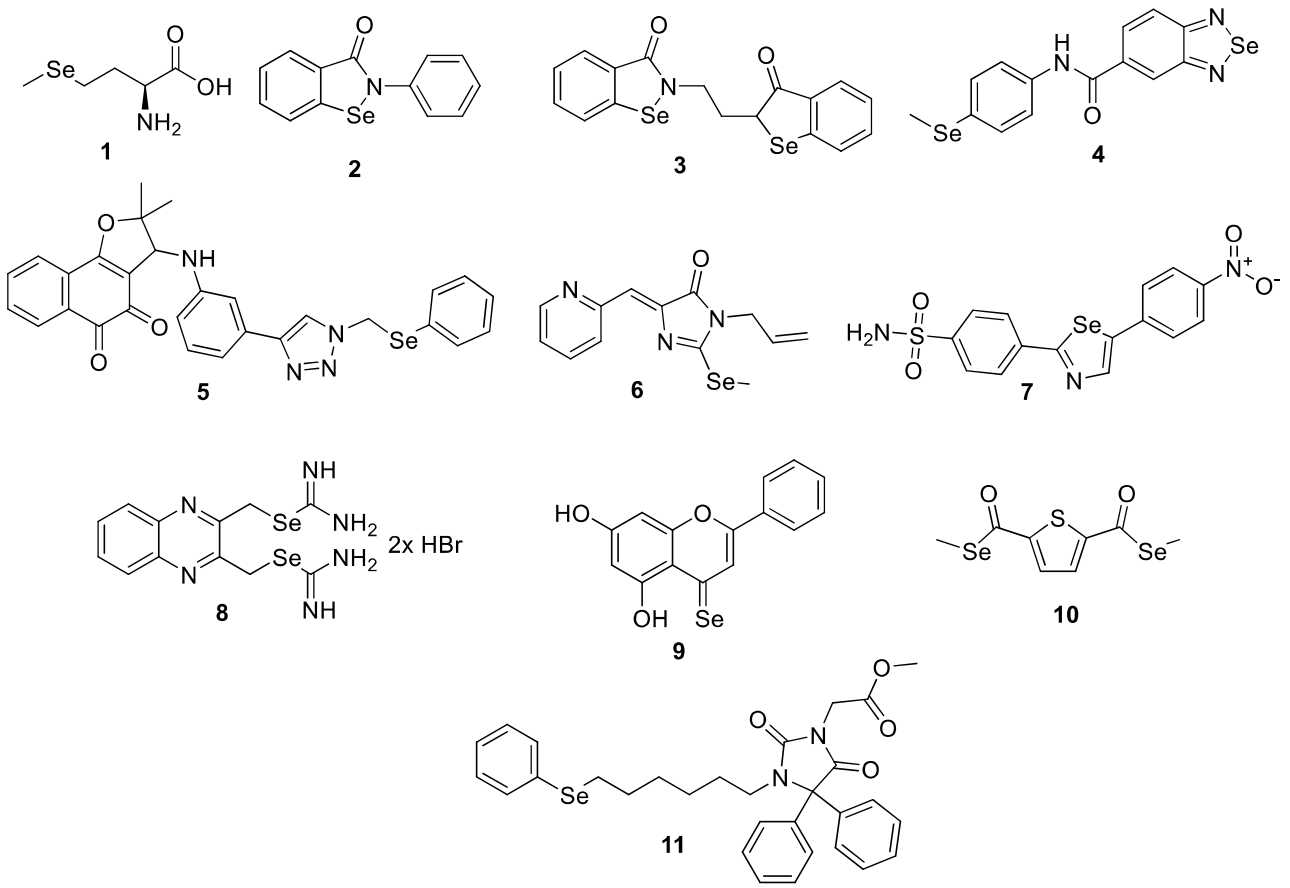

Figure 1. Organoselenium compounds for anticancer therapy

At the molecular level, it has also been elucidated that in poor prognosis gastric cancer, the treatment with sodium selenite caused cell proliferation block, already at 10μM after 48h, induced apoptosis at 30 μM and increased expression levels of Selenium-binding protein 1 (SBP1), an important mediator of selenium's anticancer functions, downregulated in gastric cancer. Furthermore, sodium selenite decreased the Nrf2 and Wnt pathway components and its downstream targets, including β-catenin, GSK-3β, c-myc, and cyclinD1 [15].

