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Research advances in the role of selenium in reversing tumor multidrug resistance

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ABSTRACT

Multidrug resistance (MDR) is a significant challenge in the cancer therapy, with mechanisms primarily involving increased drug efflux mediated by ABC transporters, leading to reduced intracellular drug concentrations. In recent years, various selenium-containing compounds have demonstrated extensive biological activities, including chemoprevention, antioxidant or pro-oxidant effects, and regulation of the nervous and immune system activities. One of the most prominent physiological characteristics of selenium is its antioxidant capacity, which can regulate the levels of reactive oxygen species (ROS) in the body, making it a promising group for reversing MDR activity. Furthermore, research has shown that natural selenium compounds, including selenate, selenite, selenomethionine, and selenocystein, can inhibit the activity of drug resistance proteins and increase the intracellular accumulation of chemotherapeutic drugs by regulating intracellular ROS levels. For instance, sodium selenite has been shown to markedly increase the sensitivity of drug-resistant cell lines to doxorubicin, exhibiting significant antitumor efficacy and potential for reversing MDR. These findings suggest that selenium compounds hold considerable promise in addressing multidrug resistance. Consequently, this review focuses on elucidating the mechanisms of MDR and the chemical properties of selenium compounds, with particular emphasis on their activities in reversing MDR, thereby providing novel strategies for overcoming MDR in tumor cells.

1. Overview of multidrug resistance

Multidrug resistance (MDR) refers to the phenomenon wherein tumor cells, after long-term exposure to a particular chemotherapeutic drug, not only develop resistance to the treated drug but also exhibit cross-resistance to a variety of other chemotherapeutic drugs with different structures, cellular targets, and mechanisms of action.[1] This resistance is a crucial defense mechanism that allows tumor cells to evade from the cytotoxic effects of chemotherapy and is a major cause of chemotherapy failure in cancer treatment.[2,3] Generally, the occurrence of MDR is attributed to multiple factors and mechanisms. Three major mechanisms have been described: i) impaired cellular internalization of water-soluble compounds such as folate antagonists, nucleoside analogues, and cisplatin, which depend on specialized membrane transporters for cellular uptake; ii) intrinsic cellular adaptations that diminish drug cytotoxicity, encompassing cell cycle modifications, enhanced DNA repair mechanisms, attenuated apoptotic response, and altered drug metabolic pathways; iii) enhanced efflux of hydrophobic agents through energy-dependent transport pumps, despite their inherent ability to passively diffuse across plasma membranes.[4–6]

For a long time, among various resistance mechanisms, the efflux mediated by ATP-binding cassette (ABC) transporters has been considered the primary cause of MDR. The most widely expressed MDR transporters include P-glycoprotein (P-gp/ABCB1/MDR1), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP).[7] Among them, the P-gp protein is widely expressed in various tissues, including the liver, kidneys, gastrointestinal tract, and blood-brain barrier.[8] Clinical investigational drugs such as verapamil,

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zosuquidar, and tariquidar primarily target the P-gp protein, which has been highly pursued as a target to overcome MDR in many cancer cells.[9] The human ABC transporter family has been identified to contain 51 members, which can be divided into seven subfamilies based on amino acid sequence homology and structural similarities. Among them, approximately 15 ABC transporters have been found to be associated with drug efflux, leading to the MDR phenomenon.[10] Most ABC transporters consist of two ATP-binding domains (NBDs) and two transmembrane domains (TMDs), as shown in Fig. 1. Each TMD contains six transmembrane α-helices (TMHs) that recognize and bind substrates. The two NBD domains serve as the binding sites for ATPase, which dimerize upon ATP binding and restore the original conformation after hydrolysis of ATP and accompanying depolymerization. The Kim group analyzed the crystal structure of P-gp glycoprotein and speculated its efflux mechanism as follows.[11] When P-gp is not bound to ATP, it has an inward-facing conformation, with the two NBD domains separated, allowing intracellular substrates to bind between the two TMDs. Then, by binding to ATP, dimerization occurs, and the conformation changes to an outward-facing conformation, expelling the substrate out of the cell, thereby reducing the accumulation of the substrate within the cell. Finally, ATP hydrolysis restores P-gp to its original conformation for the next cycle, as shown in Fig. 2. This cycle repeats, reducing the accumulation of drugs in cells and preventing chemotherapy from achieving the desired effect.

According to the concept of cancer stem cells, these cells possess the ability to repair DNA, and the overexpression of the aforementioned ABC transporters results in decreased intracellular drug accumulation, which contributes to chemotherapy resistance.[12,13] Therefore, targeting MDR transporters may represent a critical strategy for effective cancer treatment and for preventing recurrence.[14] Previously, this resistance pattern was managed through combination chemotherapy involving multiple agents, which, however, led to a substantial increase in toxicity. The current approach is to identify ABC transporter inhibitors that can synergize with chemotherapeutic drugs. Three categories of inhibitors have been identified: competitive inhibitors that compete with chemotherapeutic drugs for the efflux pump binding sites, non-competitive inhibitors (allosteric inhibitors), and inhibitors that suppress the expression of efflux pumps. Despite the identification of these inhibitors, they all have limitations such as inadequate selectivity and elevated toxicity. For example, tariquidar (**1**, Fig. 3) demonstrates unacceptable toxicity when administered in conjunction with anticancer agents and leading to its failure in Phase III clinical trials for non-small cell lung cancer.[15] To date, no single specific inhibitor has succeeded in clinical trials. Consequently, there is an urgent need to develop a low-toxicity, highly efficient, and highly selective inhibitor to counteract MDR.

2. Biological properties of selenium

In 1973, the World Health Organization (WHO) officially declared selenium to be an essential trace element. Currently, selenium is regarded as a vital nutritional element on par with biochemical substances such as vitamins and carotenoids. It has been acclaimed by the global medical community as a fundamental element of life and is renowned for its potential role in cancer prevention. Selenium plays a critical role in the prevention of various diseases, including cancer, viral infections, infertility, cardiovascular conditions, and neurological disorders. It exerts its influence on multiple systems within the human body, such as the central nervous system, male reproductive system, endocrine system, cardiovascular system, immune system, and muscle function.[13,16–23] Maintaining an adequate level of selenium is crucial for many aspects of human health.

The biological activities of selenium encompass a range of functions including antioxidant, pro-oxidant, antibacterial, anti-aging, and anti-inflammatory activities, as well as the regulation of the immune and nervous systems.[24–30] Notably, selenium's antioxidant properties are among its most renowned physiological effects. The antioxidant capacity of selenium can be attributed to its strong nucleophilic ability and loosely arranged outer valence electrons. This characteristic enables selenium compounds to function as efficient two-electron and one-electron transfer reductants, thereby exhibiting significant antioxidant activity by scavenging reactive oxygen species (ROS).[31] Given that the overproduction of ROS is a hallmark of various diseases such as inflammation, atherosclerosis, and stroke, selenium-containing drugs hold considerable promise for therapeutic applications.[32] Recently, some researches have demonstrated that the overall oxidative state of cells and the levels of ROS significantly influence the expression of transmembrane transport proteins and the total amount of ATP available for transport[33] (Fig. 4). Therefore, organic selenides are capable of modulating intracellular ROS, thereby influencing the expression and function of transmembrane transport proteins. Furthermore, given that the efflux of chemotherapeutic drugs is energy-dependent, this insight offers a potential strategy to inhibit the process by seeking inhibitors of ATP transporters.[34] These transporters belong to the solute carrier transporter family (SLC), which is responsible for the transport of various nutrients, including glucose and ATP. SLC transporter inhibitors can induce cell starvation by inhibiting ATP transport, thereby blocking the entire energy-dependent process and inhibiting the function of transmembrane transport proteins, leading to a reduction in the efflux of chemotherapeutic agents.[35] In conclusion, the role of selenium in regulating ROS and its mechanism of action related to MDR suggest that selenium-based compounds capable of reversing MDR may be identified at each stage of the MDR process, including as competitive inhibitors competing with a chemotherapeutic agent for an efflux pump binding site, non-competitive inhibitors (both allosteric or ATPase domain inhibitors), and efflux pump expression inhibitors. For instance, in 2015, the Chakraborty group reported a combination drug strategy involving the use of diphenylmethyl selenocyanate (**2**, Fig. 5) and cisplatin.[36] It was found that this selenium compound can regulate intracellular ROS levels, resulting in DNA damage and ultimately inducing apoptosis in murine tumor cells.

