New organoselenides (NSAIDs-Se derivatives) as potential anticancer agents: Synthesis, biological evaluation and in silico calculations

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Abstract:

Herein we reported the synthesis of twenty new organoselenium compounds (**2a-2j** and **3a-3j**) based on the hybridization of nonsteroidal antiinflammatory drugs (NSAIDs) skeleton and organoselenium motif (-SeCN and -$SeCF_3$), the anticancer activity was evaluated against four types of cancer cell lines, Caco-2 (human colon adenocarcinoma cells), BGC-823 (human gastric cancer cells), MCF-7 (human breast adenocarcinoma cells), PC-3 (human prostatic cancer cells). Interestingly, the introduction of the -SeCN or -$SeCF_3$ moiety in corresponding parent NSAIDs results in the significant effect on cancer cell lines. Moreover, the most active compound **3a** showed IC_{50} values lower than 5 μM against the four cancer cell lines, particularly to BGC-823 and MCF-7 with IC_{50} values of 2.5 and 2.7 μM, respectively. Furthermore, three compounds **3a**, **3g** and **3i** were selected to investigate their ability to induce apoptosis in BGC-823 cells via modulating the expression of anti-apoptotic Bcl-2 protein, pro-inflammatory cytokines (IL-2) and proapoptotic caspase-8 protein. The redox properties of the NSAIDs-Se derivatives prepared herein were conducted by 2, 2-didiphenyl-1-picrylhydrazyl (DPPH), bleomycin dependent DNA damage and glutathione peroxidase (GPx)-like assays. Finally, molecular docking study revealed that an interaction with the active site of thioredoxin reductase 1 (TrxR1) and predicted the anticancer activity of the synthesized candidates. Overall, these results could serve a promising launch point for further design of NSAIDs-Se derivatives as potential anticancer agents.

Keywords: selenium; selenocyanates; trifluoromethyl selenides; anticancer; in *silico* calculations

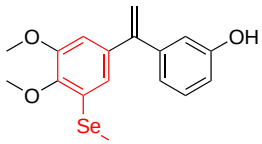
Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of often chemically unrelated compounds commonly used to treat symptoms of inflammatory diseases such as osteoarthritis and rheumatoid arthritis, and are among the most widely used drugs worldwide [1, 2]. In the field of cancer research, a large body of evidence from epidemiological and preclinical studies have shown that NSAIDs have used for chemo-preventive agents, especially in colorectal cancer (CRC) and prostate cancer [3-6]. Several modifications, based on NSAIDs scaffolds, have demonstrated stronger cytotoxicity and chemo-preventive than corresponding NSAID alone [7, 8]. NSAIDs framework modification has become a structure-based medicinal chemistry strategy to design novel anticancer agents in the past decades [9-12].

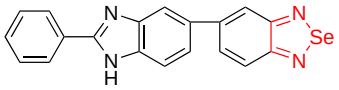
Selenium (Se) is an essential trace element that is of importance to human health and disease [13]. There are three main categories Se-containing compounds (inorganic, organic and selenoproteins) with potential pharmacological properties, the most developed and studied are the org-Se derivatives [14]. Different organic selenium compounds with diverse functional groups, including selenocyanates, selenoureas, heterocycles with endocyclic selenium, selenides and diselenides, have been reported to exhibit anticancer activity (**Fig 1)** [10, 15-21]. Although the mechanisms that underlie the potential anticancer activity of seleno compounds are very diverse (including protein modification, cell growth arrest, anti-angiogenic effects, etc) [22], the most frequent one is the reduction of oxidative stress through the elimination of free radicals [23-25].

In the previous study, the modification of NSAID framework with Se functionalities is the novel celecoxib-Se derivatives, which exhibited anti-inflammatory and anti-cancer activity [11, 12]. Very recently, we have reported the synthesis of a series of novel NSAIDs-Selenium derivatives and screened their anticancer activity by *vitro* study, the modification of NSAIDs scaffolds with Se functionalities (-SeCN, -Se-Se-, -$SeCF_3$) demonstrated potent inhibition of human tumor cell [21, 26-27]. Along with the reports that support the modification of NSAIDs scaffolds with Se functionalities and in continuation of our research program

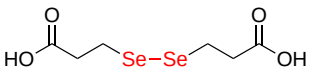
on design and synthesis of new NSAIDs-Se derivatives as potential anticancer agents [28, 29], twenty new NSAIDs-SeCN and NSAIDs-$SeCF_3$ derivatives were designed by the incorporation of an appropriate Se moiety into various NSAIDs with a general model consist of three essential fragments in their molecular: i) NSAIDs fragment; ii) electron donating group (X = NH, O, Se); iii） functional group bearing the Se atom (**Fig 2**). Their anticancer activities against the human cancer cell lines Caco-2, BGC-823, MCF-7 and PC-3 in *vitro* using the MTT assay. Three compounds **3a, 3g** and **3i** were selected to test the protein expression levels of Bcl-2, IL-8 and caspase-8 biomarkers in BGC-823 cells. Furthermore, the antioxidant potential of the compounds was investigated by employing DPPH, bleomycin-dependent DNA damage and GPx-like assays. Finally, TrxR1 (Thioredoxin Reductase) was selected as docking protein in order to predict the target and anticancer activity of the prepared NSAIDs-Se hybrid compounds.



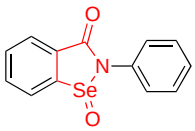
Methyl(phenyl)selane [15]



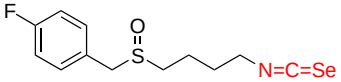
Selenadiazole [16]



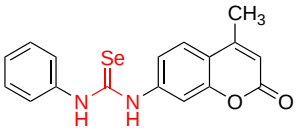
Diselenides [17]



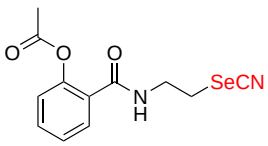
Ebselen [18]



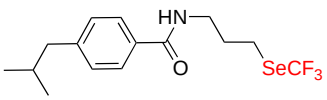
Isoselenocyanate [19]



Selenium-Urea [20]



Aspirin-SeCN Derivative [10]



Ibuprofen-$SeCF_3$ Derivative [21]

Fig. 1. Organic selenium compounds previously reported with anticancer activity

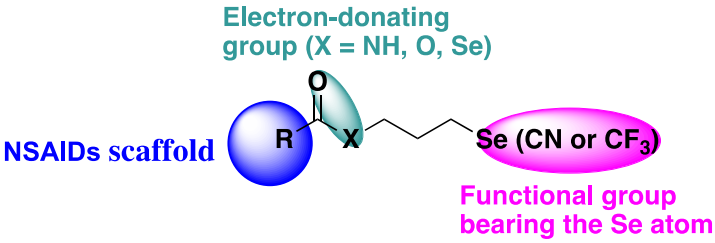


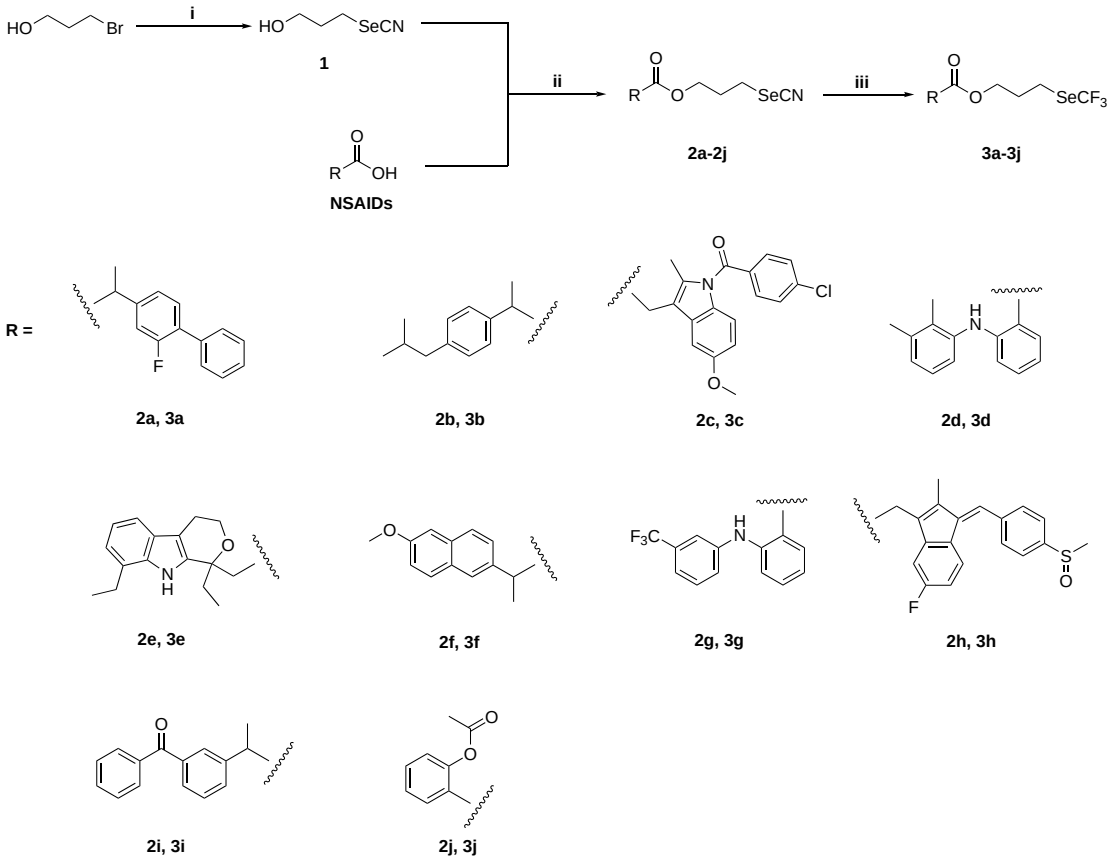
Fig. 2. General pattern of NSAIDs-Se derivatives with anticancer activity