Ebselen **2**, after its first preparation in 1924, was first considered to possess no pharmacological activity, and only 60 years later, its GPx-mimic activity has been described. Since then, numerous papers and clinical trials examined the broad spectrum of applications making use of its anti-inflammatory, antioxidant, and cytoprotective properties [1,3,4]. For instance, **2** has been investigated for the treatment of bipolar disorders and hearing loss, well summarized in a recent review showing the great interest in this molecule [16].

A close analog Ethaselen **3** inhibits mammalian Thioredoxin reductase (TrxR), by selectively targeting the C-terminal active sites SeCys498/Cys497. TrxR inactivation results in cell death *via* apoptosis induction in numerous cancer cell lines [17]. Compound **3** is the second organoselenium that reached clinical trials phase II for the treatment of non-small cell lung cancers overexpressing TrxR [17,18].

Roughly 10 years ago, Se-enriched polysaccharides were proposed to possess a significant effect against tumor cell proliferation (*e.g.* in osteosarcoma and breast cancer [19,20]). Recently, it has been shown that Selenium-enriched polysaccharides from *Pyracantha fortuneana* (Se-PFPs) caused cell growth inhibition (at a concentration between 100 and 1000 μg/ml) through the impairment of β-catenin signaling in ovarian cancer and reduction of cyclin D1, Bcl-2, and MMP-9 expression, while enhancing the cleavage of PARP and caspase-3, the activity of caspase-3 and caspase-9 (at 200 and 400 μg/ ml for 24 hr). Furthermore, Se-PFPs increased the expression of E-cadherin and cytokeratin 19, reducing the expression of N-cadherin, vimentin, ZEB1, and ZEB2 (200 and 400 μg/ ml for 48 hrs) [21]. All the studies using **1**, sodium selenite or Se-PFPs provide the proof of concept to study involvement of Se in cancer biology; this might help medicinal chemists to develop innovative Se-containing compounds as **1**, sodium selenite or Se-PFPs can not be considered potential hit compounds. Since the effects of Se-compounds depend on the different drugs that exert a variety of biological effects in a dose and time dependent manneron distinct cancer contexts, here we focus on the recent findings in this research field, highlighting the mode of action of Se-derivatives and the molecular and cellular influenced patterns. A series of benzo[c][1,2,5]selenadiazole-5-carboxylic acids (BSCAs) has been developed exerting cancer selective antiproliferative effects in solid and hematological malignancies. Compound **4** exhibited the most promising antiproliferative activity with a GI_{50} 3.7 μM in MCF-7 [22]; thus, this compound could serve as a new lead for developing effective chemotherapeutics, particularly for breast cancer.

Following advancements in chemical synthesis, an innovative click chemistry approach led to the discovery of double redox center lapachones containing selenium and a triazole moiety of the structure **5**. In more detail, da Cruz *et al.* described the design, synthesis and antitumor activity for these novel compounds. The compounds presented high activity against several cancer cell lines such as leukemia, colon carcinoma, prostate cancer, or glioblastoma cells, exhibiting IC_{50} values < 0.3 μM often being more potent than doxorubicin [23]. Furthermore the authors gave a first insight into the mechanism of action of **5** very likely acting on GPx and/or the quinone oxidoreductase 1 (NQO1) [23]. In 2016, the synthesis of a small series of 2-selenohydantoin derivatives was reported being. Among them, **6** was the best one, exhibiting an IC_{50} value of 3.66 μM in SiHa cervix cancer cells [24]. Compound **6** displayed better antioxidant properties than the sulfur-containing analogs and comparable or even better ones regarding ebselen **2**.