As a non-metallic element, selenium occupies a position below sulfur in the periodic table and exhibits analogous physicochemical properties. However, selenium is larger and "softer" than sulfur, which results in less tightly bound outer valence electrons and enhanced nucleophilic reactivity. The longer Se=O bonds lead to weaker π-bond characteristics, rendering selenium more susceptible to reduction compared to sulfur.

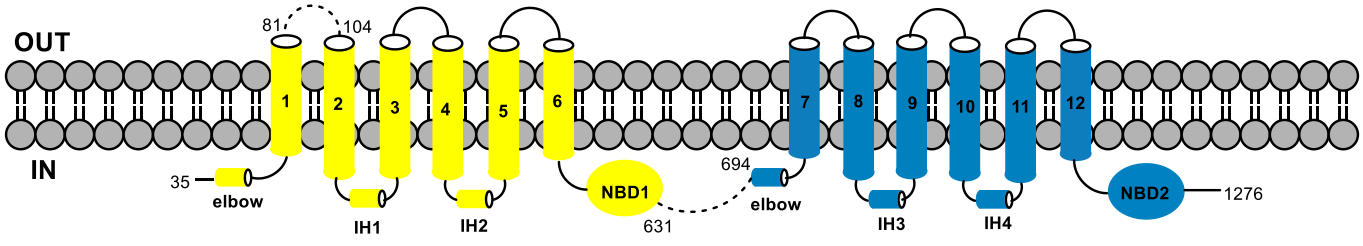


Fig. 1. Protein structure of P-gp in ABC transporter family.

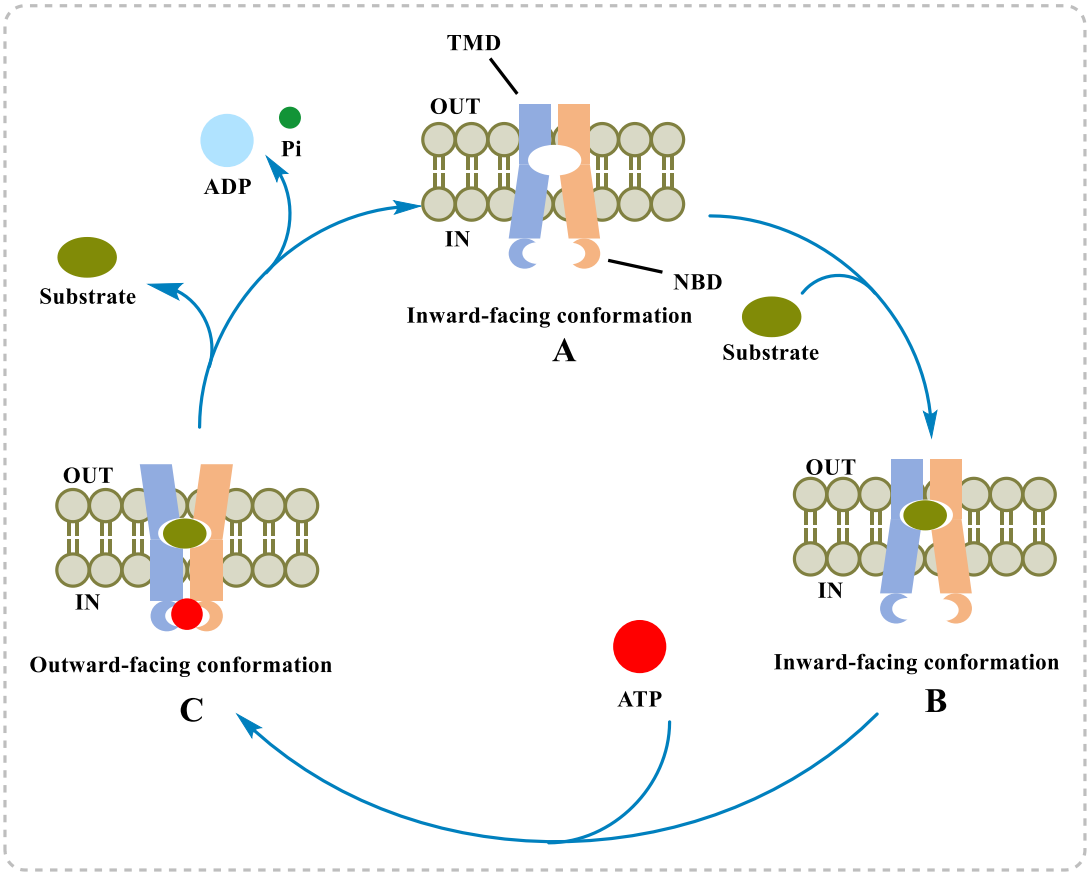


Fig. 2. Efflux mechanism of P-gp.

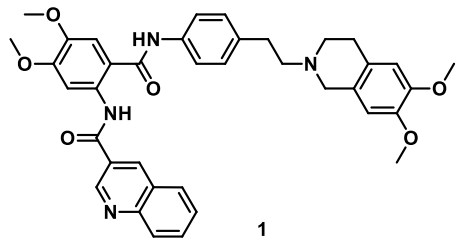


Fig. 3. The chemical structure of tariquidar (**1**).

The low-lying σ* orbitals facilitate selenium in forming potential chalcogen bonding (ChB) interactions with electron-donating atoms such as oxygen and nitrogen.[31] The physicochemical properties of selenium in small molecules and biomacromolecules are intricately linked to a wide range of biological and pharmacological activities. Recently, the integration of selenium into natural products and small molecules has yielded valuable intermediates for drug development, emerging as a potent tool for drug design and natural product modification.[37] Our group is currently concentrating on high throughput seleno-medicinal chemistry, and chemical biology, and has developed a series of selenium-nitrogen exchange (SeNEx) chemistry to efficient construct organic selenium compounds library for target or phenotype based screening.[38–41] These reactions exhibit high atom economy, excellent yield, and superior functional group compatibility. It serves as an invaluable tool for expanding the repertoire of selenium-containing compounds and DNA-encoded chemical libraries.[42–44] These attributes underscore the importance and feasibility of designing and synthesizing selenium-containing compounds.

3. Seleno-compounds with applications against cancer MDR

The antioxidant properties of the aforementioned selenium compounds stem from the distinctive chemical attributes of selenium. This biochemical characteristic is effectively harnessed by cells to regulate redox homeostasis. Selenium exhibits significant potential in reversing MDR. In this section, we will delve into specific selenium compounds that have important applications in mitigating cancer MDR, albeit currently there are no approved clinical drugs available. Table 1 summarizes the chemistry of small-molecule compounds containing selenium in their structures and summarizes their applications targeting MDR.

