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New Selenoderivatives as Antitumoral Agents

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1. Introduction

Prostate cancer (PC) is the most common male malignancy in Western countries and the second most common urological malignancy (Knudsen & Vasioukhin, 2010). In 2008 the estimated new cases for PC in the European Union were 382.000 (Ferlay et al. 2010). The possibility of early detection is attractive to clinicians and potential patients in spite of the fact that until recently concrete evidence that screening would influence PC mortality was lacking (Schröder, 2010). There are many risk factors for PC occurrence. The family history, genetic and environmental factors and their interaction can contribute to develop PC (Colloca & Venturino, 2011). Other risk factors are age, ethnic-racial-geographic factors, named constitutional factors, though it is not possible to know what percentage of these neoplasms are a result of these risk factors (Ferris-i-Tortajada et al. 2011). The polymorphisms in genes associated with PC probably represent the most part of familial PC burden. The recent advances in genomic research have made it possible to identify several new genomic based biomarkers for PC. These markers are easy to measure and stable over time but only one biomarker, prostate specific antigen (PSA), is used in the clinical today (Aly et al. 2011). The PSA screening allows to detect PC years before the emergence of clinically evident disease, which usually represents locally advanced or metastatic cancer (Gjertson & Albertsen, 2011). Treatment options for advanced PC – including hormone ablation therapy, radiation and surgery – do not offer cure but delay the inevitable recurrence of the lethal hormone-refractory disease. Chemotherapy using available anticancer drugs, with the exception of the taxane drug docetaxel, for late stage PC does not offer any survival benefit. All of these treatments are costly and have significant side effects including impotence and incontinence, which negatively affect the quality of life of the patients. Prevention is an important strategy for limiting PC morbidity and mortality. Pharmacological and dietary interventions have potentials functions in reduction of incident cases and in inhibition of disease progression and recurrence (Silberstein & Parsons, 2010). 5-alpha reductase inhibitors remain the predominant therapy to reduce the future risk of a PC diagnosis. Dutasteride and finasteride are currently the only proven agents for PC risk reduction (Strope & Andriole, 2010). Among the potential dietary intervention efforts to use of the micro-nutrient selenium (Se) in PC clinical trials is emerging as an important highlight and the outcomes indicate that Se is a promising treatment. Furthermore, Se inhibits PC through multiple mechanisms, and it is beneficial in controlling the development of this disease (Abdulah

et al. 2011). Se is an essential trace element for humans, animals and some bacteria and it is important for many cellular processes, cardiovascular disease, central nervous system pathologies and may prevent cancer (Dennert et al. 2011). The evidence that Se is a cancer preventive agent includes that from geographic, animal, prospective and intervention studies (Tabassum et al. 2010, Schmid et al. 2011).

Furthermore, literature reports have consistently shown that the different effects of different chemical forms and dose of Se (Algotar et al. 2011) on signaling and expression of transcripts in PC cells might have important implications in the outcome of ongoing PC prevention clinical trials. These include the forms of Se present in the diet and in the body, their functions and mechanisms of action, and methods employed in assessing an individual's Se nutritional status – both in general and in epidemiological studies into the risk of cancer in relation to diet, as well as in connection with long-term trials for investigating the disease-preventive potential of selenium supplementation. Several mechanisms have been suggested to mediate the anticancer effects of Se. The major ones are reduction of DNA damage; oxidative stress; inflammation; induction of phase II conjugating enzymes that detoxify carcinogens; enhancement of immune response; incorporation into selenoproteins; alteration in DNA methylation status of tumor suppressor genes; inhibition of cell cycle and angiogenesis and induction of apoptosis. The specific mechanisms for PC are the inhibition of androgen receptor (AR) signaling, reduction in the mRNA, and protein levels of the AR, recruitment of corepressors to the AR elements in the promoters of androgen responsive genes, inhibition of signaling pathways like NF-$_k$B, IL-6, Stat3, and induction of apoptosis (Nadiminty & Gao, 2008) (Figure 1).

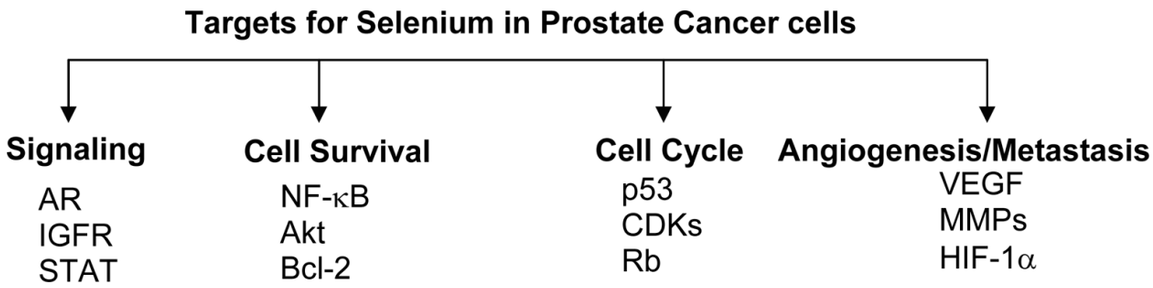


Fig. 1. Schematic representation of cellular processes targeted by Se and some specific molecular targets in each pathway. Figure from Nadiminty & Gao, 2008 with permission from John Wiley and Sons.