2. Results and Discussion

2.1 Chemistry

The synthetic route for target compounds (**2a-2j** and **(3a-3j)** were prepared as outlined in Scheme **1** according to the procedure described in the literature with some modifications [30]. Compound **1** was obtained by the nucleophilic substitution of -Br atom in 3-bromo-1-propanol by -SeCN, using KSeCN as nucleophilic donor, in acetonitrile as solvent and under a nitrogen atmosphere. The selenocyanate derivatives **2a-2j** were readily obtained by reacting 3-selenocyanatopropan-1-ol with commercially available NSAIDs in the present of DCC and DMAP as condensation agent. The trifluoromethyl selenide derivatives were obtained by conducting corresponding selenocyanate derivative with trimethyl(trifluoromethyl)silane ($TMSCF_3$) in the present of tetrabutylammonium fluoride (TBAF) as catalyst to afford **3a-3j** in good yields (yield ≥ 80 %) (Scheme **1**) [31].

The purity of all final compounds was 95% or higher and their chemical structures were characterized using ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS (ESI).



Scheme 1. i) KSeCN, CH_3CN, 80 °C, 24 h, 90 %; ii) DCC, DMAP, DCM, 25 °C, 16 h 70% - 90%; iii) TBAF, $TMSCF_3$, THF, 25 °C, 2 h, 80 % - 85%.

2.2. Cell viability assay

The synthesized compounds (**3a, 3g** and **3i**) and selected patent NSAIDs (Aspirin, Ibuprofen and Naproxen) were evaluated for their anticancer activity towards human tumor cell lines: Caco-2 (human epithelial colorectal adenocarcinoma cell line), BGC-823 (human gastric cancer cell line), MCF-7 (human breast adenocarcinoma cell line) and PC-3 (human prostate cancer cell line). In vitro evaluation of anticancer activity was determined by the MTT assay. 5-Fluorouracil was used as positive control because it is commonly used in adjuvant and palliative cancer chemotherapy.

Overall, the IC_{50} values obtained and summarized in Table **1** shows that all of the tested organoselenium compounds exhibit growth inhibition in all cancer cell lines, while the selected patent NSAIDs (Aspirin, Ibuprofen and Naproxen) are inactive against all cells even in the maximum dose of 50 μM. The IC_{50} values obtained for the

NSAIDs-Se derivatives **2j**, **3b** and **3f**, showed that introduction of the -SeCN or -$SeCF_3$ moiety in corresponding parent NSAIDs scaffold result in the significant effect on cancer cell line.

An overview analysis of the IC_{50} values obtained and summarized in Table 1 showed that most of the NSAIDs-$SeCF_3$ derivatives presented better effectiveness than NSAIDs-SeCN derivatives and previous reported NSAIDs-diselenides derivatives against all four cancer cell lines [27]. Furthermore, the most active compounds of these two series are NSAIDs-$SeCF_3$ derivatives **3a**, **3g** and **3i**. These three compounds show IC_{50} values below 10 μM in all of tested cancer cell lines. Compound **3a** emerges the most potent agent with IC_{50} values below 5 μM in all cancer cell lines and with remarkable anticancer activity against BGC-823 (2.5 μM) and MCF-7 (2.7 μM).

Interestingly, among the tested compounds, most of the NSAIDs-$SeCF_3$ derivatives except **3f** and **3h** displayed IC_{50} values below 10 μM against MCF-7 cells. The anticancer activity of NSAIDs with trifluoromethyl selenides moiety is better than corresponding NSAIDs with selenocyanates moiety, considering the lipophilicity and electron withdrawing effect.

Table 1

Cytotoxic activity expressed by IC_{50} of NSAIDs-Se hybrid compounds (**2a**-**2j** and **3a**-**3j**) on different cancer cell lines.

Compound	**IC_{50}(μM)**[a]			
	Caco2	**BGC-823**	**MCF-7**	**PC-3**
Aspirin[b]	>50	>50	>50	>50
Ibuprofen[b]	>50	>50	>50	>50
Naproxen[b]	>50	>50	>50	>50
2a	27.5±3.1	29.4±3.3	22.4±2.1	19.7±1.8
2b	14.5±1.3	24.5±2.3	19.5±1.7	22.5±3.4
2c	32.4±3.5	35.5±3.4	29.3±1.9	21.8±1.6
2d	17.2±1.4	22.1±1.9	17.4±2.1	33.2±3.3
2e	11.5±1.1	21.4±2.3	14.4±1.3	31.4±3.0
2f	21.5±2.4	17.3±2.3	32.8±3.1	22±1.7
2g	8.4±0.8	13.7±1.2	14.2±1.1	7.5±1.3
2h	28.6±2.5	17.5±1.8	31.3±3.2	22.3±2.1
2i	19.7±2.0	12.6±1.4	8.3±0.7	12.6±1.5
2j	14.5±1.8	17.3±2.3	8.9±0.8	11.2±2.3
3a	4.5±0.6	2.5±0.4	2.7±0.2	3.3±0.3
3b	9.5±0.6	14.3±1.5	9.9±0.7	10.4±2.0
3c	10.5±1.1	7.3±0.5	9.3±0.7	7.8±0.7
3d	13.3±1.6	19.6±2.1	8.5±1.3	24.5±2.3
3e	10.4±1.3	18.5±1.7	8.7±0.7	19.7±1.9
3f	16.3±1.4	10.8±0.8	12.4±0.4	18.4±1.7
3g	3.5±1.8	2.7±1.8	4.2±1.8	5.8±1.8
3h	16.4±2.2	14.4±1.6	19.6±2.4	11.6±0.7
3i	9.5±1.1	4.8±0.3	6.5±1.8	8.8±1.3
3j	11.3±1.5	8.2±0.7	7.7±0.6	10.4±0.9
5-Fu[c]	7.8±3.1	15.4±1.8	12.3±2.2	9.5±1.1

[a] IC_{50} values (±SD) of % cell viability determined by the MTT assay of three repititions

[b] Patent NSAIDs

[c] Standard benchmark compound.

2.3. Detection of Bcl-2, IL-2 and caspase-8 protein expression levels in BGC-823 cells.

In order to further understand the possibly addressed signaling pathways and obtain hints on the mode(s) of action of the synthesized compounds, we selected the most promising derivatives **3a**, **3g** and **3i** and investigated their ability to induce

apoptosis in BGC-823 cells via modulation the expression of anti-apoptotic Bcl-2 protein, pro-inflammatory cytokines (IL-2) and proapoptotic caspase-8 protein.

As shown in **Fig 3**, all the three compounds were able to downregulate the expression of Bcl-2 and upregulate the expression of IL-2 and Caspase-3 in BGC-823 cells compared with untreated cells. Interestingly, compound **1g** downregulate over 50% the expression levels of Bcl-2 compared to untreated cells. Further more, compounds **1g** and **1h** modulate the Caspase-8 level at most 1.5 fold increase in expression when compared to the untreated control cells. From these results, it's likely that organic selenocyanates may induced apoptosis to inhibit tumor cells growth, and in line with the first selenocyanate (1,4-phenylenebis(methylene)selenocyanate) which proved to be effective against prostate and oral carcinoma cells [32, 33].