An upregulated glucose metabolism and hypoxia characterize many tumor types. Specifically, the metalloenzyme human(h) carbonic anhydrase (CA, EC 4.2.1.1) hCA IX is overexpressed in different hypoxic tumors since it is induced by the transcription factor hypoxia-inducible factor-1a (HIF-1a) and contributes to stimulate cell survival and proliferation as well as to increase metastasis formation

[25]. The metalloenzyme hCA IX is therefore a valuable target for cancer therapy, though at the moment a single inhibitor, tureido-substituted benzenesulfonamide derivative (SLC-0111), was characterized [26]. Angeli et al. developed a series of 2,5-disubstituted 1,3-selenazoles able to significantly inhibit hCA I and hCA II and, above all, hCA IX in a low nanomolar range. One of their best compounds (**7**) with a K_i of 8.2 nM against hCA IX impaired cell viability in human breast and prostate cancer cell lines up to 60% at 1μM [26].

A series of novel selenourea derivatives and corresponding thiourea analogs were synthesized and tested on different cancer cell lines spanning from melanoma to lung, from colon to prostate and pancreas. Se-containing analogs exhibited more potent IC_{50} values spanning from 0.7-6.6 μM (especially compound **8**), comparing to their sulfur isosters. Mechanistically speaking, compound **8** induced apoptosis is mediated by caspases activation, and inhibition of anti-apoptotic proteins Bcl-2 and XIAP [27].

Moreover, the possibility to combine Se-compound with classical chemotherapeutic drugs underlined the feasibility of a co-treatment allowing the specific targeting of tumor drug-resistant cells [9,28]. With regards to the complexity of cancer landscape, some studies have used multiple conventional chemotherapeutic agents and Se-containing compounds such as diphenylmethyl selenocyanate, selenocysteine, methylseleninic acid, cyclic selenoanhydrides on a wide class of both solid and hematological tumors [9,29-31]. In 2015, the selenium-containing flavonoid chrysin (SeChry, **9**) was synthesized by a microwave-based methodology possessing potential GPx or Trx like activities. When **9** was tested in a panel of cancer cell lines, it showed its best effect in MCF7 ovarian cancer cells. The crucial role of selenocabonyl moiety is quite evident as the relative oxo and thioanalogs, were less potent; **9** was also more potent than cisplatin (mean IC_{50} values 18- and 3-fold respectively). Interestingly, **9** was able to overcome also cisplatin and multidrug resistance [32]. Recently Spengler *et al.* combined topotecan, doxorubicin, vincristine, cisplatin, cyclophosphamide, methotrexate, and 5-fluorouracil and the efflux pump inhibitor verapamil, with various selenoesters in a mouse T-lymphoma cell line, aiming to avoid multidrug resistance (MDR) through synergistic effects, thus extent patients survival [31]. The authors tested numerous organoselnoesters and the thiophene-containing compound **10** exhibited synergistic interactions with all tested drugs except cisplatin, whereas other selenoesters were less efficient. Very recently, our research team described the discovery of potent selenium-containing ABCB1 MDR efflux pump modulator **11** with promising anticancer activity giving a first insight into its cellular mechanisms of anticancer action as well as an ADMET-screening *in vitro*. Compound **11** exhibited cytotoxic and antiproliferative effects, in particular, in resistant cancer cells possessing a better ABCB1-efflux pump modulating activity than verapamil. In human JURKAT T-lymphocytic cancer cells **11** was inducing apoptosis *via* decreasing of cyclin D1 and increasing p53 expression, alone or in combination with the chemotherapeutic agent doxorubicin. The hydantoin derivative **11** opens a new chemical space of highly active Se-containing anticancer agents, warranting a more in-depth biological evaluation and a further medicinal chemistry optimization [9].