The rapid advance in the knowledge of different selenoproteins and their biological functions has opened up new possibilities to increase our understanding of the biological effects of Se supplementation (Rebsch et al. 2006). Selenoprotein deficiency leads to the accelerated development of lesions associated with PC progression, implicating selenoproteins in cancer risk and development and raising the possibility that Se prevents cancer by modulating the levels of these selenoproteins. Recently, it has been reported that the new discovered selenoprotein, SEP15, which is highly expressed in the prostate, may play a role either independently or by modifying the effects of Se in PC survival (Penney et al. 2010). Moreover, further research and additional trials of this type are needed to define the benefits and risks of different types and doses of Se supplements that in the future may be implemented for public health reasons. Another necessary focus for future research is a better understanding of the mechanisms by which Se interferes with the carcinogenic

processes. The direction of future studies lies in clarifying the effects of these products and exploring the biological mechanisms responsible for the prevention of prostate cancer (Fairweather-Tait et al. 2011). This chapter includes information on twenty eight general chemical structures containing Se that have shown either anticancer, chemopreventive or apoptotic activities. Thus, Se derivatives emerge as promising downstream candidates for cancer therapy.

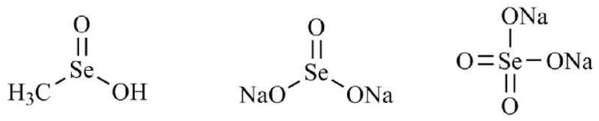
2. Selenoderivatives against prostate cancer

2.1 Methylseleninic acid, sodium selenite and sodium selenate

Some studies have shown that the selenium-based compound methylseleninic acid (MSeA, Figure 2) can disrupt AR signaling in PC cells by reaction with reduced glutathione within the PC cell (Husbeck et al., 2006). On the other hand, it was observed that a combination of MSeA with bicalutamide produced a robust downregulation of PSA through the identification of *hTERT*/telomerase as an important AR target. Telomerase activation has been reported in >90% of prostate cancer samples, but not in normal or benign prostatic hyperplasia tissues. Telomerase activation play an essential role in cell survival and oncogenesis, and inhibition of telomerase has been shown to suppress growth and tumorigenic potential of PC (S.A. Liu et al., 2010). Other mechanisms have demonstrated that the growth inhibitory effect could be attributed to cell cycle modulation and apoptosis induction provoked by MSeA by activation the forkhead box O1 (FOXO1) (H.T. Zhang et al., 2010). This compound has shown efficacy in transgenic adenocarcinoma of mouse prostate model (Wang et al., 2009). Too, it has been investigated in mice model treated with this Se form and were observed changes in its proteome (Zhang et al., 2011). In addition, MSeA exerted a dose-dependent inhibition of DU145 xenograft growth without genotoxic properties (Li et al., 2008). Moreover, in advanced and hormone refractory prostate cancer the efficacy of MSeA is based on down regulating hypoxia inducible factor 1α (HIF-1α) accompanied of a reduction of vascular endothelial growth factor (VEGF) and glucose transporter 1 (GLUT1) (I. Sinha et al., 2011). On the other hand, MSeA inactivated protein kinase C (PKC), particularly the promitogenic and prosurvival epsilon isoenzyme, acting through a redox modification of vicinal cysteine sulfhydryls in the catalytic domain of PKC (Gundimeda et al., 2008). Some metabolites of MSeA such as methylselenol may contribute to their anticancer activities. For example, an upregulation of cyclin dependent kinase inhibitor (CDKI) proteins p21Cip 1 and/or p27Kip 1 was observed in DU145 prostate cancer cells (Wang et al., 2010). Too, a novel mechanism of Se action has been proposed for methylselenol due to its ability to inhibit histone deacetylase (HDAC) (Kassam et al., 2011). Recently, speciation analysis showed that MSeA was completely transformed during the incubations while metabolic conversion of the other Se compounds was limited (Lunoe et al., 2011).

Sodium selenite (Figure 2) is another compound that has been studied in relation to PC and it may modulate the androgen receptor through the repression of interleukin-6 (IL-6) (Gazi et al., 2007). Too, it was observed that selenite decreased HDAC activity and increased levels of acetylated lysine 9 on histone H3, but decreased levels of methylated H3-Lys 9 (Xiang et al., 2008). Other mechanisms of action have been postulated such as an increase of the activity of the tumor suppressor protein (PTEN) and of the thioredoxin reductase (TR) (Berggren et al., 2009). Too, selenite is able to induce cell death and apoptosis by production of superoxide in mitochondria in LNCaP cells (Xiang et al., 2009). In 2010 was reported that

sodium selenite inhibited the lipopolysaccharide (LPS)-induced TLR4-NF-kB signaling in PC-3 (Pei et al., 2010). Sodium selenite can act alone or in combination with other treatments for PC. So, this compound significantly enhances the effect of radiation on well established hormone-independent prostate tumors and does not sensitize the intestinal epithelial cells to radiation. These results suggest that may increase the therapeutic index of radiation therapy (Tian et al., 2010). In addition, the effectiveness on PC treatment of the association between sodium selenite and docetaxel has resulted as a new strategy in PC therapeutic approach (Freitas et al., 2011). Too, combination of genistein and selenite has shown synergistic effects on apoptosis, cell cycle arrest associated signaling pathways in p53 expression (Zhao et al., 2009). Actually, other inorganic forms of Se as sodium selenate (Figure 2), where Se is in oxidation state + 6, are in Phase I studies and have shown antiangiogenic properties (Corcoran et al., 2010).