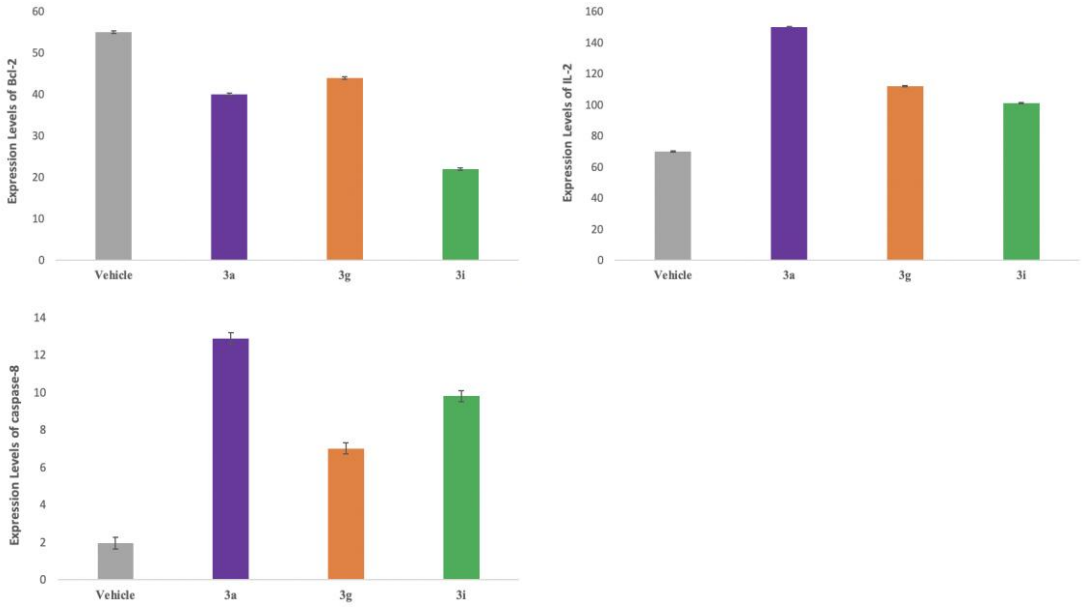


Fig. 3. Protein expression levels of Bcl-2, IL-2 and caspase-8 in BGC-823 cells after 48 h incubation with compounds **3a, 3g** and **3i** at their respective IC_{50}s compared to untreated cells.

2.4. Antioxidant assay

Reactive oxygen species (ROS) is a broad term that encompasses both oxygen free radicals, which have unpaired electrons, such as superoxide, hydroxyl and peroxyl as well as oxidizing agents that are not free radicals such as hydrogen peroxide, hypochlorous acid and ozone [34]. ROS play essential roles in altering

protein structure, thereby changing its function and participate in many pathological processes [35, 36]. Various human diseases, including different types of cancer, are associated with a disturbed intracellular redox balance and oxidative stress (OS) [37，38].

Owing to the fact that a number of synthetic organoselenium compounds have been synthesized for their use as redox-modulators in the last few years [39-41], the antioxidant activity of compounds (**3a**, **3g**, **3i**) are further estimated employing different biochemical assays such as DPPH, bleomycin-dependent DNA damage and Gpx-like assays [42, 43].

2.4.1. Radical scavenging capacity (DPPH) assay.

There are various methods which have been developed to provide fast prediction of antioxidant of natural compounds [44], however, the DPPH chemical assay is considered to be the rapid tools to evaluate the radical-scavenging activities of nutritional products and organic selenides [45]. The antioxidant activity of a compound is assessed by its ability to decolorize $DPPH^{\cdot}$ radical (purple color in methanol) to DPPHH (colorless) and the corresponding radical-scavenging activity is estimated by the decrease in the absorbance at 517 nm [46]. Vitamin C was used as a positive control (**Table 2**). Antioxidant activity was calculated as follows:

$$\%\ \text{Antioxidant activity} = [(\text{control absorbance} - \text{sample absorbance}) / \text{control absorbance}] \times 100\%$$

As depicted in **Table 2**, NSAIDs-$SeCF_3$ derivatives **3h** and **3i** were the most active compounds in this assay, demonstrating a good free-radical scavenging activity compared to Vitamin C. The family of NSAIDs-$SeCF_3$ derivatives is better than the corresponding NSAIDs-SeCN derivatives on this assay except for the compare of **2d** and **3d**.

2.4.2. Bleomycin DNA damage assay.

Bleomycin (BLM) is a complex of related glycopeptide from Streptomyces verticillus, it inhibits DNA metabolism and is used as an antineoplastic, especially for

solid tumors [47]. The bleomycin-iron DNA damage assay has been routinely used as a preliminary method to test potential of drugs and organic selenium compound [48, 49]. As shown in **Table 2**, compounds **3a**, **3g** and **3i** induced DNA degradation significantly more than other tested compounds.

Table 2

Redox modulation activity of NSAID-Se hybrid compounds.

Compd. No.	DPPH assay		Bleomycin-dependent DNA damage assay
	Inhibition %	Fold	Absorbance
Vitamin C	96.4±1.3	1	297±2.83
2a	17.2±1.4	0.2	86.5±0.54
2b	31.2±2.8	0.3	60.3±0.43
2c	44.3±36	0.4	72.4±0.33
2d	29.6±2.7	0.3	95.6±1.82
2e	30.4±1.4	0.3	69.4±0.42
2f	24.6±1.3	0.2	81.6±0.48
2g	51.5±1.2	0.5	76.1±0.39
2h	45.7±4.3	0.5	91.3±1.63
2i	57.1±4.3	0.6	67.6±1.83
2j	27.3±3.1	0.3	78.3±1.17
3a	73.5±4.1	0.8	119.4±1.78
3b	48.5±2.8	0.5	95.7±2.27
3c	36.6±2.2	0.4	62.6±1.18
3d	23.3±1.2	0.3	77.6±1.40
3e	41.4±2.2	0.4	86.4±1.21
3f	37.0±1.0	0.4	91.4±1.13
3g	68.6±2.6	0.7	114.8±2.32
3h	44.9±2.3	0.5	73.7±1.12

3i	66.3±2.6	0.7	128.4±1.38
3j	32.4±1.8	0.4	88.7±1.32

2.4.3. Glutathione peroxidase-like activity assay.

Glutathione peroxidase (GPx) is a selenoenzyme that protects cells by catalyzing the reduction of peroxides with the stoichiometric reductant glutathione (GSH) [50, 51]. The potential antioxidant activity of all of the NSAIDs-Se derivatives were estimated using NADPH-reductase coupled assay [52]. The GPx activity of the synthesized compounds was estimated by the decrease in absorbance (340 nm) due to the oxidation of NADPH to $NADP^+$. Ebselen was used as the positive control.

As shown in **Fig. 4**, compounds **2h**, **2i**, **3b**, **3e**, **3h** and **3i** displayed a GPx-like activity better than other derivatives. Compound **3h** was the most active derivatives in this assay, up to 3 fold to the GPx mimetic ebselen.

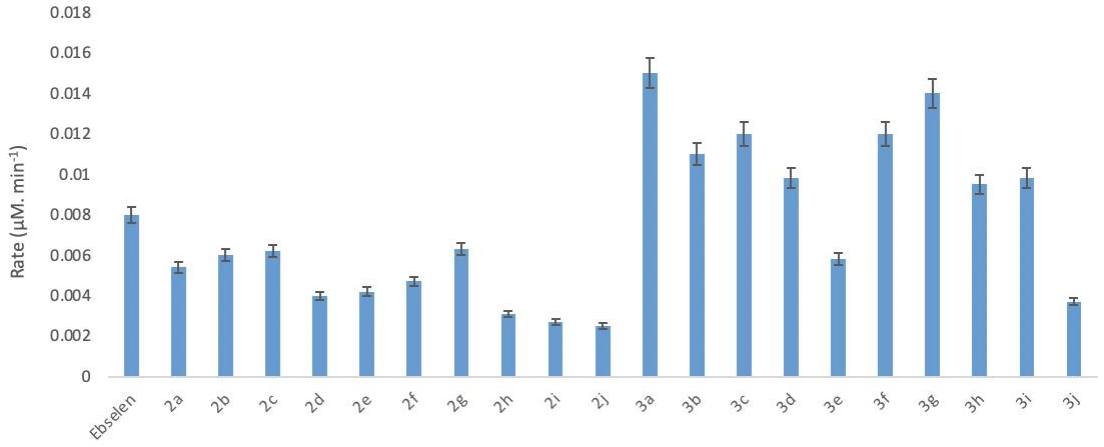


Fig. 4. GPx-like activity assay of NSAID-Se hybrid compounds in μM. Min^{-1}.