3.1. *Naturally occurring selenocompounds*

Natural selenium compounds, including selenate, selenite, selenocysteine (**3**, Fig. 5), and selenomethionine (**4**), plays a crucial role in modulating intracellular ROS. This modulation facilitates the oxidation of NADH to NAD^+, thereby reducing the overall ATP levels, which ultimately leads to a decrease in ATP-dependent drug efflux. Sodium selenate and its palladium complexes have demonstrated the ability to modulate ROS levels in cancer cells. Beyond their antiproliferative properties, these compounds also exert antimigratory effects on the human metastatic MDA-MB-231 breast cancer cell line.[45] Notably, however, the mechanisms by which they influence MDR in tumor cells remain unexplored in the literature. The Bjorkhem-Bergman group reported that selenite has been utilized as a sensitizer for anticancer drugs, such as doxorubicin, in multidrug-resistant cancer cells.[46] Their study demonstrated that the doxorubicin-resistant MRP-expressing cell lines U-1285dox and GLC_4/ADR are found to be 3- and 4-fold, respectively, more sensitivity to the cytotoxicity of sodium selenite compared to the

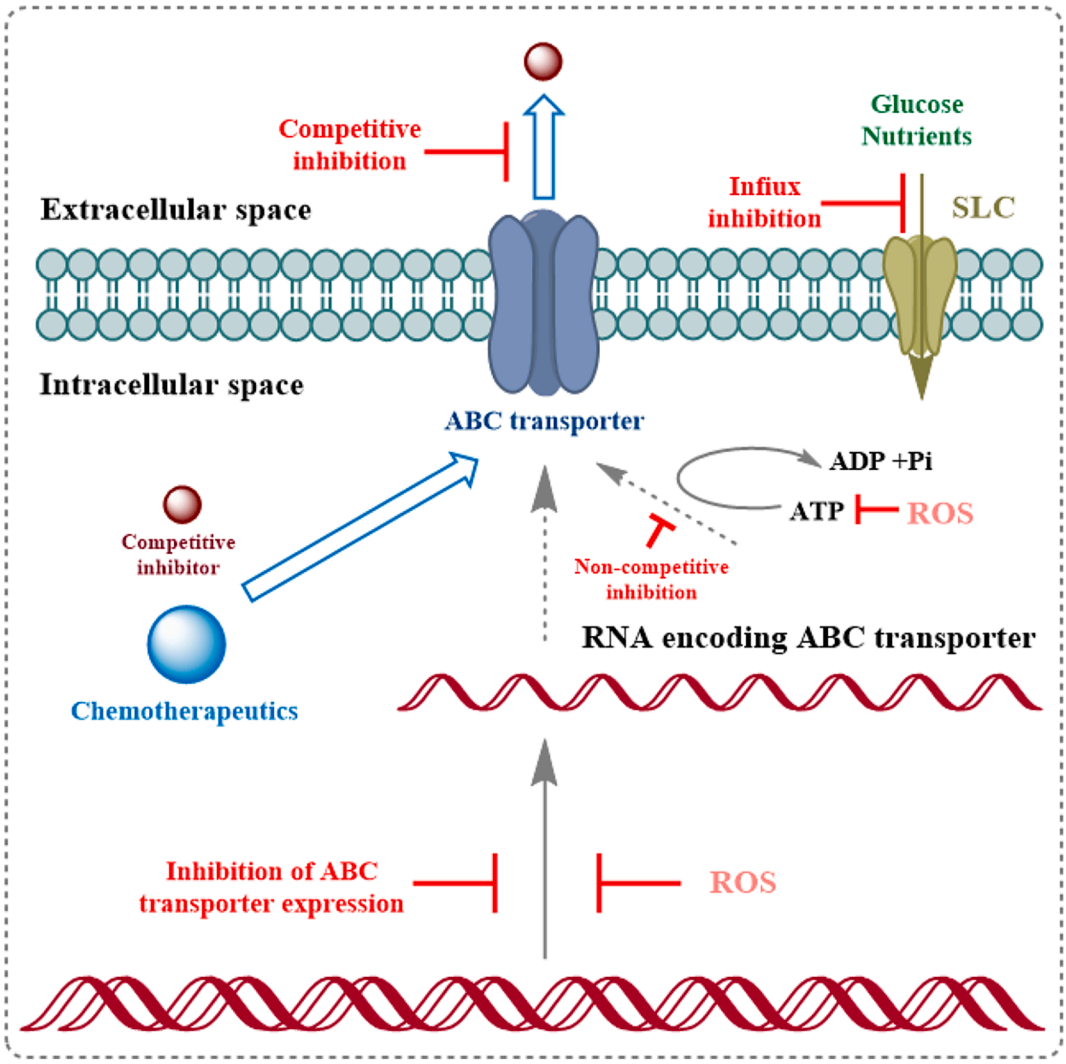
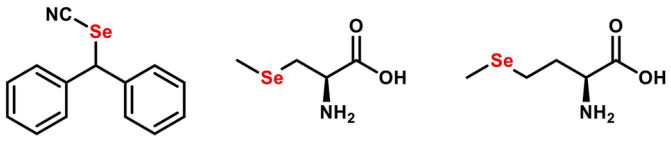


Fig. 4. The mechanism of ABC transporter.



2 3 4

Fig. 5. The chemical structures of compounds **2**, **3** and **4**.

doxorubicin sensitive cell lines U-1285 and GLC_4. 5-Methylselenocysteine and selenomethionine significantly enhanced the cure rates of human head and neck squamous cell carcinoma and colorectal cancer xenografts in nude mice that were resistant to irinotecan.[47] Notably, the combination of 5-methylselenocysteine and irinotecan yielded a higher cure rate compared to the combination of irinotecan and 5-fluorouracil. Additionally, other studies have confirmed synergistic effects between selenium compounds and chemotherapeutic agents, including the combinations of selenite and irinotecan,[48] sodium selenite and cisplatin,[49] selenocysteine and doxorubicin,[50] as well as selenocysteine and auranofin.[51] To date, these selenium compounds have demonstrated efficacy-enhancing effects on anti-cancer drugs exclusively in drug-resistant cell lines. However, no mechanistic investigations or clinical trials have been conducted to further explore these findings.

Furthermore, selenite at micromolar and nanomolar concentrations facilitates the intracellular formation of endogenous selenium nanoparticles (SeNPs) within the cytoplasm and organelles of H157 buccal mucosa squamous carcinoma cells. This occurs via the reduction of selenium anions to elemental selenium by cellular enzymes. The generation of these endogenous SeNPs may represent a potential mechanism underlying the anticancer activity of selenite. Although sodium selenate

Table 1
Selenium containing small-molecules and their anticancer activity.