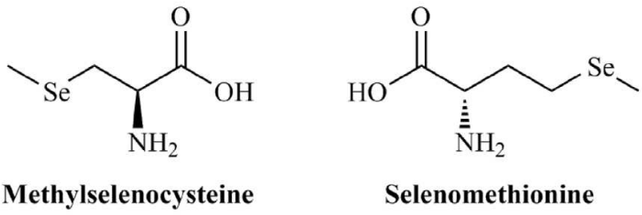
Methylseleninic acid **Sodium selenite** **Sodium selenate**

Fig. 2. Methylseleninic acid, sodium selenite and sodium selenate structures.

2.2 Methylselenocysteine and selenomethionine

Se may exert its beneficial effects through incorporation into selenoproteins including, glutathione peroxidases, selenoprotein P, iodothyronine deiodinases and thioredoxin reductases. There are more than 30 selenoproteins that have been identified in humans and they are involved in a range of cellular functions including immune function and protection against lipid and DNA damage. The cancer preventive mechanisms of action of methylselenocysteine (MeSeCys) (Figure 3) in human prostate cells are variable. A mechanism of action proposed for MeSeCys is that can alter the expression of several types of collagen gene and protein expression and thus may impact on the extracellular matrix and alter prostate cell progression and invasion (Hurst et al., 2008). Other authors affirm that the effect is due to methylselenol, a metabolite active in a study carried out in the transgenic adenocarcinoma mouse prostate model by oral administration of MeSeCys (J. Zhang et al., 2010). This hypothesis has been reinforced and completed in 2011 with the inclusion of new metabolites, the α-keto acids analogues of MeSeCys (Pinto et al., 2011). Related to selenomethionine (SeMet) (Figure 3) one of the mechanism that is gaining interest is the HDAC inhibition by metabolites of SeMet accompanied of redox signaling proteins modulation (J.I. Lee et al., 2009). Too, in combination with genistein induced growth arrest with modulation of expression of matrix metalloproteinase-2 (MMP-2) (Kumi-Diaka et al., 2010). On the other hand, this compound has been employed in order to reduce the toxic effects of di(2-ethylhexyl)phthalate (DEHP), an abundant plasticizer environmental contaminant that causes alterations in endocrine and spermatogenic functions mediated by induction of reactive oxygen species (ROS) and activation of nuclear p53 and p21 proteins in LNCaP cells. The SeMet supplementation reduced ROS production with modulation of intracellular redox status that is related to response against testicular toxicity (Erkekoglu et al., 2011). If we consider the possibility of combination between SeMet and other compound for modulating PC development the results are drug dependent. So, SeMet

and alpha-tocopherol do not inhibit prostate carcinogenesis in the testosterone plus estradiol treated NBL rat model (Ozten et al., 2010). However, the selected combination of silymarin and SeMet significantly reduced two markers of lipid metabolism known associated with PC progression (Vidlar et al., 2010). In order to improve the activity and safety inorganic and organic hybrid nanoparticles are potentially useful in biomedicine, mainly for tumor treatments (Choi et al., 2010). Se nanoparticles are safer compared with SeMet isolated and was observed an inhibition of the growth of prostate LNCaP cancer cells partially through caspases mediated apoptosis, Akt kinase modulation and by disrupting AR (Kong et al., 2011).



Methylselenocysteine **Selenomethionine**

Fig. 3. Methylselenocysteine and selenomethionine structures.

2.3 Selenocyanate derivatives

The first selenocyanate described was 1,4-phenylenebis(methylene)selenocyanate (*p*-XSC) (Figure 4). The most recent studies postulate that this compound is capable of altering cofilin-2, single-stranded mitochondrial DNA binding protein, chaperonin 10, nucleoside diphosphate kinase 6 and chain A Horf 6 human peroxidase enzyme in LNCaP cells and in its androgen independent clone (AI) (R. Sinha et al., 2008). Too, this compound can induce apoptosis, inhibits AR expression and decreases Akt phosphorylation (Facompre et al., 2010). Other organic selenocyanates have emerged during the last years. So phenylalkyl isoselenocyanates (Figure 4), isosteric selenium analogues of naturally occurring phenylalkyl isothiocyanates, have shown a reduction in tumor size associated to apoptosis. The structure activity relationship studies concluded that an increase in the alkyl chain length is critical for the activity being n = 4, named ISC-4, the optimal (Sharma et al., 2008). In 2011, these same authors have reported that ISC-4 activates prostate apoptosis response protein 4 (Par-4) (Sharma et al., 2011). As a continuation of the synthesis of novel alkyl selenocyanates in 2010 was described the synthesis of substituted naphthalimide based organoselenocyanates (Figure 4) with the alkyl chain length n = 5 and investigated their systematic toxicity profile in mice by consideration changes in body weight, hepatotoxicity and nephrotoxicity resulting less toxic than other selenium forms but retaining the efficacy (Roy et al., 2010). Numerous studies have been conducted to elucidate the mechanism underlying the antitumor effects associated with cyclooxygenase 2 (COX-2) inhibitors. However, this mechanism has not yet been clearly defined. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to retard the progression of PC in men and NSAIDs have been used in clinical trials for prostate cancer. Celecoxib (Celebrex), a specific COX-2 inhibitor, reduces prostate tumors in experimental models mainly through cell cycle regulation and angiogenesis. However, the growth inhibitory properties of Celecoxib may be COX-2 independent. Considering this possible effect a novel strategy