2.5. Docking Studies

The interaction mode between our organoselenium compounds and Mammalian TrxR1 protein, which is closely related to the anticancer activity of compounds, need to be further explained by docking studies. TrxR1 consists of four monimers which have the FAD and NAD binding domains at the N-terminal and the dimerization interface domain at the flexible C-terminal side [53-55]. In the insufficiency of human

3D structure complexes cocreytallized of human TrxR1 with inhibitors, flexible docking was considered to be a practical method according to the literature [56]. With good antioxidant activity, compounds **3a**, **3g** and **3i** were docked into the TrxR1 protein (PDB id: 1H6V) using Flexible Docking Protocol as reported in the literature [56]. All three compounds showed acceptable docking results (**Table 3-5** are reported in the supporting information). It is thought that the distance between the selenium atom and Cys497/Cys498 is closely related to the accessibility of cysteine thiol attacking the selenide. Therefore, for each structure, the selection of the best pose of the docking results is related to the value of binding energy, while the distance would also be focused. Among the three compounds, Pose 3 of **3a** showed a better docking results with the relatively good value of -CDOCKER energy (30.184 kcal/mol). Meanwhile, the distance between the selenium atom and Cys498 was only 4.388 Å (**Table 3,** Pose 3). This good result may be related to the key hydrogen bond interaction between the Fluorine on benzene group and His472 (2.11 Å). In addition, **3a** also formed two hydrogen bonds, which are the hydrogen bond between -$SeCF_3$ group and His472 (2.97 Å) and the hydrogen bond between the oxygens of ester groups and Cys475 (2.62 Å) (**Figure 5**). For compound **3g**, the interactions shown in pose 3 are not only the hydrogen bonds, but also a π-π stacking between the benzene ring and Phe406 (**Figure 6**). However, the distance between the selenium atom and Cys497/Cys498 is far than **3a** (**Table 4**). For **3i**, although there are multiple hydrogen bonds near the carbonyl group, the long distance between the selenium atom and Cys497/Cys498 may be related to the long linear structure of the whole compound (**Figure 7**, **Table 5**). This structure makes it difficult for molecule to penetrate into the pocket as a whole, thus affecting the interaction between molecule and protein.

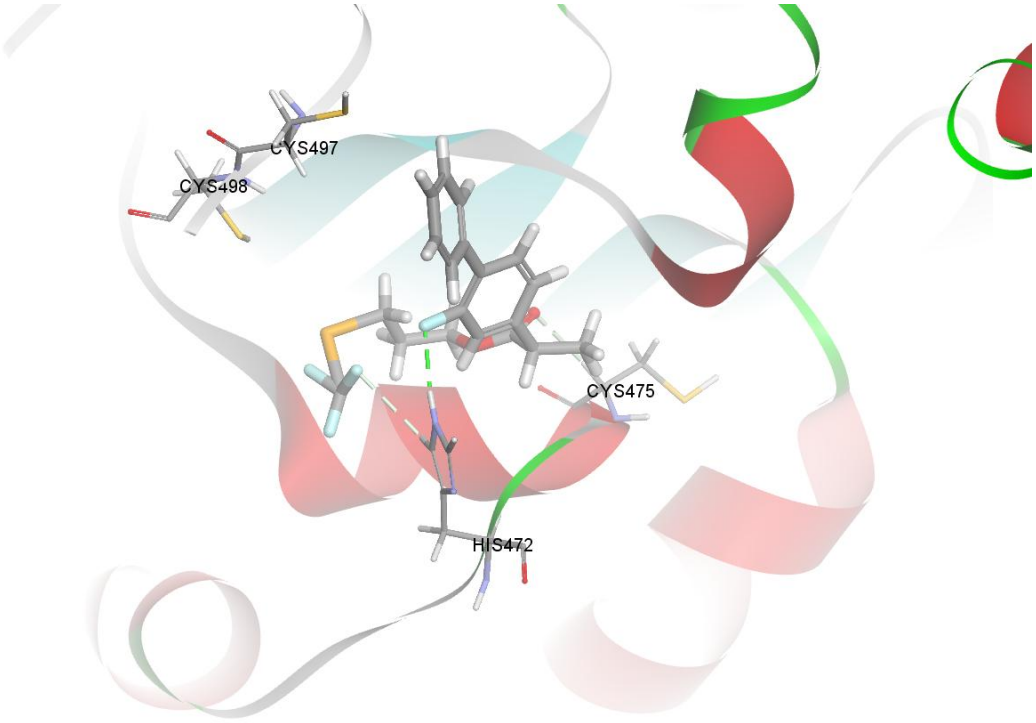


Fig. 5. The pose 3 of **3a**. Three interactions are shown: hydrogen bonding between the Fluorine on benzene group and His472 (2.11 Å); hydrogen bonding between the Fluorine of -SeCF3 group and His472 (2.97 Å) and hydrogen bonding between the oxygens of ester groups and Cys475 (2.62 Å).

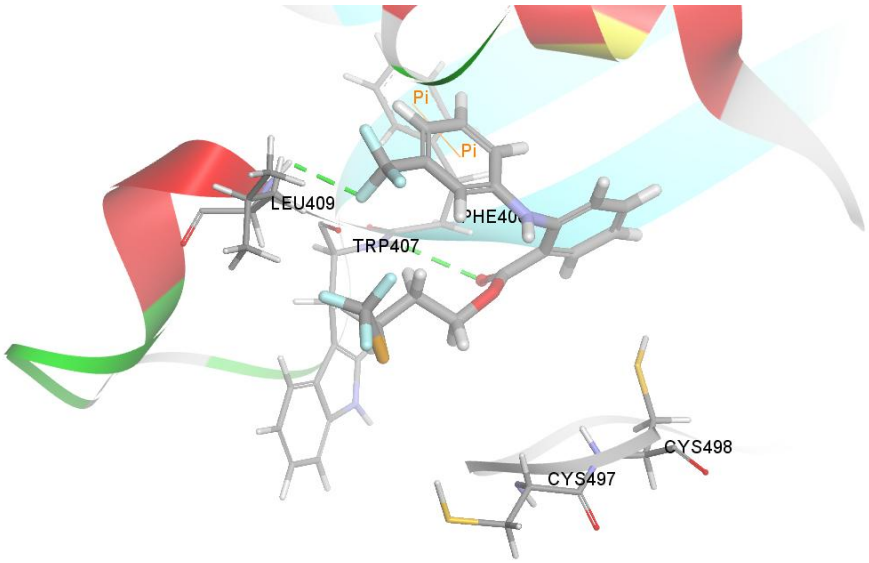


Fig. 6. The pose 3 of **3g**. Three interactions are shown: hydrogen bonding between the Fluorine of -CF3 group and LEU409 (2.57 Å); hydrogen bonding between the oxygens of ester groups and Trp407 (2.78 Å) and π-π stacking between the benzene ring and Phe406.

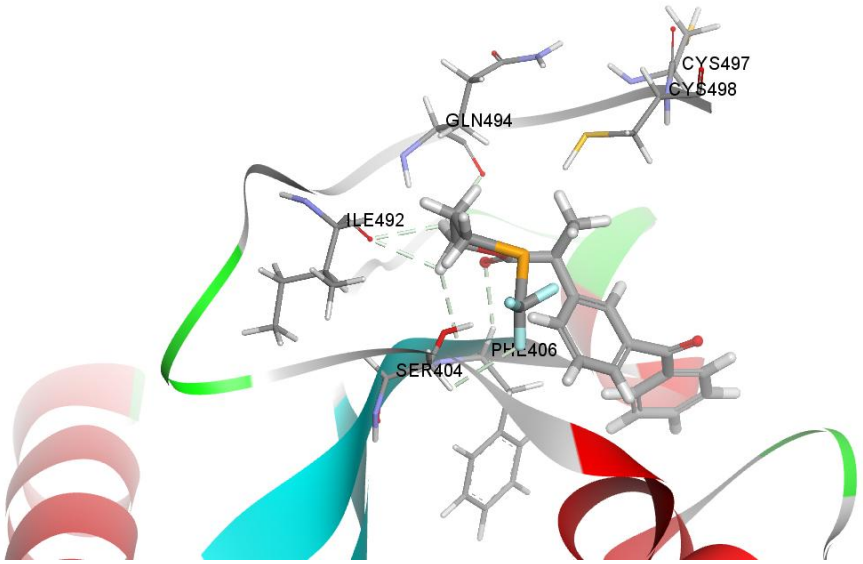


Fig. 7. The pose 4 of **3i**. Three interactions are shown: hydrogen bonding between the Fluorine of -SeCF3 group and Ser404 (2.80 Å); hydrogen bonding between the two hydrogens on carbonyl group α postion and Ile492 (2.54 Å, 2.64 Å) or Gln494 (2.90 Å); hydrogen bonding between the oxygens of ester groups and Phe406 (2.46 Å).

