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Synthesis, isomerization and biological activity of novel 2-selenohydantoin derivatives

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ABSTRACT

A set of novel selenohydantoins were synthesized via a convenient and versatile approach involving the reaction of isoselenocyanates with various amines. We also revealed an unexpected *Z*→*E* isomerization of pyridin-2-yl-substituted selenohydantoins in the presence of Cu^{2+} cations. The detailed mechanism of this transformation was suggested on the basis of quantum-chemical calculations, and the key role of Cu^{2+} was elucidated. The obtained compounds were subsequently evaluated against a panel of different cancer cell lines. As a result, several molecules were identified as promising micromolar hits with good selectivity index. Instead of analogous thiohydantoins, which have been synthesized previously, selenohydantoins demonstrated a relatively high antioxidant activity comparable (or greater) to the reference molecule, Ebselen, a clinically approved drug candidate. The most active compounds have been selected for further biological trials.

1. Introduction

Elemental selenium was discovered in 1817 by Berzelius.[1] Till recently, Se-containing compounds have mainly been out of practice within the field of organic synthesis, medicinal chemistry, enzymology and bioinorganic chemistry mainly due to a widespread myth that they are highly toxic and should be classified as biological poisons rather than drug-like molecules even in anticancer therapeutic area. However, the myth was completely discredited by the discovery of Se-containing enzymes, such as glycine reductase,[2] glutathione peroxidase,[3] thioredoxin reductase,[4] kinases,[5] and others. Among a wide number of available organoselenium compounds at least two molecules are currently evaluated in clinics as promising neuroprotectants and antioxidants, including Ebselen by Sanofi and Sound Pharmaceuticals[6] as well as anticancer agents, including L-selenomethionine and Se-methylselenocysteine by National Cancer Institute (Fig. 1).[7,8] Selenoxocib-1,[9] ISC-4,[10,11] EI-201[12] and other compounds[13–16] presented in Figure 1 are being evaluated in preclinical studies against various pathologies. Molecules from this group have been shown to exert relevant anti-proliferative and pro-apoptotic activity against a huge number of cancer cell types, immune and endothelial cells. They also prevent drug resistance and enhance chemotherapy/radiotherapy efficacy.[17–19] Moreover, Se-containing compounds were shown to effectively block some angiogenic factors thereby suppressing cancer-associated angiogenesis.[20–22] They have also been demonstrated to inhibit crucial signaling pathways and proteins deeply implicated in cancer grow and progression; these include: calcium-insensitive nitric oxide synthase and mitogen-activated protein kinase,[18] Akt3 kinase and histone deacetylases[23] as well as melanin biosynthesis by melanocytes.[24] For instance, Ebselen is now undergoing Phase II clinical trial for the prevention and treatment of noise-induced hearing loss, and chemotherapy-induced hearing loss in advanced

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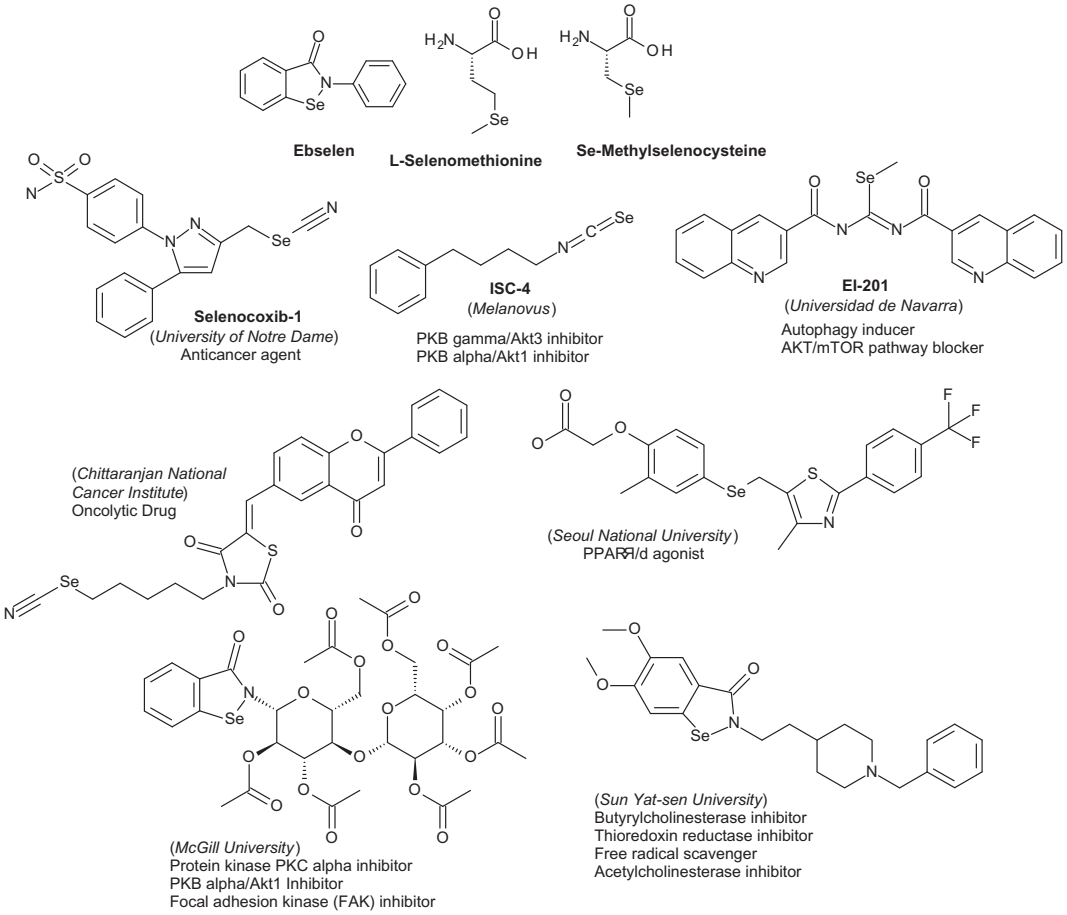