has been proposed based on to combine selenium and COX-2 inhibitor. Considering that sulfonamide moiety and pyrazole ring are important for the proapoptotic activity of Celecoxib against PC, the Selenocoxib-1 (Figure 4) was synthesized. The structural modifications introduced were the replacement of the trifluoromethyl group by methyleneselenocyanate fragment and the elimination of the methyl group. The study carried out against PAIII cells derived from a metastatic prostate tumor that arose spontaneously in a Lobund-Wistar (LW) rat. In addition, human metastatic prostate cancer cells, PC-3M, were tested for antitumor effect of Selenocoxib-1 *in vitro*. Selenocoxib-1 induced apoptosis in a dose-dependent manner in the PAIII cells and resulted more effective against PC than Celecoxib (Desai et al., 2010a). Other modulations have been introduced maintaining the methyl group in order to obtain Selenocoxib-2 (Figure 4) but it has not been studied as antitumoral yet (Desai et al., 2010b).

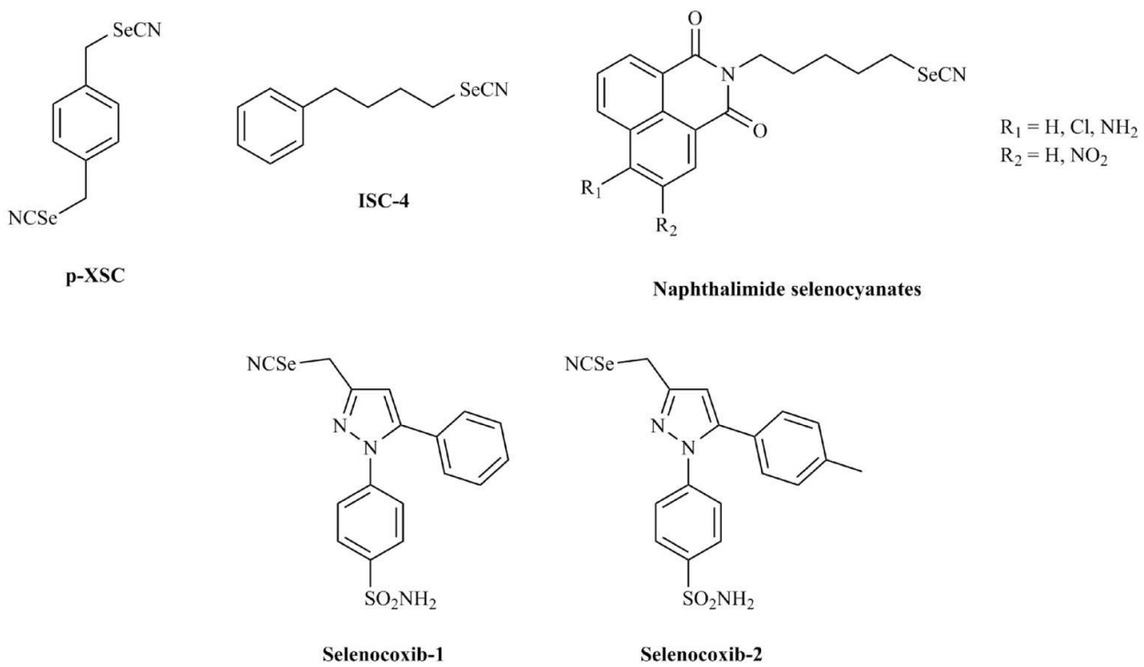


Fig. 4. Chemical structures for selenocyanate derivatives.

2.4 Heterocycles containing selenium

Ebselen (Figure 5) is one of the most relevant heterocyclic compounds derived from selenium. Ebselen is a glutathione peroxidase mimetic seleno-organic compound that attenuates the H_2O_2 level. In this process a hydroxylamine spin trap reacts with oxygen-centered radicals, including superoxide. It was seen that this compound blocked the expression of the disintegrin and metalloprotease ADAM9 in LNCaP or C4-2 PC cells through inhibition of ROS production (Sung et al., 2006). In other studies Ebselen was used as an external agent for reverting biochemical processes such as glycolysis. For example, ABC transporters like P-glycoprotein (P-gp/ABCB1), that are membrane proteins responsible for the transport of toxic compounds out of non-malignant cells and tumor

tissue can be modified in their expression by coincubation with ebselen (Wartenberg et al., 2010). Too, it has been used for protecting PC-3 cells against apoptosis induction provoked by curcumin, a potent anticancer agent (Hilchie et al., 2010). On the other hand, ebselen has been reported as a covalent inactivator of α-methylacyl coenzyme A racemase (AMACR), a metabolic enzyme whose overexpression has been shown to be a diagnostic indicator of prostatic adenocarcinoma and other solid tumors and has been employed as reference drug for screening of approximately 5000 unique compounds as AMACR inhibitors (Wilson et al., 2011). In structural relation with ebselen is the organoselenium compound 1,2-bis-[1,2-benzisoselenazolone-3(2*H*)-ketone]ethane (BBSKE) (Figure 5), which has shown an inhibitory effect on the growth of a variety of human cancer cells, provokes S phase arrest accompanied by increases in the protein levels of cyclin A, E and p21 and decreases in levels of cyclin B1, D1 and Cdk4 (Shi et al., 2003a, 2003b). A recent study carried out in rats affirms that the metabolites of BBSKE can act as antitumoral agents (Zhou et al., 2010). Too, in association with cisplatin increases the sensitivity of the colon cancer cell line LoVo towards cisplatin via regulation of G_1 phase and reversal of G_2/M phase arrest (Fu et al., 2011). The formulation as copolymer micelles allows the accumulation into tumor efficiently due to an increase in water solubility (M. Liu et al., 2010).