Recently, an innovative Selenium-coated nanoparticles-based approach has been developed to enhance the anticancer effects of commonly used chemotherapeutics. Selenium-functionalized liposomes (SeLPs) with a size of 107 nm have been produced to increase the loading, delivery, and cellular uptake of anticancer drugs (*e.g.*, doxorubicin). These spherical particles can enter the cell through a mechanism of clathrin-mediated endocytosis and macropinocytosis and show a significantly higher ability (Dox-SeLPs showed an IC_{50} of 0.92μg/mL on A549 cells, free Dox (4.40μg/mL) to be internalized, representing a real strategy for efficient drug delivery, as "in cells"

as “in vivo” [33]. In this regard, it has been proposed by Kumari *et al.* [34] that curcumin-loaded SeNPs (Cur-SeNPs) enhanced therapeutic effects on colorectal carcinoma cells (HCT116) increasing autophagy and apoptosis and reducing NFκB signaling and epithelial to mesenchymal transition, one of the main signature of invasive cancer cells. Similarly, the delivery of paclitaxel (PTX) through SeNPs showed a significant antiproliferative effect (G2/M phase arrest) and the induction of apoptosis in cancer cells and the SeNPs-mediated co-delivery of epirubicin and the apoptosis inducer NAS-24 aptamer to cancer cells enhanced tumor response *in vitro* and *in vivo* at lower micromolar doses than PTX or epirubicin alone [35,36]. This approach can also be considered as a promising paradigm against MDR in cells showing mutations in the drug efflux pumps. Among the causes of resistance, the overexpression of ATP binding cassette, including P-glycoproteins (P-gp) and MDR proteins have been characterized.

Selenium containing antiviral agents

Organoselenium compounds were described to possess also antiviral activities roughly 40 years ago (Figure 2). The first compound was selenazofurin (**12**) as ribavirin analog [37] with a broad spectrum for DNA and RNA viruses being either virucidal or virustatic, depending on the virus type. Besides its capability to inhibit *Herpesviridae*, **12** inhibited the replication of influenza A virus (IVA) *in vitro* better than ribaverin, but the results could not be confirmed *in vivo* [38], however, there seems to be a promising activity against the West Nile virus [39].

Compound **12** was only the starting point for the development of numerous other selenium-containing compounds as antivirals. In the following paragraph, we would like to highlight, after a brief historical overview, the most recent advances divided by pathogen.