Compounds	Activities	Disadvantages
Selenate and selenite	Chemosensitization	mechanism remains unclear
Selenomethionine (**3**)	Chemosensitization ROS generation Apoptosis induction	mechanism remains unclear
Selenocysteine (**4**)	Chemosensitization	mechanism remains unclear
Selenium anhydride and selenium acid esters (**6–9**)	Efflux pump inhibition cytotoxicity	low potency and high toxicity
Derivatives of seleno-containing sodium phenobarbital and selenide triazine (**12–15**)	P-gp inhibition Apoptosis induction	low potency
Diselenoesters and triselenoesters (**18–19**)	Efflux pump inhibition	higher cytotoxicity
Indole selenides (**21**)	P-gp inhibition	weak cytotoxicity
Compounds **22–27**	Reduction of ROS	cytotoxicity

exhibits lower activity compared to selenite, it demonstrates sensitivity towards the highly resistant oral cancer cell line KBV20C.[52]

3.2. Selenium anhydride and selenium acid esters

In addition to the mechanism of indirectly affecting the expression of drug efflux transporters through ROS, many selenium compounds are able to directly inhibit the activity of transporters. Gajdacs group reported that selenic anhydride and selenic ester exhibited inhibitory activity against P-gp glycoprotein in multidrug-resistant mouse T-lymphoma cells and human colorectal adenocarcinoma cell lines, while also exhibiting cytotoxic and pro-apoptotic activities.[53] A key advantage of these compounds is their low toxicity, with effective concentrations (IC_{50}) typically in the nanomolar range and lethal doses (LD_{50}) in the micromolar range. Therefore, the low toxicity of selenic anhydride and selenic ester is unlikely to induce drug resistance in tumor cells. verapamil (**5**), a calcium channel blocker, competitively inhibits P-gp. However, certain selenium compounds demonstrate significantly greater inhibitory activity compared to this established inhibitor at just one-tenth the concentration of it (**5**: 20 μM; **6**–**9**: 2 μM). Specifically, Phthalic Selenic Anhydride (**9**, 2 μM, Fig. 6) exhibits inhibitory effects on P-gp in multidrug-resistant T lymphoma and colorectal adenocarcinoma cells that are 3.6 and 4.3 times more potent than those of verapamil, respectively. Methyl ketone selenic ester (**6**) exhibits inhibitory effects on P-gp in multidrug-resistant T lymphoma and colorectal adenocarcinoma cells that are 3.4 times and 4.0 times greater than those of verapamil, respectively. Tert-Butyl ketone selenic ester (**7**) demonstrates lower activity compared to methyl ketone; however, it still exerts an inhibitory effect on P-gp that is 1.7–2.3 times higher than verapamil at the same concentration. Furthermore, the aforementioned compounds exhibit significant apoptotic induction.[54] Notably, methyl ketone selenic ester, methyl selenic ester, and methyl ketone selenic ester (**8**) containing a 3,5-methylene fragment demonstrate excellent selectivity, with selectivity indexes of 10.0, 8.0, and 3.4, respectively.[55] These selenium-based compounds also display enhanced antiproliferative effects when combined with doxorubicin in breast cancer cells that overexpress P-gp protein.[56] Notably, their P-gp inhibitory effect was evaluated for their efflux modulating effects in mouse T-lymphoma cell line transfected with the human MDR1 gene that codes for the P-gp protein to measure the accumulation of fluorescent molecule rhodamine 123, which is a substrate of P-gp. The percentage of mean fluorescence intensity was calculated for the treated MDR cells compared to the untreated cells, and then a fluorescence activity ratio (FAR) was determined: FAR = (MDR treated/MDR control)/(parental treated/parental control).[57] The FAR values are directly proportional to their P-gp inhibitory effects.

3.3. Derivatives of seleno-containing sodium phenobarbital

The structure-activity relationship of a large number of P-gp inhibitors indicates that the hydrophobic aromatic motif in their structures plays a vital role in improving their potency, and a certain degree of flexibility is required in the middle part. In current discoveries, the most active derivatives of sodium phenobarbital are **10** and **11**, whose potency are 4–7 times over P-gp inhibitor verapamil (Fig. 7). In addition, in the studies on aromatic selenocarboxylates and selenocarboxylic anhydrides, Gajdacs and coworkers found that they showed anticancer and P-gp inhibitory properties.[54] However, the low chemical stability and strong odor of these selenocarboxylates and selenocarboxylic anhydrides limit their further development into drugs. In contrast, the selenides are more chemically stable. Therefore, Handzlik[57] group designed a series of selenide contained sodium phenobarbital derivatives. Among them, three compounds significantly outperformed verapamil in inhibiting the P-gp mediated drugs efflux (up to 2.6 times higher efficacy) at just one-tenth the concentration of verapamil and. In the P-gp efflux regulation experiments, compounds **13–15** demonstrated higher inhibitory activity against P-gp, confirming their substrate binding potency and possible competitive interaction with the Rhodamine binding site. Furthermore, it is indicated that compound **13** exhibited the most effective cytotoxicity and antiproliferative effects on sensitive and resistant mouse T-lymphoma cell lines. Finally, mechanistic studies revealed that compound **13** exhibited potent anticancer activity by inhibiting the expression of cyclin D1 (a cell cycle enhancer) and increasing the expression of p53 (an inhibitor of cell proliferation). Moreover, the authors conducted a structure-activity relationship analysis on the derivatives of selenide contained sodium phenobarbital and discovered that the lipophilicity of the new family of selenium compounds, as well as the length of the selenide chain, may be important factors in influencing the antiproliferative and cytotoxic effects.

Besides, the Handzlik[58] group also designed selenide triazine compounds to search for new anti-cancer drugs to overcome MDR in lymphoma. Among these compounds, compound **12** exhibited limited activity in reversing MDR (Fig. 7). However, with regard to its selective anti-proliferative effect on multidrug-resistant cancer cells, it demonstrated a potent synergistic interaction with doxorubicin. Furthermore, mechanistic investigations during the cell cycle revealed that it induced high-level expression of p21 and, when combined with doxorubicin, more effectively modulated cell cycle-related genes. Additionally, compound **12** represents a highly promising therapeutic candidate.

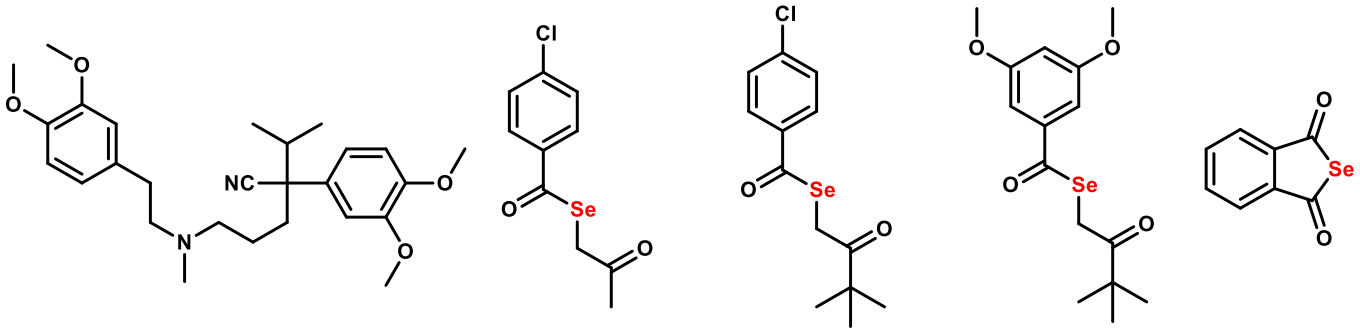


Fig. 6. The chemical structures of verapamil (**5**) and compounds **6–9**. @: The test concentration used in the experiment to test the anti-drug resistance of the compound; FAR: fluorescence activity ratio.