D-501036, 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-*N*-methylpyrrole (Figure 5), has been identified as a novel antineoplastic agent with a broad spectrum of antitumoural activity against several human cancer cells and has an IC_{50} value in the nanomolar range. This compound induces cell death associated with the DNA damage-mediated induction of ataxia telangiectasia-mutated activation without interfering with topoisomerase-I and topoisomerase-II function (Juang et al., 2007). Another mechanism that has been proposed for the activity of D-501036 is angiogenesis inhibition. Although anti-angiogenesis strategies have generated a great deal of enthusiasm for therapeutic applications, it is still unknown whether these systems would be feasible for prevention. The possibility of interfering very early in tumour progression by modulating the cancer angiogenic switch is appealing, though there is increasing evidence for close correlation between inflammation, the micro-environment and tumour-associated neo-angiogenesis causing the adverse outcomes of prostate cancer (Araldi et al., 2008).

In 2010, a new series of heterocyclic organoselenium compounds were synthesized and evaluated as possible chemopreventive agents in human prostate cancer LNCaP cells. Two of this 3-selena-1-dethiacephem derivatives (Figure 5) strongly activated nuclear factor E2-related factor 2 (Nrf2)/ antioxidant response element (ARE) signaling that regulate expression of phase II antioxidant and detoxifying enzymes such as glutathione peroxidase (GPX), γ-glutamylcysteine synthetase (γ-GCS), heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase (NQO-1), and glutathione S-transferase (GST) expression. These two compounds also possessed a potent antioxidant activity. Furthermore, both compounds were capable of inhibiting cell growth via cell cycle arrest. Related to structure activity relationship the presence of the exo-olefin (carbon–carbon double bond) as well as the aliphatic substitution at the imine part is critical for these compounds to activate Nrf2/ARE signaling (Terazawa et al., 2010). Other interesting derivatives are 2-substituted selenazolidine-4(*R*)-carboxylic acids (Figure 5). There are numerous studies that concern the induction of a protective hepatic enzyme related to gluthathione-S-tranferase and gluthathione peroxidase and it seemed of interest to evaluate these compounds in PC cells (El-Sayed et al., 2007, Poerschke & Moos 2011).

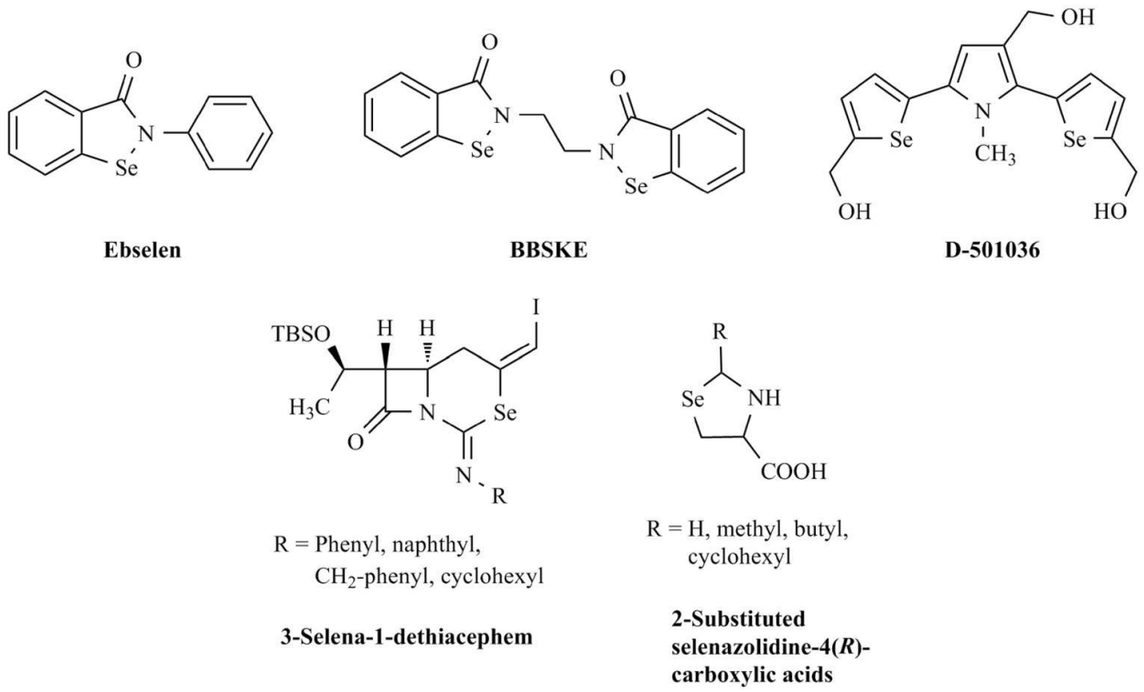


Fig. 5. Chemical structures for heterocycles containing selenium.