3. Conclusions

In summary, twenty new organoselenium compounds were synthesized and characterized. Four human cell lines (Caco-2, BGC-823, MCF-7 and PC-3) were selected to test anticancer activity of the compounds. Compound **3a** showed most potent anticancer activity with IC_{50} values below 5μm against four cancer cell lines. Moreover, three compounds were selected to test their ability to induce apoptosis in BGC-823 cells via modulation the expression of anti-apoptotic Bcl-2 protein, pro-inflammatory cytokines (IL-2) and proapoptotic caspase-8 protein. Compounds **3a**, **3g** and **3i** were able to downregulate the expression of Bcl-2 and upregulate the expression of IL-2 and Caspase-8 in BGC-823 cells. Furthermore, most of the organoselenium compounds exhibited moderate to good CPx-like activity compared to ebselen. Finally, in flexible docking study performed into TrxR1 enzyme, compound **3a** showed a promising binding energies and binding mode that the distance between the selenium atom and Cys497/Cys498. At this point, compound **3a** may act as TrxR inhibitors.

4. Experimental section

4.1. General methods

All chemical reagents for the synthesis of the compounds were purchased from Macklin (Shanghai, China) or TCI (Shanghai, China) and used without further purification unless stated otherwise. Thin-layer chromatography (TLC) was performed on aluminium pre-coated sheets (E. Merck Silica gel 60 F254). Melting points were recorded on an Electrothermal apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 MHz (for ^{1}H), 100 MHz (for ^{13}C) and 376 MHz (for ^{19}F) spectrometer with 5 mm PABBO probe. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS and the coupling constants (*J*) are expressed in Hertz (Hz). High-resolution MS were performed on a SCIEX，TripleTOF 5600+, operating in ionization mode.

4.2. Experimental procedures

*4.2.1. Procedure for the synthesis of compound **1***

To a solution of 3-bromopropan-1-amine hydrobromide (3g, 13.7 mmol) in anhydrous acetonitrile (40 mL) was added KSeCN (1.97 g, 13.7mmol). The mixture was stirred at 80°C for 24 hours. Then the mixture was cooled to 25°C and filtered. The filter cake was washed with acetonitrile (5mL×2) and dried under vacuum to obtain the brown solid 3.1g (Yield = 91%). The isolated solid was used without purification for further reactions.

*4.2.2. General procedure for the synthesis of compounds (**2a-2j**)*

To a solution of patent NSAIDs (1.0 eq) in DCM (5 mL) and DMF (5 mL) was added EDCI (1.2 eq.), HOBT (1.2 eq.) and TEA (3.0 eq.). The mixture was stirred at 25℃ for 30 minutes. Then 2-selenocyanatoethanamine hydrobromide (1.2 eq) or 2-selenocyanatopropanamine hydrobromide (1.2 eq.) was added into the mixture. The mixture was stirred at 25℃ for 16 hrs. TLC showed the reaction was complete. The

mixture was diluted with H_2O (20 mL), the aqueous layer was extracted with DCM (15 mL×2), the combined organic layer was washed with brine (20 mL×2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane /methanol solution to obtain the desire compound.

4.2.2.1.3-selenocyanatopropyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate **(2a)**. Yield: 78 %. White solid. Mp: 103-105°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J* = 8.00 Hz, -CH_3), 2.20-2.23 (m, 2H, -CH_2), 2.94-2.99 (m, 2H, -CH_2), 3.76 (q, 1H, *J* = 8.00 Hz, -CH), 4.23-4.24 (m, 2H, -CH_2), 7.09-7.15 (m, 2H, ArH), 7.37-7.43 (m, 4H, ArH), 7.46-7.54 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 25.7, 29.8, 45.0, 63.0, 101.1, 115.2 (d, *J* = 23.0 Hz), 123.5 (d, *J* = 3.0 Hz), 127.8, 127.9 (d, *J*= 14.0 Hz), 129.0, 128.9 (d, *J* = 2.0 Hz), 130.9 (d, *J* = 4.0 Hz), 135.3 (d, *J* = 2.0 Hz), 141.4 (d, *J* = 7.0Hz), 159.5 (d, *J* = 247.0 Hz), 173.8. HRMS calcd. For $C_{19}H_{18}FNO_2Se$ $[M+Na]^+$: 414.0385, found 414.0365 $[M+Na]^+$.

4.2.2.2. 3-selenocyanatopropyl 2-(4-isobutylphenyl)propanoate **(2b)**. Yield: 82 %. White solid. Mp: 97-99°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, 6H, *J* = 8.00Hz, 2-CH_3), 1.49 (d, 3H, *J* = 8.00Hz, -CH_3), 1.84 (q, 1H, *J* = 8.00Hz, -CH), 2.14-2.17 (m, 2H, -CH_2), 2.45 (d, 2H, *J* = 8.00Hz, -CH_2), 2.78-2.88 (m, 2H, -CH_2), 3.69 (q, 1H, *J* = 8.00 Hz, -CH), 4.12-4.27 (m, 2H, -CH_2), 7.10 (d, 2H, ArH), 7.18 (d, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 22.4, 25.7, 29.7, 30.2, 45.0, 45.1, 62.5, 127.1, 129.5, 137.6, 140.9, 174.6. HRMS calcd. For $C_{17}H_{23}NO_2Se$ $[M+Na]^+$: 376.0792, found 376.0770 $[M+Na]^+$.

4.2.2.3.3-selenocyanatopropyl2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3 -yl)acetate **(2c)**. Yield: 78 %. White solid. Mp: 110-112°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19-2.25 (m, 2H, -CH_2), 2.40 (s, 3H, -CH_3), 2.92-3.00 (m, 2H, -CH_2), 3.69 (s, 2H, -CH_2), 3.84 (s, 3H, -CH_3), 4.24-4.26 (m, 2H, -CH_2), 6.66 (d, 1H, *J* = 4.00 Hz, ArH), 6.86(d, 1H, *J* = 8.00 Hz, ArH), 6.93(s, 1H, ArH), 7.48 (d, 2H, *J* = 8.00 Hz,

ArH), 7.66 (d, 2H, *J* = 8.00Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 25.8, 29.7, 30.4, 55.8, 63.1, 101.2, 101.4, 111.5, 112.2, 115.1, 129.2, 130.5, 130.8, 131.2, 133.7, 136.1, 139.4, 156.0, 168.3, 170.7. HRMS calcd. For $C_{23}H_{21}ClN_2O_4Se[M+H]^+$: 505.0433, found 505.0400 $[M+H]^+$.

4.2.2.4. 3-selenocyanatopropyl 2-((2,3-dimethylphenyl)amino)benzoate

(2d). Yield: 80 %. White solid. Mp: 90-92°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H, $-CH_3$), 2.33 (s, 3H, $-CH_3$), 2.40-2.43 (m, 2H, $-CH_2$), 3.21-3.24 (m, 2H, $-CH_2$), 4.46-4.49 (m, 2H, $-CH_2$), 6.66 (t, 1H, *J* = 8.00 Hz, ArH), 6.74 (d, 1H, *J* = 8.00Hz, ArH), 7.03 (d, 1H, *J* = 8.00 Hz, ArH), 7.11-7.15 (m, 2H, ArH), 7.26-7.27 (m, 1H, ArH), 7.91 (d, 1H, *J* = 8.00 Hz, ArH), 9.20 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.6, 26.1, 30.1, 62.5, 101.2, 110.1, 113.8, 116.1, 123.2, 126.0, 127.0, 131.3, 132.6, 134.5, 138.3, 138.5, 149.8, 168.4. HRMS calcd. For $C_{19}H_{20}N_2O_2Se[M+H]^+$: 389.0768, found 389.0761 $[M+H]^+$.

4.2.2.5. 3-selenocyanatopropyl 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate

(2e). Yield: 85%. White solid. Mp: 130-132°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, *J* = 8.00Hz, $-CH_3$), 1.37 (t, 3H, *J* = 8.00Hz, $-CH_3$), 1.63 (s, 2H, $-CH_2$), 1.94-2.22 (m, 4H, 2-CH_2), 2.71-3.04 (m, 8H, 4×-CH_2), 3.93-4.06 (m, 2H, $-CH_2$), 4.18-4.30 (m, 2H, $-CH_2$), 7.01-7.09 (m, 2H, ArH), 7.36 (d, 1H, *J* = 8.00Hz, ArH), 8.78 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.7, 13.8, 22.3, 24.2, 25.6, 29.7, 31.0, 43.1, 60.7, 63.0, 74.7, 101.2, 108.7, 116.0, 119.8, 120.6, 126.2, 126.6, 134.5, 135.5, 172.3. HRMS calcd. For $C_{21}H_{26}N_2O_3Se[M+H]^+$: 435.1187, found 435.1165 $[M+H]^+$.