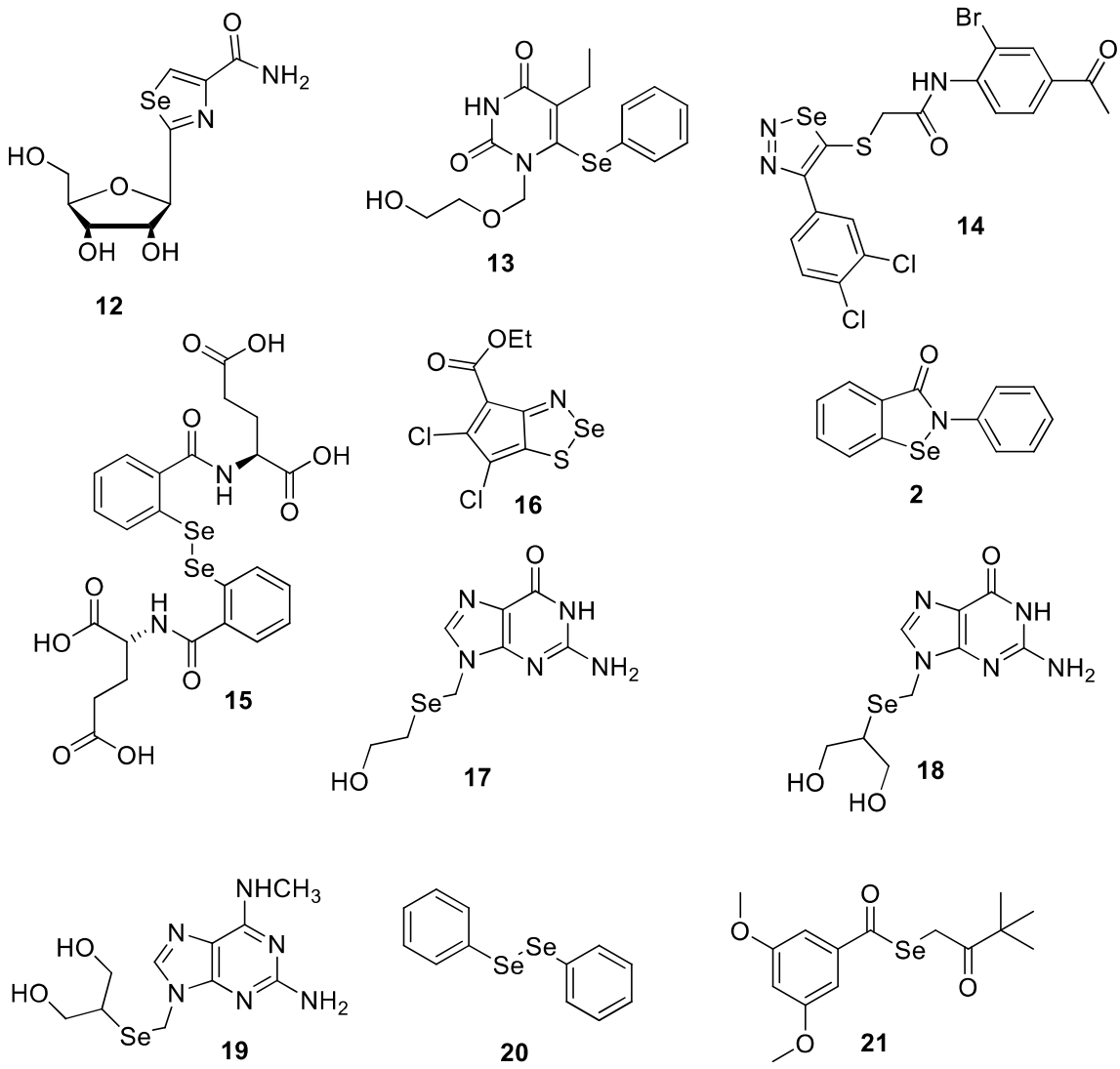

Figure 2. Organoselenium compounds as antiviral agents

Anti-HIV agents

Even if, in recent times, other viruses are in the focus of researchers and the general public, the human immunodeficiency virus (HIV) remains an important health asset worldwide. Although drug discovery in the last decades made huge progress towards effective HIV-treatments with the most FDA-approved antivirals, there is still an urgent need for novel, inexpensive drugs, aiming not only to be virustatic but virucidal [40].

The first evidence of Se-containing compounds capable to positively influence HIV was described in 1991 [41]. The acyclovir analog **13** (Figure 2) was endowed with a good potency against HIV-1 and HIV-2, probably due to a glutathione peroxidase related mechanism, but without inhibiting the reverse transcriptase despite being structurally similar to nucleoside reverse transcriptase inhibitors (NRTIs).

In 2009 the first Se-based non-NRTI appeared in the literature, such as selenodiazole **14** able to inhibit only HIV-1 replication [42].

More recently, innovative organoselenium HIV-antivirals were described to target the nucleocapsid protein 7 (NCp7), playing a crucial role in the replicative cycle of HIV. Interestingly NCp7 is highly

conserved in HIV-strains, and upon inhibition, resistant strains are not favored [43-45].
The diselenobisbenzamides (DISeBAs) **15** are targeting the two zinc finger motifs in a covalent way ejecting the Zn-ions [43], as they possess a high structural similarity to other known NCp7 inhibitors [44,45].
Sancineto *et al.* prepared a series of compounds and the compound with the most promising biological activity turned out to be **15**. Compound **15** is a potent and selective anti-HIV1/2 agent even in resistant HIV-1 strains (EC_{50} 3.31 and 3.18 μM, respectively) with a good toxicity profile. Proteomic analysis revealed that DISeBA-treated latently infected cells accumulate unprocessed Gag polyprotein, a precursor of NCp7, thus suggesting already an early recognition of NCp7 by **15** [43].
Recently synthetically challenging 1,2,3- thiaselenazoles such as **16** were proposed as potential HIV agents. The small series was, however, tested in a feline immunodeficiency virus (FIV) model, which possesses certain similarities to HIV. FIV possesses like HIV a similar to NCp7 nucleocapsid protein, and it is speculated supported by docking studies that **16** acts as Zn-ejector as well. Unfortunately, it remains unclear why the authors did not test at least their best nanomolar compound **16** (EC_{50} 82 nM) with a good toxicity profile in an HIV model directly. Interestingly regarding the SAR analysis, the Se-containing compounds were not always superior in respect to their sulfur analogs [46].
Last but not least, in 2016, one of the most famous organoselenium compounds, Ebselen **2**, was identified in a high-throughput screening based to possess also important HIV antiviral properties. **2** was exerting it's antiviral activity through blocking the C-terminal domain capsid assembly with an EC_{50} of 1.99 μM. The mechanism was confirmed in an NMR and mass-based approach [47].
A more recent study gave an insight into another potential target of **2** regarding HIV. Ebselen disrupted the interaction with Lens epithelium-derived growth factor (LEDGF/p75), an essential cellular cofactor, hijacked by HIV to integrate into the host cell [48]. Indeed, more research needs to be devoted to elucidate the precise mechanisms regarding the HIV inhibition capabilities of this compound.

