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Synthesis of amphiphilic seleninic acid derivatives with considerable activity against cellular membranes and certain pathogenic microbes

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HIGHLIGHTS

- Synthesis of seleninic acid based redox modulators with amphiphilic properties.
- Surface tension measurements to show aggregation in the low millimolar range.
- Pronounced activity of these novel molecules on cell membranes.
- Regulation of Ca^{2+} influx at lower and lysis of membranes at higher concentrations.
- Activity of these compounds against the representative fungus *S. cerevisiae*.

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ABSTRACT

Selenium compounds play a major role in Biology, where they are often associated with pronounced antioxidant activity or toxicity. Whilst most selenium compounds are not necessarily hazardous, their often selective cytotoxicity is interesting from a biochemical and pharmaceutical perspective. We have synthesized a series of amphiphilic molecules which combine a hydrophilic seleninic acid head group – which at the same time serves as thiol-specific warhead – with a hydrophobic tail. These molecules possess a surface activity similar to the one of SDS, yet their biological activity seems to exceed by far the one of a simple surfactant (e.g. SDS) or seleninic acid (e.g. phenyl seleninic acid). Such compounds effectively haemolyse Red Blood Cells and exhibit pronounced activity against *Saccharomyces cerevisiae*. From a chemical perspective, the seleninic warheads are likely to attack crucial cysteine proteins of the cellular thiolstat.

1. Introduction

In Biology, redox active Group 16 compounds are often able to modulate the intracellular redox balance of living cells and hence play a major role in biological processes, medicine and drug development [1–6]. Nonetheless, such compounds are not outrightly hazardous but often possess a certain selectivity. Their inherent (cyto-)toxicity may even be used to single out and selectively kill certain target cells. For instance, naturally occurring sulfur-based pro-oxidants, such as allicin from garlic, effectively kill various microorganisms and also attack cancer cells fairly selectively. Certain selenium and tellurium compounds are also effective against a range of cancer cells in cell culture, animal models and in patient-derived materials, although this kind of selective cytotoxicity is not yet fully understood [5–9]. The circumstance that such chalcogen-based agents are effective, yet also selective cytotoxic agents is probably the result of the specific reactivity of these agents towards the thiol groups found in cysteine-containing proteins. The latter become oxidized in the process and hence trigger an appropriate pro-apoptotic signal [10–12]. Indeed, a selective attack on the intracellular 'thiolstat' with subsequent apoptosis of cells with an impaired intracellular redox balance, such as diverse cancer cells, holds considerable promise, as normal cells seem to be less affected [10,11,13].

The last decade has therefore witnessed a growing interest in redox modulation and novel redox modulating substances, with