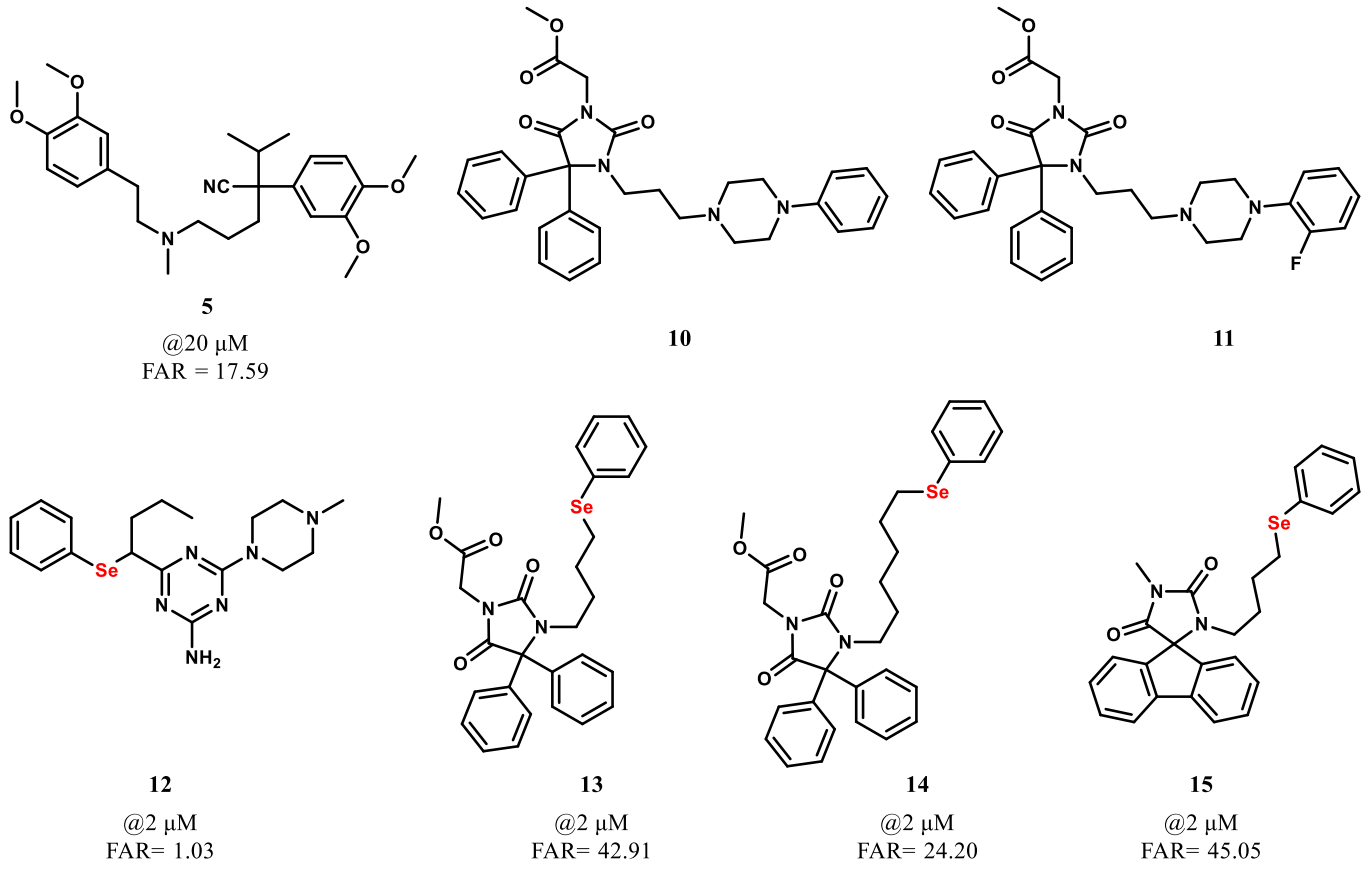


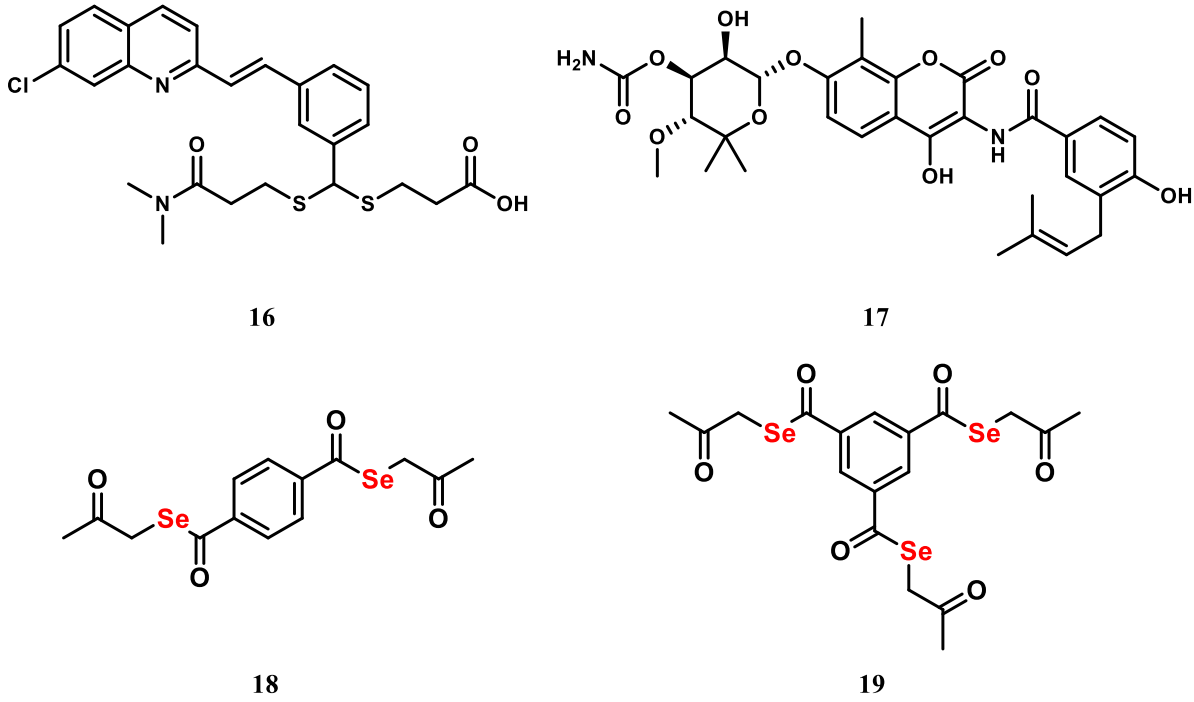
Fig. 7. The chemical structures of compounds **10–15**. @: The test concentration used in the experiment to test the anti-drug resistance of the compound; FAR: fluorescence activity ratio.

3.4. Diselenoesters and triselenoesters

Recent reports have indicated that certain selenium compounds are more effective in inhibiting P-gp activity than verapamil. Therefore, Krzysztof[59] group evaluated the effects of diselenoester (**18**, Fig. 8) and triselenoester (**19**) on the three transporters, BCRP, P-gp, and MRP1, as well as their sensitivity in triple-negative breast cancer cells.[60,61] The results showed that at a concentration of 1 μM, the selenides exhibited inhibitory activities comparable to those of verapamil (an MDR1 inhibitor), MK-571 (**16**) (an MRP1 inhibitor), and novobiocin (**17**) (a BCRP inhibitor), with multidrug resistance activity factor (MAF) all below 20 (samples with MAF values less than 20 are classified as MDR negative (that is, it is less likely to develop MDR), and the tested samples inhibit the respective ABC transporter. Whereas, those with MAF values greater than 25 are categorized as MDR positive (this means it is prone to developing MDR), and the tested samples do not inhibit the respective ABC transporter). In triple-negative breast cancer cells, triselenoesters at a concentration of 0.5 μM were able to inhibit the activities of BCRP, P-gp, and MRP1, with MAF values all below 20. However, at the same concentration of 0.5 μM, diselenoesters exhibited markedly diminished inhibitory activities against P-gp and MRP1, with MAF values exceeding 20. The tested selenides, while being effective inhibitors of ABC transporters in breast cancer cells, also exhibited strong cytotoxicity in the nanomolar range. Nevertheless, given their inhibitory activities against these efflux proteins, selenides remain a promising scaffold for research in the field of MDR.