Agents against *Herpesviridae*

Besides the well-known *Herpes simplex* viruses 1 and 2 (HSV-1/-2) also varicella-zoster virus (VZV), Epstein–Barr virus (EBV), human cytomegalovirus (HCMV), and Kaposi's sarcoma-associated herpesvirus (KSHV) belong to the family of *Herpesviridae*. An infection with one of these DNA-viruses is often latent, and recurring and effective treatments are often lacking [49].
Acyclovir and ganciclovir are known antimetabolites, exhibiting their activity through the inhibition of the viral DNA polymerase. For both compounds, the relative Se analogs have been described and tested against various *Herpesviridae*. Sahu *et al.* revealed that selenoacyclovir **17** exposed promising potent anti-HSV-1/-2 properties (EC_{50} 1.47 and 6.34 μM, respectively) and selenoganciclovir **18** revealed moderate anti-HCMV activity (EC_{50} 53.1 μM) without being toxic up to 100 μM [50]. Subsequently, the same authors extended their SAR analysis by modifying the purine core. **The** selenoganciclovir analog **19** was the most potent compound against HCMV (EC_{50} 32.1 μM) better than the parent **18**. Notably, no improvement could be obtained for the selenoacyclovir analogs. However, despite being interesting compounds, the antivirals **17, 18** and **19** are less potent than their parent oxygen-containing compounds, probably due to steric effects of the bulky Se atom hindering the phosphorylation step, necessary for their incorporation in the viral DNA [51,52]. Thus, the Se-approach for this class of compounds might not be very promising.
Another well-known organo-selenium compound for its immunomodulatory, antioxidant, and anti-

inflammatory properties (**20**), has been found to possess anti-HSV-2 activities. Diphenyl-diselenide **20** was shown to possess good antiviral and virucidal properties *in vitro* and *in vivo* by lowering reactive species such as superoxide dismutase (SOD), catalase (CAT), GPx, and glutathione reductase (GR). Compound **20** turned out to be effective in a Vero cell culture model as well as reduced lesions and histological damage in vagina tissue of a BALB/c mouse model at 5 mg/kg [53,54]. Very recently, Spengler *et al.* described interesting selenoester compounds with a potent antiviral activity against HSV-2. Their best in the series, compound **21,** exhibited an IC_{50}=1.25 μM; however, this compound was slightly cytotoxic in Vero cells. The authors speculated about a ROS dependent mechanism, but no proof has been given yet [55]. Unfortunately, a detailed SAR analysis is rather difficult, as the presented series is quite small.

Other antiviral activities of organoselenium compounds

As already outlined for cancer, Se-nanoparticles gained much interest in the last two years. The research team around Li and Lin described in two research papers innovative approaches to fight IVA.

In the first one, they were able to show that the surface decoration of Se nanoparticles by amantadine, a well-known antiviral drug, resulted in a reversed amantadine resistance in IAV infection model. These nanoparticles seem to act *via* a ROS- mediated AKT dependent signaling pathway [56]. In the second study, they successfully prepared, validated, and evaluated *in vitro* and *in vivo* Se nanoparticles loaded with ribavirin. Their innovative approach led to restrained apoptosis, influencing the caspase-3 signaling pathway with a better outcome than ribavirin alone [57]. These pivotal studies might pave the way for exciting new antiviral treatment options.