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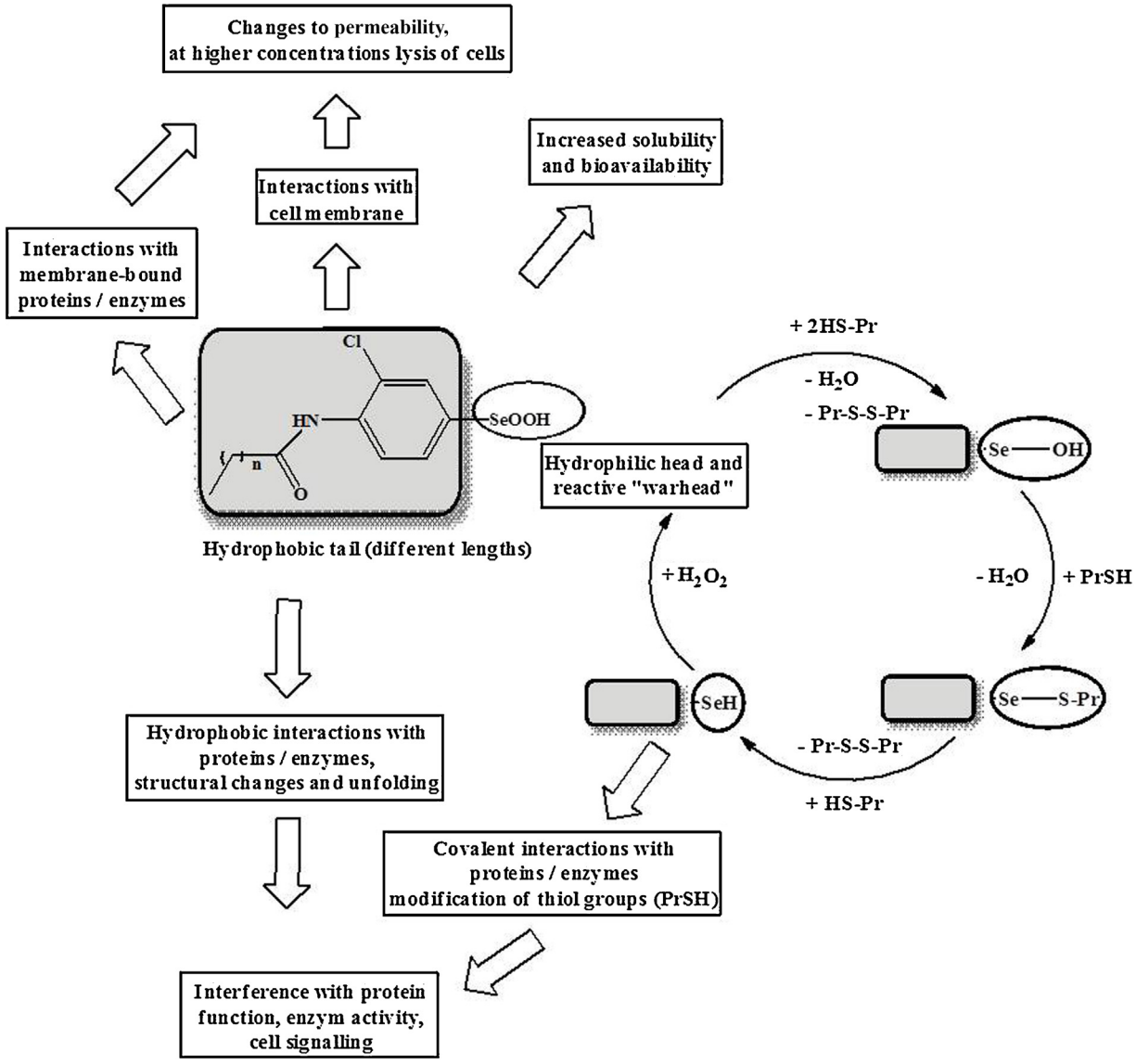

Fig. 1. Design and reactivity of amphiphilic seleninic acids which combine redox modulating properties with the ability to form aggregates (*e.g.* micelles), and to interact with membranes and (hydrophobic parts) of proteins. Some of the expected biological activities are highlighted.

many selenium agents at the forefront of these developments [14]. Selenium compounds generally are more reactive and hence active than their sulfur analogues, yet are less hazardous and toxic than the tellurium ones. Nonetheless, selenium compounds cannot be employed in biological systems easily due to often unfavourable physico-chemical properties, low bioavailability and the fact that such compounds tend to act 'alone', as single molecules.

We have therefore synthesized a novel class of bifunctional agents comprised of a biologically active seleninic acid moiety embedded in an overall amphiphilic structure. The latter should endow such compounds with additional properties, such as good solubility and permeability through membranes, and hence improve handling and biological activity (Fig. 1). Furthermore, such molecules can aggregate (*e.g.* in form of micelles) or attach to membranes and proteins, and hence may show synergistic or collective (re-)activities when compared to their monomeric forms. Such synergy has been seen already in the case of sulfur, selenium and tellurium nanoparticles [15–17].

Whilst some amphiphilic selenium-containing agents have been reported before, such compounds had to rely on complex 'head' and 'tail' groups or on co-micellation [6,17]. In order to address this apparent lack of suitable molecules available, we have recently reported the synthesis and biological activity of a series of selenium- and tellurium-containing surfactants based on a hydrophilic sulfate head group [18]. The synthetic approach used by us at the time (*i.e.* a multi-step synthesis including an aggressive *O*-sulfation step) has been rather cumbersome, however, and marred by overall low yields, and difficulties to apply it to a wider range of structures. Importantly, *O*-sulfation has been achieved with the use of chlorosulfonic acid, and this final step required to introduce the hydrophilic head group can lead to an overall damage and subsequent instability of the molecule in question (including hydrolysis of the sulfate head group). Indeed, the use of common hydrophilic head groups, such as a sulfate, phosphate or ammonium group, poses certain challenges as far as their introduction and subsequent chemical stability are concerned (carboxylic acids are easier to use but often of insufficient hydrophilicity) [19–22].

As part of this study, we have therefore explored the use of a seleninic acid as 'head' group as elegant alternative to conventional approaches, hence removing the need for a separate hydrophilic head and, at the same time, endowing the head with considerable (thiol-)specific chemical reactivity (Fig. 1). Indeed, while seleninic