3.5. Indole selenides

P-gp is the most widely expressed protein in tumor cells responsible for drug efflux. Our group has developed a novel indole selenide scaffold with good inhibitory activity against P-gp by employing a 5-phenylfuran-tetrahydroisoquinoline derivative **20** (Fig. 9) as a lead compound.[62] It is reported that L-shaped and U-shaped conformations are crucial for effective P-gp inhibition.[63] However, since **20** contains only three rotatable bonds, it is not conducive to forming a pharmacologically favorable conformation. Compound **21** was thus synthesized by strategically elongating the molecular structure to more effectively engage the active pocket and incorporating a pyrazole group at the C-5 position of the indole ring. These modifications help to orient the molecular structure towards U-shaped and L-shaped conformations, enhancing P-gp inhibitory activity.[64] In molecular docking analysis, the 6,7-dimethoxy-tetrahydroisoquinoline moiety of **21** was shown to reside in a hydrophobic pocket composed of Tyr953, Tyr950, Met949, Met986, and Met69 (Fig. 10). Additionally, a hydrogen bond interaction was observed between the nitrogen atom of the pyrazole group and the residue Gln725, as well as a π-H interaction between the aromatic-H of the indole structure and the Phe343 residue. These interactions contribute to the overall stability of the **21**-P-gp complex. Moreover, given that many effective P-gp inhibitors exhibit higher lipophilicity, the larger size and softer nature of selenium can lead to increased lipophilicity,[31,65] which is a favorable factor for enhancing pharmacological efficacy. In the activity analysis, **21** was the most potent, with the reversal activity even slightly stronger than that of the third-generation P-gp inhibitor tariquidar (RF: 271.7 vs. 261.6) (RF is defined as the ratio of the IC_{50} value for doxorubicin when administered alone to the IC_{50} value when doxorubicin is used in combination with P-gp inhibitor). Notably, the series of seleno-containing compounds showed inhibition rates of no more than 33.7% at 5 μM in MCF-7/ADR cells, indicating good safety profiles. These data have validated that indole selenide is a new scaffold for the development of P-gp inhibitor. However, the



	@1 μM	@0.5 μM	@1 μM	@0.5 μM
P-gp	MAF: <20	MAF: >25	MAF: <20	MAF:<20
MRP1	MAF: <20	MAF: >20	MAF: <20	MAF:<20
BCRP	MAF: <20	MAF: <20	MAF: <20	MAF:<20

Fig. 8. The structures of **MK-571** (**16**), **novobiocin** (**17**) and compounds **18**, **19**. @: The test concentration used in the experiment to test the anti-drug resistance of the compound; FAR: fluorescence activity ratio.

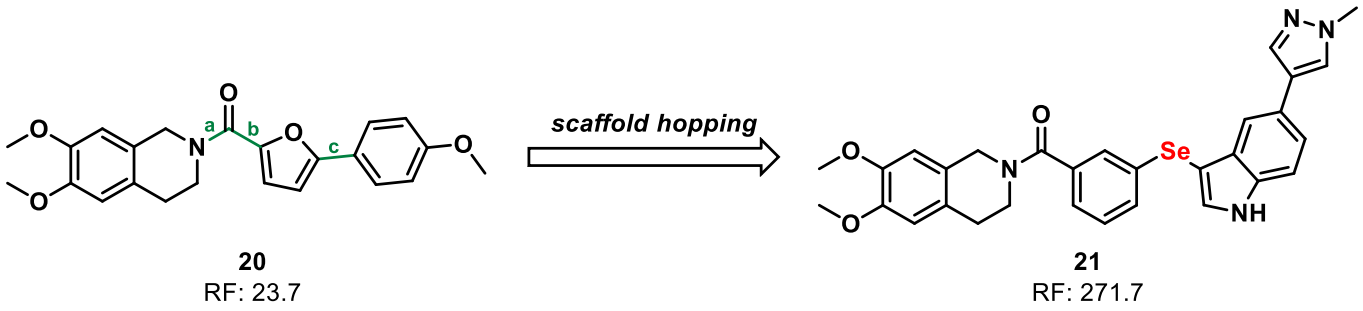


Fig. 9. The chemical structures of compounds **20** and **21.**

potency and cytotoxicity of **21** is very close to tariquidar, and it is known that tariquidar has failed in clinic study. Therefore, the *in vivo* efficacy of **21** was not conducted at this stage. Instead, it was selected as a lead compound to conduct further modifications to pursue a more potent but less toxic candidate.

3.6. Other seleno-containing compounds

The role of ROS in cancer cells is currently a matter of debate. It is known that ROS is present at high levels during carcinogenesis and the cancer process, exhibiting dual functionality.[66] On one hand, they can act as signaling molecules to promote cell proliferation, while on the other hand, ROS can induce the cell death through apoptosis. The antioxidant properties of organic selenium derivatives are diverse, encompassing activities such as free radical scavenging,[67] metal chelation,[68] and mimicking natural antioxidant enzymes to remove harmful hydrogen peroxide and alkyl peroxides. Based on the strong antioxidant properties of selenium compounds, the Fernandez-Bolanos group[69] designed and synthesized a series of small-molecule seleno-containing compounds. In the DPPH assay, compared to **22** (EC_{50}: 23.2 μM) and **24** (EC_{50}: 10.8 μM), compound **23** (EC_{50}: 9.3 μM) and **26** (EC_{50}: 7.8 μM) exhibited stronger free radical scavenging activity (Fig. 11). Compound **23** and **26** also served as notable examples, capable of clearing approximately 50% of H_2O_2. The removal of the catechol structure from the molecule led to a complete loss of ROS scavenging ability (**27**, EC_{50} > 250 μM). The ability of them to clear ROS may suggest their potential to reverse MDR. In terms of antiproliferative activity, diselenide **25** demonstrated high potency (GI_{50} = 0.88–2.0 μM, GI_{50} refers to the concentration of the compound that inhibits 50% of the culture growth) and good selectivity (selectivity index: 14–32). It contains two methylenedioxyphenyl groups, with the two pharmacophores linked by a diethyl diselenide chain. Compound **27**, which has an amide bond in its

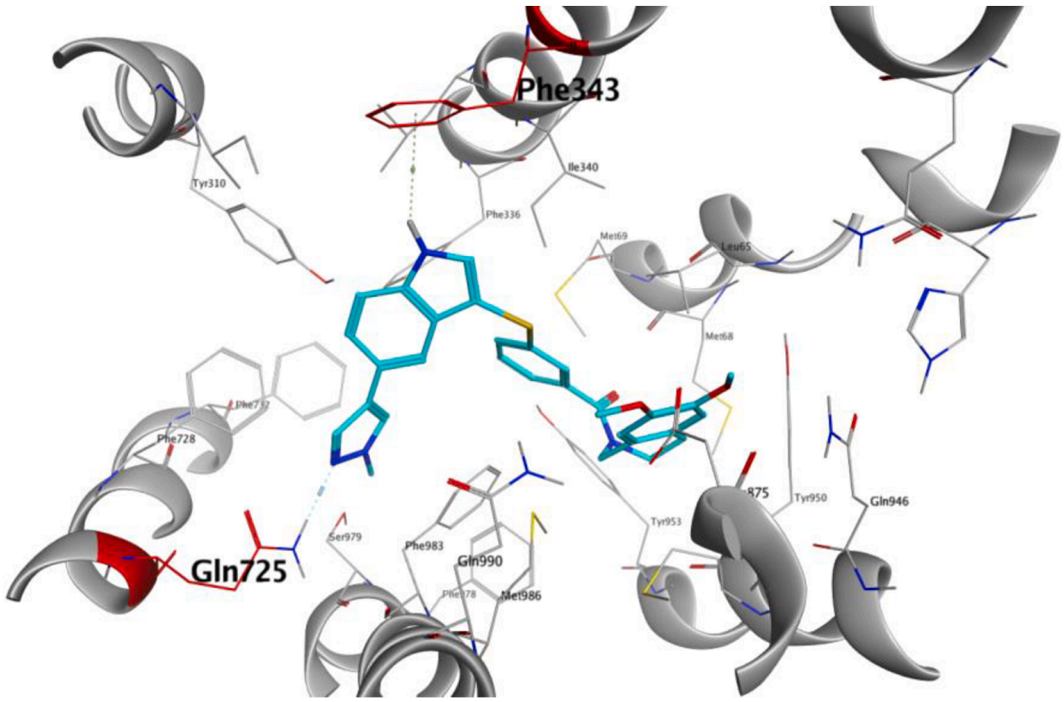


Fig. 10. Predicted binding model of **21** with the receptor P-gp.