Even significant progress in the treatment of HCV infections has been made in the past years leading to the recent FDA approval of inhibitors targeting the vital viral non- structural protein 3 or 5B (NS3/NS5B), still safe and effective treatments are urgently needed as HCV infections lead to liver cirrhosis and at late stage often to liver carcinoma [58].

Ebselen **2** was already reported in 2010 with a good HCV activity [59], but the molecular target of this compound was only identified in 2014 being the protease/helicase NS3. Mechanistically **2** interacts with key cysteine residues blocking 50% of the helicase activity at 1 μM but not the protease one [60].

Since a few months, COVID-19 is a daily reality for all of us. Right now, we do not have an effective vaccine or other treatments such as small molecules against COVID-19 or other similar pathogenic coronaviruses. Researchers around the globe are urgently seeking for novel, innovative antiviral agents [61].

In a very recent study, Jin *et al.* presented a very innovative drug design approach converging a structure-based *ab initio* technique followed by virtual screening and high-throughput assay discovering a potent organoselenium compound against the COVID-19 virus [62].

In more detail, they aimed to identify new lead structures targeting the COVID-19 virus main protease (M^{pro}), a key enzyme in the viral replication and transcription. First, they solved the crystal structure of the small peptidic compound N3, a known M^{pro} inhibitor, and subsequently, they developed *in silico* and *in vitro* screening methods. Out of more than 10.000 compounds, they discovered seven hits, and the best one turned out to be ebselen **2,** inhibiting the M^{pro} activity with an IC_{50} of 0.67 μM. A mass spectrometry-based assay revealed that ebselen is partially covalently binding to C145 of the catalytic dyad of Mpro, but given the most potent activity against M^{pro} of all tested compounds, the authors also assume a noncovalent binding mode of **2**. Next, ebselen **2** was evaluated together with the initial lead N3 in a cellular model of Vero cells infected with COVID-19 exhibiting EC_{50} values

320 of 4.67 μM and 16.77 μM, respectively [62]. To sum up, this compound displayed promising anti-
321 COVID19 properties; however, it might be a promiscuous binder, as we have seen at various points
322 in this review, thus it may have limited potential for a precise therapeutic application, but certainly,
323 it can be seen as an excellent lead structure for various drug targets.
324
325 **Concluding remarks**

326 Herein we shed light on the most auspicious Se-containing compounds which represented in the last
327 years to be an emerging promise for the treatment of viral infections, tumor development and
328 dissemination, as well as for their role in drug delivery (Figure 3) [2]. Slowly Se is less considered to
329 be toxic, possessing no or rather little beneficial effects.

330 Organoselenium compounds such as **5, 7** or **8** often exhibit excellent cytotoxic properties with little
331 systemic effects compared to conventional chemotherapeutic agents [23,26,27,63]. More recently,
332 also Selenium-based nanomedicines, pointing at the design of selenium nanoparticles, have been
333 proposed as an efficient strategy to ameliorate drug delivery, thus cancer treatment [64]. In the second
334 part, we summarized novel Se-containing antiviral agents for HIV, HCV, or influenza. COVID-19
335 brought the usual public life to an abrupt halt, and viral infections all of a sudden came back to interest
336 even for a general audience. Researchers are now urgently seeking for novel therapeutic approaches.
337 Se-based nanoparticles are not only studied in the field of cancer but also as innovative antiviral
338 therapies [57]. This month a major breakthrough paper has been published, putting at the center a Se-
339 containing small molecule ebselen **2** [62], which possesses also numerous other effects not only as
340 antiviral but also as an anticancer agent. Although this compound has been demonstrated to be safe
341 to use and to bind selectively to numerous enzymes, **2** can not be considered as a good drug candidate
342 as it is rather promiscuous. In an interdisciplinary approach, medicinal chemists can bring in their
343 expertise, as this figure is capable to design from the rather small molecule **2**, a more specific drug
344 leads with clinical potential in response to new emerging infectious diseases lacking specific
345 treatment options.