4.2.2.6. 3-selenocyanatopropyl 2-(6-methoxynaphthalen-2-yl)propanoate

(2f). Yield: 78%. White solid. Mp: 88-90°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3H, J = 8.00Hz, $-CH_3$), 2.11-2.18 (m, 2H, $-CH_2$), 2.76-2.90 (m, 2H, $-CH_2$), 3.83-3.88 (m, 2H, $-CH_2$), 3.92(s, 3H, $-OCH_3$), 4.15-4.26 (m, 1H, -CH), 7.15 (t, 1H, J = 8.00Hz, ArH), 7.37 (d, 1H, J = 8.00Hz, ArH), 7.65 (s, 1H, ArH), 7.71(d, 2H, J = 8.00Hz, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 25.7, 29.7, 45.2, 55.4, 62.7, 101.3, 105.6, 119.3, 126.0, 126.1, 127.3, 128.9, 129.2, 133.7, 135.4, 157.8, 174.5. HRMS calcd. For $C_{18}H_{19}NO_3Se[M+H]^+$: 378.0608, found 378.0596 $[M+H]^+$.

4.2.2.7. 3-selenocyanatopropyl 2-((3-(trifluoromethyl)phenyl)amino)benzoate **(2g)**. Yield: 77%. White solid. Mp: 121-123°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38-2.45 (m, 2H, -CH_2), 3.19-3.23 (m, 2H, -CH_2), 4.46-4.49 (m, 2H, -CH_2), 6.82 (t, 1H, *J* = 8.00Hz, ArH), 7.28-7.49 (m, 6H, ArH), 7.96 (d, 1H, *J* = 1.0Hz, ArH), 9.54 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 30.1, 62.9, 101.1, 112.3, 114.3, 118.2 (q, *J* = 4.0 Hz), 118.3, 119.8 (q, *J* = 4.0 Hz), 123.9 (q, *J* = 271.0 Hz), 124.9, 130.0, 131.6, 131.9 (q, *J* = 32.0 Hz), 134.7, 141.4, 147.1, 168.1. HRMS calcd. For $C_{18}H_{15}F_3N_2O_2Se[M+H]^+$: 429.0329, found 429.0318 $[M+H]^+$.

4.2.2.8. 3-selenocyanatopropyl (Z)-2-(5-fluoro-2-methyl-1-(4-(methylsulfinyl)benzylidene)-1H-inden-3-yl)acetate **(2h)**. Yield: 82%. White solid. Mp: 91-93°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21-2.26 (m, 2H, -CH_2), 2.22 (s, 3H, -CH_3), 2.82 (s, 3H, -CH_3), 3.00 (t, 2H, *J* = 8.00 Hz, -CH_2), 4.26 (t, 2H, *J* = 8.00 Hz, -CH_2), 6.56-6.61(m, 1H, ArH), 6.87 (d, 1H, *J* = 8.00 Hz, ArH), 7.15-7.18 (m, 2H, ArH), 7.67(d, 2H, *J* = 8.00 Hz, ArH), 7.72 (d, 2H, *J* = 8.00 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 25.7, 29.7, 31.8, 43.9, 63.2, 101.2, 105.9 (d, *J* = 24 Hz), 110.9 (d, *J* = 23 Hz), 123.8, 123.9, 128.6 (d, *J* = 2.0 Hz), 129.5 (d, *J* = 3.0 Hz), 130.3, 131.4 (d, *J* = 3.0 Hz), 138.4, 139.5, 141.5, 145.5, 146.5 (d, *J* = 9.0 Hz), 163.3 (d, *J* = 245.0 Hz), 170.1. HRMS calcd. For $C_{24}H_{22}FNO_3SSe[M+H]^+$: 504.0548, found 504.0528 $[M+H]^+$.

4.2.2.9. 3-selenocyanatopropyl 2-(3-benzoylphenyl)propanoate **(2i)**. Yield: 85%. White solid. Mp: 96-98°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, 3H, *J* = 8.00Hz, -CH_3), 2.18-2.21 (m, 2H, -CH_2), 2.94-2.98 (m, 2H, -CH_2), 3.82 (q, 1H, *J* = 8.00Hz, -CH), 4.21-4.25 (m, 2H, -CH_2), 7.43-7.54 (m, 4H, ArH), 7.61(t, 1H, *J* = 8.00 Hz, ArH), 7.67 (d, 1H, *J* = 8.00 Hz, ArH), 7.76(s, 1H, ArH), 7.80 (d, 2H, *J* = 8.00 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 25.7, 29.7, 45.4, 63.0, 101.2,

128.4, 128.6, 129.0, 129.2, 130.1, 131.4, 132.7, 137.4, 138.1, 140.7, 173.8, 196.4. HRMS calcd. For $C_{20}H_{19}NO_3Se[M+H]^+$: 402.0608, found 402.0588 $[M+H]^+$.

4.2.2.10. 3-selenocyanatopropyl 2-acetoxybenzoate **(2j)**. Yield: 90%. White solid. Mp: 117-118°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, -CH_3), 2.33-2.40 (m, 2H, -CH_2), 3.11-3.17 (m, 2H, -CH_2), 4.44-4.46 (m, 2H, -CH_2), 7.12 (d, 1H, *J* = 8.00Hz, ArH), 7.33 (t, 1H, *J* = 8.00Hz, ArH), 7.58 (t, 1H, *J* = 8.00Hz, ArH), 7.99 (d, 1H, J = 8.00Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 25.8, 30.0, 63.1, 101.3, 122.8, 123.9, 126.1, 131.5, 134.3, 150.7, 164.3, 169.8. HRMS calcd. For $C_{24}H_{23}FN_2O_2SSe[M+Na]^+$: 349.9908, found 349.9896 $[M+Na]^+$.

*4.2.3. General procedure for the synthesis of compounds **3a-3j***

To a solution of compound **2a-2j** (300 mg, 1.0eq.) in THF (10ml) was added TBAF (1 eq.) and $TMSCF_3$ (10 eq.). The mixture was stirred at 25℃ for 2 hours. TLC showed the reaction was completed. The mixture was concentrated under reduced pressure. The desire compound was purified by column chromatography on silica gel.

4.2.3.1.3-((trifluoromethyl)selanyl)propyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate **(3a)**. Yield: 80 %. White solid. Mp: 113-115°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J* = 8.00 Hz, -CH_3), 2.09-2.12 (m, 2H, -CH_2), 2.90-2.93 (m, 2H, -CH_2), 3.75 (q, 1H, *J* = 8.00 Hz, -CH), 4.20-4.22 (m, 2H, -CH_2), 7.13 (t, 2H, *J* = 8.00 Hz, ArH), 7.37-7.39 (m, 2H, ArH), 7.44 (t, 2H, *J* = 8.00 Hz, ArH), 7.53(d, 2H, *J* = 8.00 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 21.8, 29.4, 45.0, 63.6, 115.2 (d, *J* = 24.0 Hz), 122.5 (q, *J* = 329.0 Hz, -$SeCF_3$), 123.4 (d, *J* = 3.0 Hz), 127.7, 128.0 (d, *J* = 13.0 Hz), 128.5, 128.9 (d, J = 5.0 Hz), 130.9 (d, *J* = 4.0 Hz), 135.4, 141.5 (d, *J* = 7.0Hz), 159.7 (d, *J* = 247.0 Hz), 173.8. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.3 (s, -$SeCF_3$), -117.5 (s, F). HRMS calcd. For $C_{19}H_{18}F_4O_2Se$ $[M+H]^+$: 435.0486, found 435.0462 $[M+H]^+$.