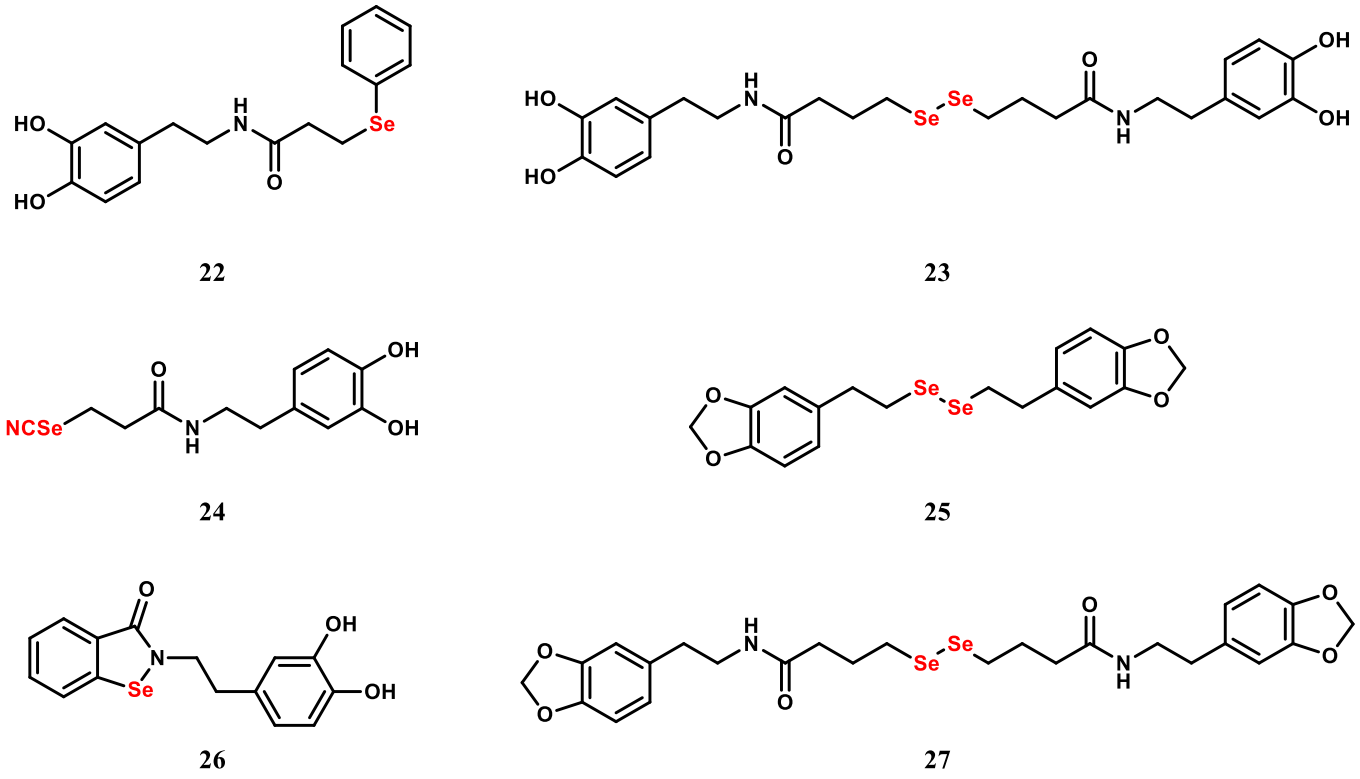


Fig. 11. The chemical structure of compounds **22–27**.

connecting chain, was the most potent compound in this series (GI_{50} = 0.12–0.27 μM), although it exhibited lower selectivity (selectivity index: 4–8). Additionally, the tested selenium compounds were found not to be substrates of the P-gp efflux pump, leading to the speculation that these compounds would not induce MDR via the P-gp efflux pump. Considering the significant antiproliferative activity and robust ROS scavenging ability of compound **27**, it demonstrates considerable potential as a lead compound for investigating MDR reversal.

3.7. Selenium nanoparticles

The variation in the intracellular redox environment due to cell

growth and metabolism constitutes a critical factor influencing drug efficacy.[70] Selenium's potent redox reactivity allows it to undergo distinct transformation pathways within varying intracellular redox conditions, enabling participation in diverse physiological processes and thereby exhibiting remarkable biological activity.[28] In this regard, Chen group[71] design and engineer Se-Se/Se-S bonds to assemble selenium nanoclusters (SeClus) with an intracellular redox environment-driven selective structural transformation. The nanoclusters exhibit a significant ability to inhibit the proliferation of cancer cells, demonstrate good safety for normal cells, and elucidate the chemical nature for the atomic engineering of SeClus (Fig. 12). This significantly facilitates the clinical translation of selenium nanoparticles (SeNPs) for anti-tumor applications. Moreover, SeNPs aslo demonstrates distinct advantages in overcoming tumorMDR. The primary strength of SeNPs resides in their sophisticated structural designability. By precisely regulating particle size and implementing surface chemical modifications, MDR can be inhibited through multiple mechanisms. On one hand, selenium nanoparticles exhibit multifaceted actions on the MDR mechanism by directly inhibiting drug efflux. For instance, the CdSe/ZnS-MPA and CdSe/ZnS-GSH nanoparticles developed by Yin research team suppress the P-gp protein through the upregulation of miR-34b and miR-185 miRNAs.[72] Additionally, Gharbavi group[73] synthesized SeNPs (NISM-B@SeNPs), which demonstrate antioxidant and cytotoxic properties while reducing the expression of the MDR-1 gene. Furthermore, the Gal/Bor@SeNPs investigated by Zeng group[74] inhibits the expression of ABC family transporters in several cancer cell lines, including HepG2, R-HepG2, and LO2 cell lines. These nanoparticles also function as nanocarriers to deliver the anticancer drugs tris(2-phenylimidazo[4,5-f][1,10]phenantroline) and $Fe(PiP)_3$ to cancer cells. Moreover, the SeNPs activate ROS-mediated signaling pathways, thereby inducing apoptosis in cancer cells. On the other hand, from the perspective of drug delivery, the Xu group[75] reported $(Cys–(PEG45)_2\text{-}b\text{-}(PMAOEFC)_2)$, which can be loaded with various forms of doxorubicin via a labile Schiff base structure that self-assembles into a globular micelle, thereby enabling the controlled release of doxorubicin. Additionally, this complex was capable of encapsulating paclitaxel as well as a paclitaxel dimer crosslinked by 3,3′-diselenodipropionic acid (PTX-SeSe-PTX). The resultant formulation exhibited significant cytotoxicity against HeLa cells when incorporated into the $(Cys–(PEG45)_2\text{-}b\text{-}(PMAOEFC)_2)$ nanocarrier. This nanocarrier not only enhanced drug accumulation in tumors but also promoted efficient drug release and induced apoptotic events. Such a design holds promise for delivering chemotherapeutic