2.5 Selenide and diselenide derivatives

The selenide function is present in a lot of organoselenium compounds. Many of the above described derivatives possess this type of bond (i.e. MeSeCys, SeMet,). One compound does not described in the above sections is *p*-xylylbis(methylselenide) (*p*-XMS) (Figure 6), a organoselenium compound that modifies the growth, secretion of PSA and the intracellular redox status and genomic profiles (Pinto et al., 2007). Too, the selenide function is present linked to nucleosides. The natural nucleosides may be used as Se-carriers. The synthesis and antitumor activity of novel nucleosides derivatized from uridine and thymidine (Figure 6), with a selenomethyl group at various positions has been described. In general, the activity against PC cells is position-dependent. Compounds with the selenomethyl group in position 5′ are more active than the corresponding in 2′ or 3′. The probable explanation is that it is easier to metabolize the Se-nucleoside containing the primary selenomethyl than the secondary selenomethyl, thereby generating more methylselenol (Lin et al., 2009). The natural products continue to be a rich source of new promising substances for cancer therapy. Sesquiterpene lactones (SQLs) are a class of naturally occurring plant terpenoids of Asteraceae family, known for their various biological activities such as cytotoxicity against different tumor cell lines. Many authors have linked this activity mainly to the α-methylene-γ-lactone functionality, which is prone to react with suitable nucleophiles, e.g., sulfhydryl groups of cysteine, in a Michael addition mechanism. These reactions are nonspecific, leading to the inhibition of a large number of enzymes or factors involved in key biological in spite of it is well known, however, that the α-methylene-γ-lactone moiety is not an absolute requirement for cytotoxicity. In this context emerge other interesting compounds such as the alpha-santonin derivatives (Figure 6) a sesquiterpene lactone isolated from *Artemisia santonica*. The compounds with higher activity showed as common structural

feature the presence of an alpha-methylidene-gamma-butyrolactone moiety in their structures (Arantes et al., 2009). This hypothesis has been corroborated in other tumoral cell lines. In addition, the bioactive α-santonin derivatives are selective against cancer cells (Arantes et al., 2010).

It is well established that various human diseases, including PC, are associated with a disturbed intracellular redox balance and oxidative stress (OS). Se based agents (Figure 6) turn the oxidizing redox environment present in certain cancer cells into a lethal cocktail of reactive species that push these cells over a critical redox threshold and ultimately kill them through apoptosis. The main advantage is that this kind of toxicity is highly selective: normal, healthy cells remain largely unaffected, since changes to their naturally low levels of oxidizing species produce little effect though the biochemical pathways triggered by these agents need to be studied in more detail such as redox modulator like cysteine-containing Bcl proteins, which control apoptosis at an early stage, certain caspases, which execute apoptotic mechanisms further downstream, are also redox sensitive (Jamier et al., 2010).

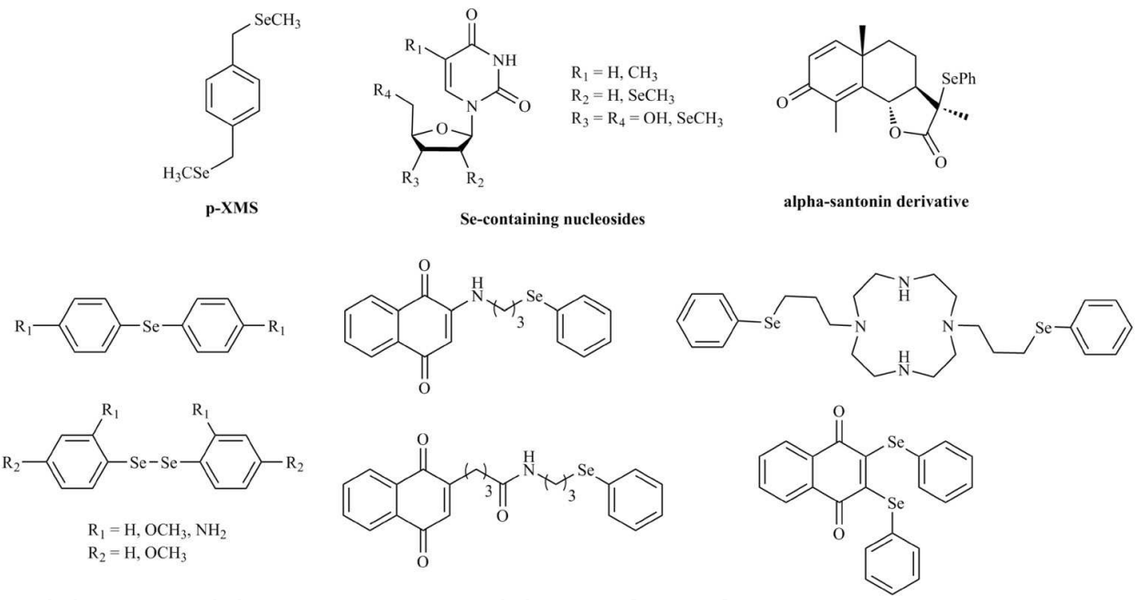
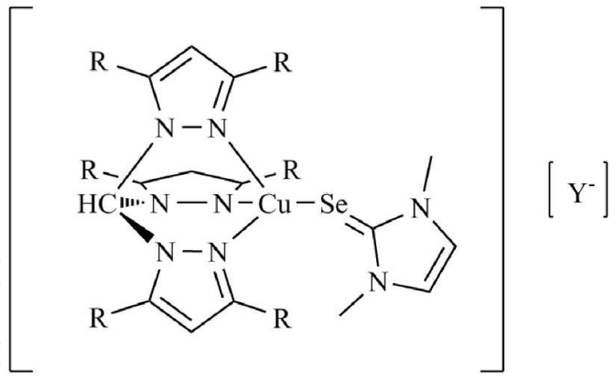


Fig. 6. Chemical structures for selenide and diselenide derivatives.