4.2.3.2. 3-((trifluoromethyl)selanyl)propyl 2-(4-isobutylphenyl)propanoate **(3b)**. Yield: 82%. Yellow solid. Mp: 102-104°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, 6H, *J* = 8.00 Hz, 2-CH_3), 1.49 (d, 3H, *J* = 8.00Hz, -CH_3), 1.84 (q, 1H, *J* = 8.00Hz, -CH), 2.04-2.07 (m, 2H, -CH_2), 2.44 (d, 2H, *J* = 8.00Hz, -CH_2), 2.78-2.83 (m, 2H, -CH_2), 3.68 (q, 1H, *J* = 8.00Hz, -CH), 4.12-4.21 (m, 2H, -CH_2), 7.09 (d, 2H, ArH), 7.18 (d, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 21.8, 22.4, 29.4, 30.2, 45.0, 45.1, 63.1, 122.5 (q, *J* = 328.0 Hz, -$SeCF_3$), 127.1, 129.4, 137.6, 140.7, 174.6. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.3 (s, -$SeCF_3$). HRMS calcd. For $C_{17}H_{23}F_3O_2Se$ $[M+H]^+$: 397.0893, found 397.0883 $[M+H]^+$.

*4.2.3.3. 3-((trifluoromethyl)selanyl)propyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (***3c)**. Yield: 80%. White solid. Mp: 131-133°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09-2.15 (m, 2H, -CH_2), 2.40 (s, 3H, -CH_3), 2.91-2.95 (m, 2H, -CH_2), 3.68 (s, 2H, -CH_2), 3.84 (s, 3H, -CH_3), 4.20-4.23 (m, 2H, -CH_2), 6.67 (d, 1H, *J* = 4.00 Hz, ArH), 6.85 (d, 1H, *J* = 8.00Hz, ArH), 6.94 (s, 1H, ArH), 7.48 (d, 2H, *J* = 8.00 Hz, ArH), 7.66 (d, 2H, *J* = 8.00Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 21.9, 29.4, 30.3, 55.7, 63.7, 101.3, 111.6, 112.3, 115.0, 122.5 (q, *J* = 329 Hz, -$SeCF_3$), 129.2, 130.5, 130.8, 131.2, 133.9, 136.0, 139.3, 156.1, 168.3, 170.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.3 (s, -$SeCF_3$). HRMS calcd. For $C_{23}H_{21}ClF_3NO_4Se$ $[M+H]^+$: 548.0354, found 508.0305 $[M+H]^+$.

*4.2.3.4. 3-((trifluoromethyl)selanyl)propyl 2-((2,3-dimethylphenyl)amino)benzoate (***3d)**. Yield: 82%. White solid. Mp: 116-118°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H, -CH_3), 2.28-2.31 (m, 2H, -CH_2), 2.33 (s, 3H, -CH_3), 3.13-3.17 (m, 2H, -CH_2), 4.41-4.44 (m, 2H, -CH_2), 6.67 (t, 1H, *J* = 8.00 Hz, ArH), 6.75 (d, 1H, *J* = 8.00 Hz, ArH), 7.02 (d, 1H, *J* = 8.00 Hz, ArH), 7.10-7.15 (m, 2H, ArH), 7.23-7.27 (m, 1H, ArH), 7.93 (d, 1H, *J* = 8.00 Hz, ArH), 9.23 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.7, 22.2, 29.7, 63.1, 110.4, 113.8, 116.1, 122.6 (q, *J* = 328.0 Hz, -$SeCF_3$), 123.2, 126.0, 126.9, 131.3, 132.5, 134.4, 138.3, 138.6, 149.7, 168.5. ^{19}F

NMR ($CDCl_3$, 376 MHz): δ -34.2 (s, -$SeCF_3$). HRMS calcd. For $C_{19}H_{20}F_3NO_2Se$ $[M+H]^+$: 432.0611, found 432.0675 $[M+H]^+$.

*4.2.3.5. 3-((trifluoromethyl)selanyl)propyl 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (***3e)**. Yield: 82%. White solid. Mp: 127-129°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, *J* = 8.00 Hz, -CH_3), 1.37 (t, 3H, *J* = 8.00 Hz, -CH_3), 1.99-2.16 (m, 4H, 2×-CH_2), 2.75-3.04 (m, 8H, 4-CH_2), 3.93-4.06 (m, 2H, -CH_2), 4.18-4.30 (m, 2H, -CH_2), 7.01-7.07 (m, 2H, ArH), 7.36 (d, 1H, *J* = 8.00 Hz, ArH), 8.94 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.6, 13.8, 21.9, 22.4, 24.2, 29.3, 30.8, 43.0, 60.7, 63.6, 74.6, 108.6, 116.0, 119.7, 120.5, 122.5 (q, J = 329 Hz, -$SeCF_3$), 126.2, 126.6, 134.5, 135.7, 172.6. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.2 (s, -$SeCF_3$). HRMS calcd. For $C_{21}H_{26}F_3NO_3Se$ $[M+H]^+$: 478.1108, found 478.1089 $[M+H]^+$.

*4.2.3.6. 3-((trifluoromethyl)selanyl)propyl 2-(6-methoxynaphthalen-2-yl)propanoate (***3f)**. Yield: 85%. White solid. Mp: 125-127°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3H, *J* = 8.00Hz, -CH_3), 2.03-2.07 (m, 2H, -CH_2), 2.82-2.86 (m, 2H, -CH_2), 3.87 (q, 1H, *J* = 8.00 Hz, -CH), 3.91(s, 3H, -OCH_3), 4.16-4.19 (m, 2H, -CH_2), 7.12 (t, 1H, *J* = 8.00Hz, ArH), 7.38 (d, 1H, *J* = 8.00Hz, ArH), 7.65 (s, 1H, ArH), 7.70 (d, 2H, *J* = 8.00Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 21.8, 29.4, 45.4, 55.3, 63.3, 105.6, 119.1, 122.5 (d, *J* = 328.0 Hz, -$SeCF_3$), 125.9, 126.1, 127.2, 128.9, 129.3, 133.7, 135.5, 157.7, 174.6. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.3 (s, -$SeCF_3$). HRMS calcd. For $C_{18}H_{19}F_3O_3Se[M+Na]^+$: 443.0350, found 443.0337 $[M+Na]^+$.

*4.2.3.7. 3-((trifluoromethyl)selanyl)propyl 2-((3-(trifluoromethyl)phenyl)amino)benzoate (***3g)**. Yield: 80%. White solid. Mp: 99-101°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27-2.33 (m, 2H, -CH_2), 3.12-3.16 (m, 2H, -CH_2), 4.42-4.45 (m, 2H, -CH_2), 6.83 (t, 1H, *J* = 8.00Hz, ArH), 7.27-7.49 (m, 6H, ArH), 7.97 (d, 1H, *J* = 1.0Hz, ArH), 9.58 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 29.6, 63.5, 112.5, 114.3, 118.2 (q, *J* = 4.0 Hz), 118.3, 119.7 (q, *J* = 4.0 Hz),

122.6 (q, *J* = 328.0 Hz, -$SeCF_3$), 124.0 (q, *J* = 270 Hz, -CF_3), 124.7, 129.9, 131.6, 131.8 (q, *J* = 32.0 Hz), 134.5, 141.5, 147.0, 168.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.2 (s, -$SeCF_3$), -62.8(s, -CF_3). HRMS calcd. For $C_{18}H_{15}F_6NO_2Se$ $[M+H]^+$: 472.0250, found 472.0233 $[M+H]^+$.

*4.2.3.8. 3-((trifluoromethyl)selanyl)propyl (Z)-2-(5-fluoro-2-methyl-1-(4-(methylsulfinyl)benzylidene)-1H-inden-3-yl)acetate (***3h)**. Yield: 80%. White solid. Mp: 116-118°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10-2.13 (m, 2H, -CH_2), 2.21 (s, 3H, -CH_3), 2.82 (s, 3H, -CH_3), 2.94 (t, 2H, *J* = 8.00 Hz, -CH_2), 3.58 (s, 2H, -CH_2), 4.22 (t, 2H, *J* = 8.00 Hz, -CH_2), 6.55-6.60(m, 1H, ArH), 6.87 (d, 1H, *J* = 8.00 Hz, ArH), 7.14-7.18 (m, 2H, ArH), 7.67 (d, 2H, *J* = 8.00 Hz, ArH), 7.72 (d, 2H, *J* = 8.00 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5, 21.8, 29.3, 31.8, 43.9, 63.7, 105.9 (d, *J* = 23 Hz), 110.4 (d, *J* = 23 Hz), 122.5 (q, *J* = 328 Hz, -$SeCF_3$), 123.7 (d, *J* = 9.0 Hz), 123.8, 128.4 (d, *J* = 2.0 Hz), 129.5 (d, *J* = 3.0Hz), 130.3, 131.5 (d, *J* = 2.0Hz), 138.3, 139.6, 141.6, 145.5, 146.5 (d, *J* = 9.0 Hz), 163.3 (d, *J* = 245 Hz), 170.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.3 (s, -$SeCF_3$), -112.8(s, -F). HRMS calcd. For $C_{24}H_{22}F_4O_3SSe$ $[M+Na]^+$: 569.0289, found 569.0263 $[M+Na]^+$.