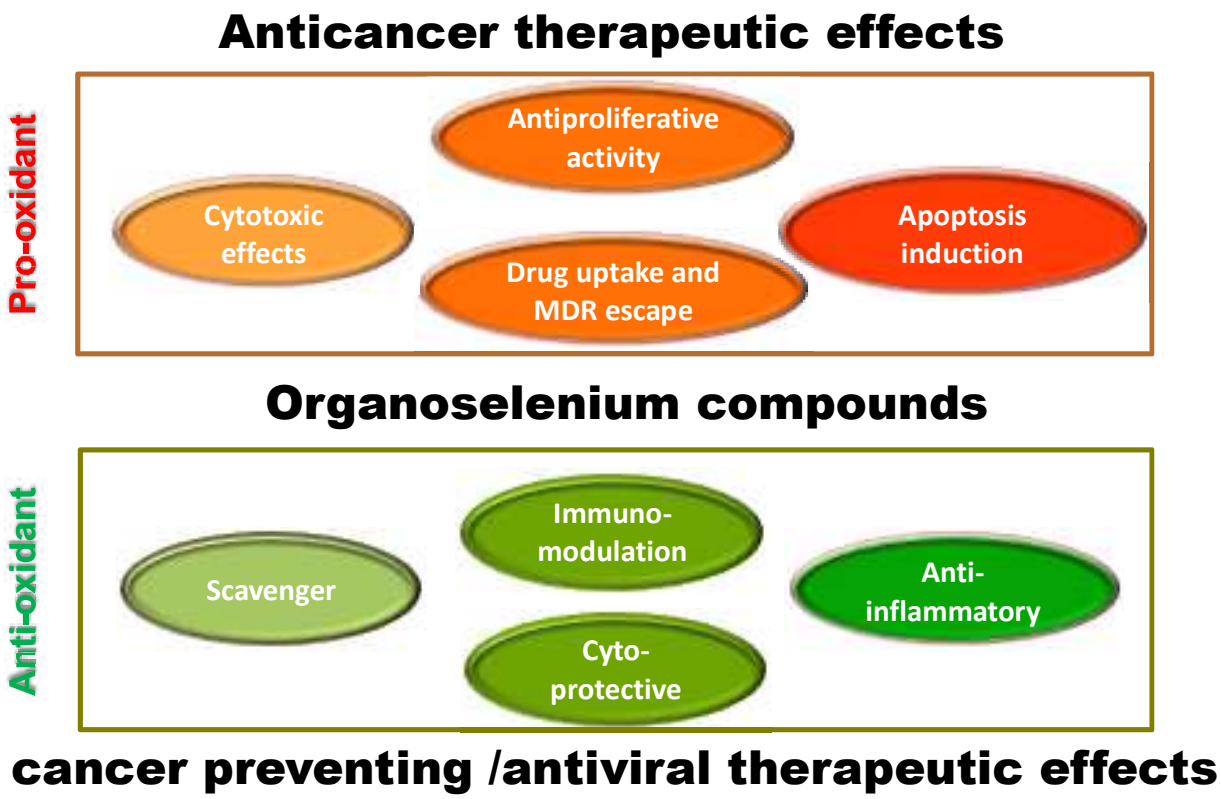

Figure 3 Schematic representation of Se and Se-containing compounds effects in counteracting cancer development and in preventing viral infection and tumour growth.

Considerable advances in the understanding of the complex biology and chemistry related to Se has been made in the last decade. For a long time, Se and Se-containing compounds were mainly tested to maintain the redox status and protect healthy cells from ROS-induced oxidative damage. However recent studies suggest that Se appears to be a redox potential modulator with a dual role on the oxidative stress, with pro-oxidant and anti-oxidant function depending on the incorporation type in organoselenium compounds as well as the dose. The ambiguity about the function of Se is also reflected in the uncertainty about its anti-cancer or antiviral effects [2], but the road ahead is still challenging. As outlined above, some compounds are rather promiscuous binders and therefore, as they stand, can be considered only as promising hit compounds. In an interdisciplinary approach the role of the various different Se incorporation in small organic molecules needs to be carefully evaluated in regards of their biological effects, enabling the possibility to develop further Se-containing hit compounds to potent specific drug leads in the years to come.

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