2.6 Selenium and metal complexes

Selenium- and sulfur-containing compounds have been widely studied as potential antioxidants for the prevention or reduction of oxidative DNA damage and the organoselenium compounds are of particular interest because they appear to be more bioavailable relative to inorganic Se compounds. The Se and sulfur antioxidant activity has been explained using copper-mediated DNA damage studies and UV-vis spectroscopy that have allowed identifying a copper coordination through a novel metal bond. For this reason has been described the synthesis of relevant copper selone complexes with tris(pyrazolyl)methane or tris(pyrazolyl)borate ligands (Figure 7) (Kimani et al., 2010). The determination of redox potential for Cu-Selone complexes indicated that Se coordination to copper in biological systems may prevent the reduction of Cu^{2+} by NADH required for the catalytic formation of damaging hydroxyl radical.



Y = BF_4, Cl
R = H, Me, *i*-Pr

Fig. 7. Chemical structure for Cu-Selone complexes. Reprinted with permission from Kimani et al., 2010. Copyright 2010 American Chemical Society.

2.7 A case study: Novel selenoderivatives as cytotoxic agents and apoptosis inducers in prostate cancer cells

In the last four years, several articles have been published by our research group related to the design, synthesis and biological evaluation of novel compounds containing Se as cytotoxic agents and apoptosis inducers. In addition, mounting evidence suggests that selenium (Se) works by inhibiting important early steps in carcinogenesis in a variety of experimental models and the anticancer activity is dependent on the chemical form of selenium. Se occurs in both organic and inorganic forms. Based on these findings we envisaged a new investigation that involves the synthesis of new compounds that incorporate the Se-containing moiety.

2.7.1 Structures and biological results

Initially, the rationale behind the design of these compounds was to maintain molecular symmetry, a structural property that is frequently present in cytotoxic and pro-apoptotic drugs (Sanmartín et al., 2006). The structures synthesised correspond to molecules with a central nucleus made up of an alkyl imidothiocarbamate (alkyl isothiourea) or alkyl imidoselenocarbamate (alkyl isoselenourea) connected by a carbonyl group on each side to two identical lateral aromatic or heteroaromatic rings mono, bi or polycyclics (Figure 8). The sulfur and selenium substituents were varied (methyl, ethyl, benzyl and isopropyl) to determine the effect of the alkyl chain length and the ramifications that this has on the activity (Plano et al., 2007, Ibáñez et al., 2011). The best results in PC-3 were obtained for the compound with X = Se, Y = C, R = CH_3 and R' = 4-CH_3. This compound was the most potent (IC_{50} = 1.85 µM) and was 4.5 times more active than standard methylseleninic acid (IC_{50} = 8.38 µM) and 7.3 times more active than etoposide (IC_{50} = 13.6 µM), an agent used in the treatment of PC. In addition, the novel compound was less toxic than the reference and apoptotic inducer in MCF-7 and CCRF-CEM. For the heteroaromatic rings thienyl and quinolinyl were the most interesting. During the course of our work a great number of different structural classes of selenocompounds were reported (Sanmartín et al., 2008). For

this reason, and in order to improve the potency of our compounds, we decided to introduce some structural modifications. Among these modifications was the preparation of new compounds with related structures based on aroyl and heteroaroyl selenylacetic acid derivatives (Figure 8). The most promising derivatives against PC-3 cancer cells were the corresponding phenyl, 3,5-dimethoxyphenyl and benzyl with TGI values of 6.8, 4.0 and 2.9 μM (Sanmartín et al., 2009). Too, there is current interest in heterocyclic compounds that contain a Se atom in the ring. Bearing this fact in mind, and as a continuation of our previous work, we proposed the synthesis 1,2,5-selenadiazolo[3,4-*d*]pyridines and 1,2,5-benzoselenadiazolo derivatives (Figure 8). The most promising molecule was a pyridine derivative (Plano et al., 2010b). Other explored structures were compounds with selenocyanate and diselenide moieties. Moreover, we evaluated their antioxidant-prooxidant properties so as their cytotoxic activities against PC-3 resulting eighteen of the fifty-nine compounds evaluated more potent than etoposide (Plano et al., 2010a). Taking into account that oxidation state for Se is related to antitumoral effect we have synthesized and evaluated an original series consisting of a small group of compounds which possess Se in the +4 states oxidation instead of Se +2 (Figure 8) (Plano et al., 2010a).