*4.2.3.9. 3-((trifluoromethyl)selanyl)propyl 2-(3-benzoylphenyl)propanoate (***3i)**. Yield: 85%. White solid. Mp: 87-89°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, 3H, J = 8.00Hz, -CH_3), 2.05-2.12(m, 2H, -CH_2), 2.87-2.89 (m, 2H, -CH_2), 3.82 (q, 1H, *J* = 8.00Hz, -CH), 4.19-4.21 (m, 2H, -CH_2), 7.43-7.59 (m, 4H, ArH), 7.60 (t, 1H, *J* = 8.00 Hz, ArH), 7.67 (d, 1H, *J* = 8.00 Hz, ArH), 7.76 (s, 1H, ArH), 7.79 (d, 2H, *J* = 8.00 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 21.8, 29.4, 45.4, 63.5, 122.5 (q, *J* = 329.0 Hz, -$SeCF_3$), 128.4, 128.6, 129.1, 129.2, 130.1, 131.4, 132.6, 137.4, 138.0, 140.7, 174.0, 195.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.2 (s, -$SeCF_3$). HRMS calcd. For $C_{20}H_{19}F_3O_3Se$ $[M+H]^+$: 445.0530, found 445.0491 $[M+H]^+$.

*4.2.3.10. 3-((trifluoromethyl)selanyl)propyl 2-acetoxybenzoate (***3j)**. Yield: 80%. White solid. Mp: 104-106°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23-2.28 (m, 2H, -CH_2),

2.35 (s, 3H, -CH_3), 3.07-3.10 (m, 2H, -CH_2), 4.38-4.41 (m, 2H, -CH_2), 7.11 (d, 1H, *J* = 8.00 Hz, ArH), 7.30-7.57 (m, 1H, ArH), 7.58-7.60 (m, 1H, ArH), 7.99 (d, 1H, *J* = 8.00 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 22.0, 29.6, 63.7, 122.6 (q, *J* = 328 Hz, -$SeCF_3$), 123.0, 123.9, 131.6, 134.1, 150.8, 164.3, 169.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -34.2 (s, -$SeCF_3$). HRMS calcd. For $C_{13}H_{13}F_3O_4Se$ $[M+H]^+$: 392.9829, found 392.9827 $[M+H]^+$.

4.3. Cell lines and culture conditions

Four human cancer cell lines Caco-2, BGC-823, MCF-7 and PC-3 cells were maintained in RPMI 1640 medium with 10% fetal bovine serum (FBS) and 100 units/mL of penicillin and streptomycin (Thermo Fisher Scientific, shanghai, China) at 37 °C and 5% CO_2 in a humidified atmosphere. Cells were passaged at preconfluent densities, using a solution containing 0.05% trypsin and 0.5 mM EDTA. Human cancer cell lines Caco-2, BGC-823, MCF-7 and PC-3 used in this work were obtained from the American Type Culture Collection (ATCC, Manassas, VA).

All the tested NSAIDs-Se derivatives were evaluated in vitro for their antitumor activity against four cancer cell lines by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay according to the method as described before [57-58]. Exponentially growing cells were harvested and plated in 96-well plates at a concentration of 1×104 cells / well. After 24 h incubation at 37 °C under a humidified 5% CO_2 to allow cell attachment, the cells in the wells were respectively treated with target compounds at various concentrations for 24 h, 48 h and 72 h. The concentration of DMSO was always kept below 1.25%, which was found to be non-toxic to the cells. Three hours prior to experiment termination, MTT solution (20 μL of 5.0 mg/mL solution) was added to each well and incubated at 37°C. At the termination time point, the medium/MTT mixtures were removed, and the formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in 100 μL of DMSO per well. The optical densities were measured at 570 nm using a 96-well multiscanner (Dynex Technologies, MRX Revelation; Chantilly, VA, USA).

4.4. Detection of Bcl-2, IL-2 and caspase-8 protein expression levels

Bcl-2, IL-2 and capase-8 levels were evaluated in BGC-823 cells treated with the corresponding IC_{50}s of each compound and incubated for 48 h and compared with their levels in control untreated BGC-823 cell line. The cells were harvested by applying trypsin and lysed by freezing with liquid nitrogen and then thawing with gentle mixing and the total proteins were isolated. Protein levels of the anti-apoptotic marker Bcl-2 were then measured using enzymelinked immunosorbent assay (ELISA) according to the manufacturers' instructions (Merck, USA). Enzyme-linked immunosorbent assay was used for quantitative detection of IL-2 and caspase-8 (Platinum ELISA). The reaction product was detected at 450 nm using enzyme-linked immunosorbent assay (Platinum ELISA; Merck) according to the instructions of the manufacturer.

4.5. DPPH free radical scavenging activity

DPPH free radical scavenging activity of corresponding compounds was measured according to the method as previous reported with little optimization [59]. Briefly, 20 mL of test samples at different concentrations was mixed with 180 mL of or DPPH solution for 30 min in the dark. Then, the change in absorbance at 517 nm for DPPH was measured on a microplate reader. Ascorbic acid (vitamin C) and ebselen were used as a positive control, DMSO was used as a negative control.

4.6. Bleomycin-dependent DNA damage

The reaction mixture contained DNA (0.5 mg/mL), bleomycin sulfate (0.05 mg/mL), $MgCl_2$ (5 mM), $FeCl_3$ (50 mM), and tested compound in a conc. of 0.1 mg/mL. L-ascorbic acid was used as positive control. The mixture was incubated at 37°C for 1h. The reaction was terminated by addition of 0.05 mL EDTA (0.1 M). The color was developed by adding 0.5 mL TBA (1% w/v) and 0.5 mL HCl (25% v/v), followed by heating at 80°C for 30 minutes. After cooling in ice water, the extent of DNA damage was measured by increase in absorbance at 532 nm [60].

4.7. Glutathione peroxidase-like activity

GPx kit (Biodiagnostic, Egypt) was used for the determination of GPx according to Paglia et al [61]. The reaction mixture contained 1ml assay buffer (50mM phosphate buffer containing 0.1% Triton X-100) and 0.1ml NADPH reagent (24 mmol Glutathione, 12 unit Glutathione reductase and 4.8 mmol NADPH) and 0.01ml (41 mM) tested compounds and the reaction was started by the addition of H_2O_2 (0.8 mM). The contents were mixed well and the absorbances were recorded at 340 nm over a period of 3 min against deionized water. The change of absorbance per minute (A340 nm/min) was estimated using ebselen (41 mM) as positive control. The values represented in Fig 3 are expressed after background correction for the reaction with H_2O_2 and GSH. In case of colored compounds, their activities were estimated after subtracting their own absorbances at the used wave length.

4.8. Molecular Modeling

4.8.1 Protein and Ligand Preparation

Prepared by Protein Preparation Wizard in Maestro 11.5 (Schrödinger, LLC, New York, NY, 2019.), the Mammalian TrxR1 protein (PDB ID: 1H6V) was obtained from Protein Data Bank. The other subunits were deleted and only one monomer F was retained. Next, subunits F was assigned in sequence, hydrogen was added, ionization and tautomerism were adjusted, hydrogen bond distribution was optimized, water was removed, and structure was minimized. The LigPrep utility in Maestro 11.5 was used to perform ligand preparation applying OPLS2005 force field. Generation of tautomers and possible ionization states was mediated by Epik utility, followed by minimization of the resulting 3D comformations.

4.8.2 Ligand Docking

The docking task was completed on Discovery Studio Client 3.1. and the binding site of TrxR1 was defined as a docking sphere with dimensions X: 27.757, Y: 6.510, Z: 33.698 and a radius of 15 Å. Before using Flexible Docking Protocol, TrxR1

protein was typed in CHARMm field force. 10 protein conformations were generated with a maximum alteration of 8 residues.

Under the conformation method FAST, every ligand were generated 25 conformations with the value of 20 kcal in the energy threshold. With all other parameters as default, three ligands were docked into protein structure in the Flexible Docking Protocol. For each poses, the distance between the compound's selenium atom and the sulfur atom of either Cys497 or Cys498 was calculated by the distance monitor in the Discovery Studio. For each ligand, average -CDocker energy and average selenium-sulfur distance were calculated. The hydrogen bond interaction and π-π stacking between the compounds and protein were analyzed.

Statistical analysis

Data were given as mean ± SD of three independent experiments, graphs and curve fitting were using origin Version 8.0 (OriginLab Corporation, Northampton, USA). P value less than 0.05 was considered statistically significant.

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