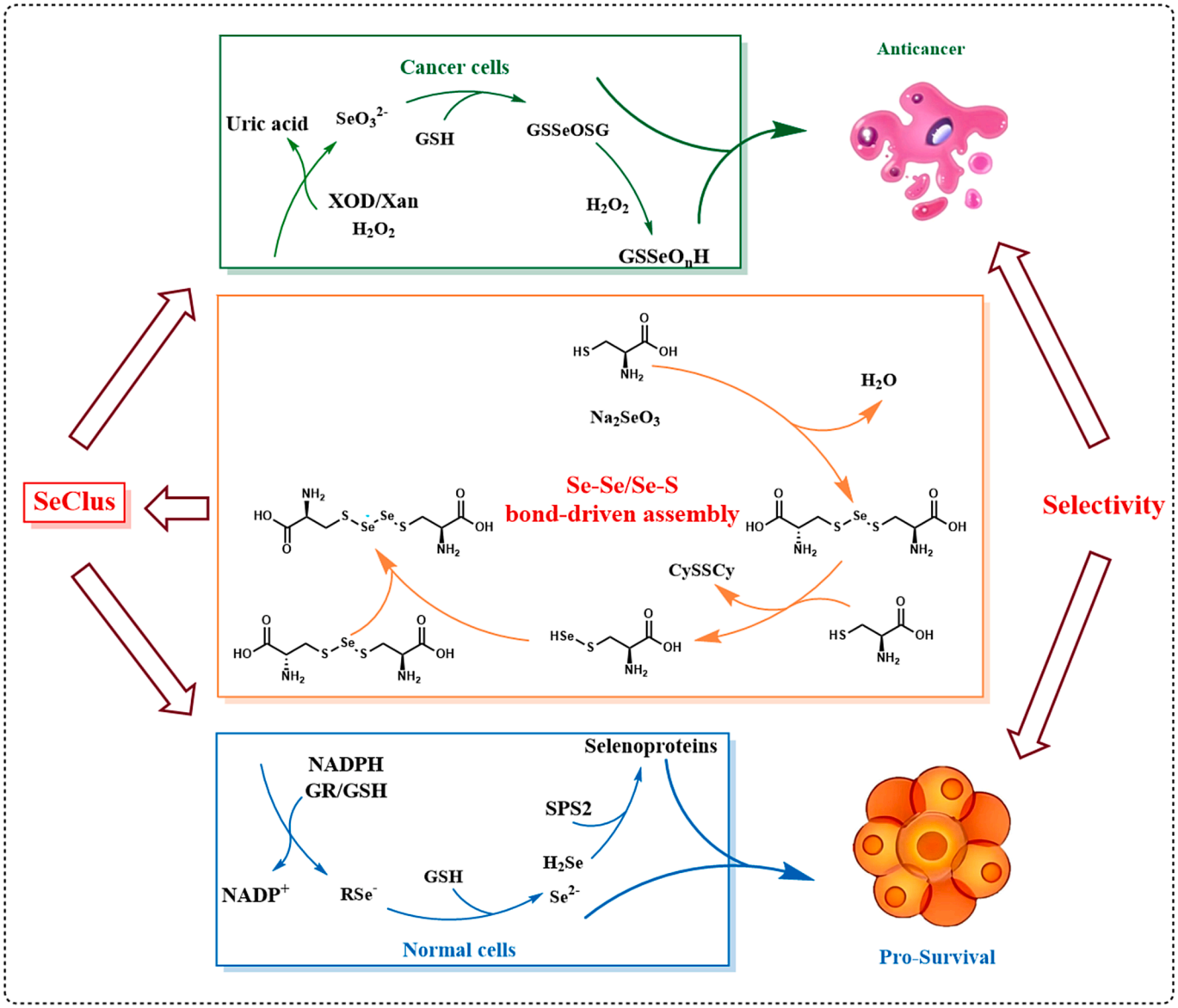


Fig. 12. Schematic illustration for the cancer-normal selectivity of SeClus.

agents to drug-resistant tumors, effectively overcoming MDR. Leveraging the unique advantages of selenium chemistry, we anticipate that SeNPs will emerge as the star molecule in the next generation of anti-MDR nano-drugs.

4. Summary and prospects

The emergence of MDR has greatly increased the complexity and challenge of cancer treatment. To date, no single specific inhibitor has succeeded in clinical trials. However, in the study of the biological properties of selenium, it has been found that organic selenium compounds possess a wide range of biological activities, and they have also been identified for their anticancer and MDR-inhibiting properties. Therefore, this review summarizes the role of selenium in inhibiting MDR and lists some selenium compounds with certain MDR-inhibiting activities. These compounds are worthy of further investigation, with the aim of providing a potentially viable new approach to overcoming MDRin cancer. This review has summarized some interesting advantages of selenium in the application of MDR inhibitors through the introduction of these different types of structures. Firstly, high lipophilicity and flexible chains are required in the design of P-gp inhibitors. Based on the fundamental properties of the element selenium, it inherently possesses high lipophilicity and a soft nature, both of which are advantageous for the design of P-gp inhibitors. Secondly, the most well-known physiological activity of selenium is its antioxidant properties, which are crucial in cancer and MDR inhibition research and deserve further exploration. Nonetheless, several selenium compounds discussed in this paper present potential toxicity concerns. Consequently, it is imperative for medicinal chemists to undertake further investigations to develop safer and more selective inhibitors. Additionally, there are instances where the incorporation of selenium into drug molecules markedly diminishes their toxicity. For instance, 6-mercaptopurine, an anti-purine metabolic agent utilized in the treatment of acute lymphoblastic leukemia, can be modified by substituting the sulfur atom at position 6 in its molecular structure with a selenium atom.[76] This substitution yields 6-selenopurine, a compound that exhibits enhanced pharmacological activity and reduced side effects. Furthermore, considering that DNA-encoded chemical library (DEL) technology can rapidly identify compounds that bind to target proteins through affinity screening and DNA sequence decoding, this approach holds significant potential for identifying new inhibitors targeting drug resistance-related proteins. Our group has successfully developed several highly efficient DNA-compatible selenylation reactions, enabling the construction of selenium-containing DNA-encoded chemical libraries (SeDEL).[77,78] These technologies facilitate high-throughput screening of a vast array of selenium-containing compounds, thereby offering substantial promise for the discovery of novel selenium-based inhibitors of drug resistance-related proteins.

Apart from these observations, some of the compounds discussed here merit further investigation through in-depth studies, such as *in vivo* experiments or ADMETox assays (Absorption, Distribution, Metabolism, Excretion, and Toxicity), to assess their viability as novel anticancer drug candidates or adjuvants. Additionally, the fine-tuning of these compounds forms a valuable library of agents that could assist medicinal chemists in conducting robust structure-activity relationships studies. This, in turn, could facilitate the design of more potent and selective selenium containing compounds for cancer therapy. Furthermore, ROS regulation related mechanism such as transmembrane transport protein expression regulation, more specific information about the involved signaling pathways (e.g., the MAPK pathway, the NF-κB pathway) should be in-depth investigated. Moreover, for seleno-compounds that induce apoptosis in tumor cells, a more detailed investigation of the apoptosis-related signaling pathways, including the activation of caspases and the role of Bcl-2 family proteins should be conducted in the future study.

CRediT authorship contribution statement

Haoqiang Hu: Writing – original draft, Data curation. **Yunjun Chen:** Writing – original draft, Data curation. **Hongtao Xu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Wei Hou:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

There are no conflicts of interest.

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