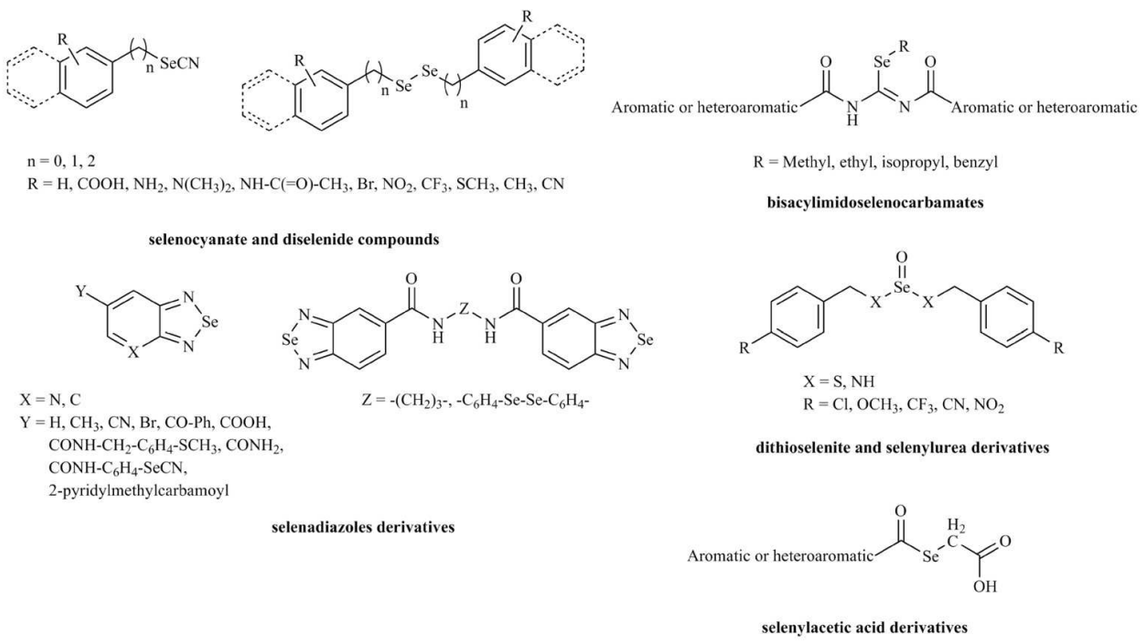


Fig. 8. Selenoderivatives obtained and evaluated by our research group.

Considering that Se has been associated with an anticancer effect via the modulation of some kinase such as Akt (J.H. Lee et al., 2008) some of these compounds have been studied as kinase modulators. Some of them modulate CK1A and GS3Ka expression and a weak modification in ErB4, GS3Ka and PKCA was detected (unpublished results).

The preliminary results from the biological screening of these novel compounds are very encouraging and these systems could offer an excellent framework in this field and may

ultimately lead to discovery of potent antitumour agent. Thus, the search for new drugs with Se continues to be a great challenge in medical science.

3. Conclusion

It is clear from the studies discussed above that Se compounds do have effects on growth, cell cycle and apoptosis and that such compounds offer great promise as anticancer and apoptotic agents in many tumoral processes, mainly for PC. In this chapter we have summarized information on more than twenty eight structures that contain Se – most of which were published in the last three years – and possess cytotoxic activity against PC. This list of compounds and references is by no means exhaustive and merely hints at the hundreds of other citations due to the ever increasing amount of work carried out in this field. As a result of these studies, Se derivatives are rapidly emerging as valid chemotherapeutic agents. However, various organic and inorganic selenium compounds used in some studies have produced variable results when they are tested in animal models and human subjects and more investigations are urgently needed in order to ascertain the safety in their use. We have included some structures that have not yet been evaluated in prostate cancer cells because we believe that the study of these compounds would be of interest. Although several possible mechanisms have been proposed to explain the anticancer and apoptotic properties of selenium compounds, the results described here suggest the following preliminary considerations:

1. The chemical form is a determinant factor for the activity and the metabolism is required for anticarcinogenic activity.
2. The effect of some selenium compounds mainly depends on the dose and the oxidation state of selenium. For inorganic selenium compounds the +4 oxidation state gives the highest anticarcinogenic properties and for organic selenium compounds the activity is mainly observed for the +2 oxidation state.
3. The existence of diverse responses for the same chemical structure suggests several mechanisms of action. For example, sodium selenite induced apoptosis by redox processes, decreased HDAC activity, increased of PTEN activity. The expectation of a broad therapeutic benefit from agents that target only one member of either pathway may be overly simplistic due to the complex interrelated network governing apoptosis.
4. Experimental evidence shows that molecular symmetry, as a broad concept, could be a positive factor for cancer prevention and apoptosis (sodium selenite, methylseleninic acid, *p*-XSC, *p*-XMS, BBSKE). The importance of molecular symmetry in cytotoxic and pro-apoptotic activities was reported by us in 2006. Recently, we described a new series of symmetrical organoselenium compounds that are potent as cytotoxic agents in prostate cancer cells.

This class of compound offers a great deal of promise to broaden significantly the horizons of modern apoptosis and anticancer drug discovery for the potential treatment of prostate cancer. Animal data, epidemiological data, and intervention trials have shown a clear role for selenium derivatives in both the prevention of specific cancers and antitumourigenic effects in postinitiation phases of cancer through apoptosis induction. Accordingly, in recent years there has been substantial interest directed toward the synthesis of selenium-containing derivatives that could be used as cytotoxic, cancer chemopreventive and apoptotic agents. However, a great deal of further research is needed to unravel the precise manner in which selenium compounds act.

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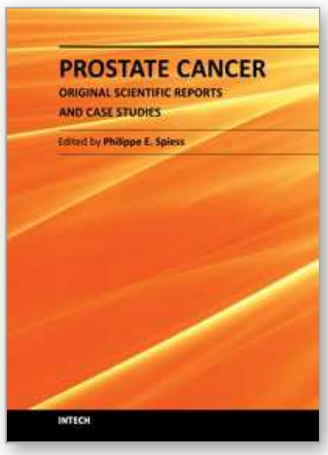
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This book encompasses three sections pertaining to the topics of cancer biology, diagnostic markers, and therapeutic novelties. It represents an essential resource for healthcare professionals and scientist dedicated to the field of prostate cancer research. This book is a celebration of the significant advances made within this field over the past decade, with the hopes that this is the stepping stone for the eradication of this potentially debilitating and/or fatal malignancy.

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