Figure 1. Representative examples of physiologically active Se-containing compounds.

stage cancers.[25] The drug candidate has also been studied at Daiichi Pharmaceutical for the oral treatment of subarachnoid hemorrhage and acute stroke, but was discontinued for this indication due to undisclosed reasons. Ebselen can be reasonably regarded as a multimodal drug-candidate that inhibits the activity of an extensive range of enzymes including NADPH oxidase and protein kinase C,[15] focal adhesion kinase and RAC-alpha serine/threonine-protein kinase,[15] lactate dehydrogenase,[26] thioredoxin-disulfide reductase,[27] glutaminase[28] and hexokinase,[29] histone deacetylases,[30] etc.

Recently, we have synthesized and evaluated a series of novel non-trivial binuclear mixed valence Cu(I,II) complexes containing 2-alkylthio-5-arylmethylene-4*H*-imidazolin-4-ones.[31] Several compounds showed a prominent anticancer activity against different cell lines reducing predominantly telomerase activity. Therefore, one of the key points of the presented paper lies in the evaluation of Se-contained analogs of thiohydantoins described previously to assess their catalytic activity as GPx mimetics as well as anticancer potency compared to the parent S-containing molecules.

Reactive oxygen species (ROS) including free radicals, superoxide anion and hydroperoxide are byproducts in the endogenous cellular metabolism. The excessive formation of ROS is commonly related with the degradation of biomolecules, for example, membrane components and can therefore be associated with chronic inflammation,[32] neurodegenerative disorders,[33] cancer[34,35] and other diseases. In recent years there has been much interest in developing new, more potent antioxidants such as Ebselen, that also acts as glutation peroxidase mimetics[36] and is due to be released for human application.

Initially, we mainly focused on the synthesis of novel 2-selenohydantoins whereas analogous thiohydantoins as well as their complexes were targeted for biological evaluation. As we revealed several types of in vitro activity for thiohydantoins, we also evaluated Se-containing series described herein. In spite of the evident therapeutic potential of Se-containing compounds the synthetic routes towards this class of molecules are mainly limited. Thus, in the most cases 2-selenohydantoins were synthesized by the reaction of aryl- or alkyl isoselenocyanates with amino acid esters.[37] The classical approach to organic isoselenocyanates involves the addition of selenium to isonitriles or the synthesis from the corresponding formamides.[38,39] In addition, other synthetic pathways were reported for the title class of compounds, however, almost all of these methods required sodium selenide, phosphorous selenide or other rare selenium reagents.[40,41] It should be especially noted that isoselenocyanates are valuable reagents for the synthesis of selenium-containing heterocycles, and only one disadvantage is the availability and stability of these reagents. Herein, we report the synthesis, isomerization and biological activity of novel 2-selenohydantoin derivatives.

2. Results and discussion

We have recently reported an efficient and versatile approach for the synthesis of various 3-substituted 5-arylidene-2-thiohydantoins, based on the condensation of thiourea with aromatic and heteroaromatic aldehydes.[42] A convenient work-up procedure, providing good to high yields, the possibility of using the available and less expensive amines instead of isothiocyanates for the