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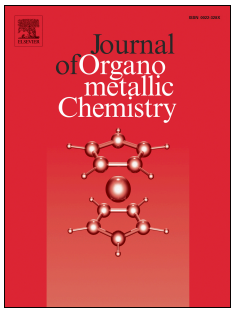

Hydrophobicity and glutathione peroxidase-like activity of substituted salicyloyl-5-seleninic acids: Re-investigations on aromatic selenium compounds based on their hydrophobicity

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Hydrophobicity and glutathione peroxidase-like activity of substituted salicyloyl-5-seleninic acids: re-investigations on aromatic selenium compounds based on their hydrophobicity

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Previously we have shown that some of 5-selenized salicylic acid derivatives exhibit glutathione peroxidase (GPx)-like activities higher than or equal to ebselen [Yu et al., *Chem. Eur. J.*, 2008, **14**, 7066; *Org. Biomol. Chem.*, 2010, **8**, 828]. For understanding the absence of GPx-like activity of the homologue of 5-seleninic anhydride of salicyloylglycine with a loger side chain, we have further synthesized 19 new derivatives (5-seleninic acids of methyl or phenyl salicylates, *N*-salicyloyl ω-carboxyalkylamines or *N*-salicyloyl alkyl/phenyl amines, and some of their diselenides). Some of the 5-seleninic acids which carry long side chains or cyclohexyl group have exerted no GPx–like activity, irrespective of whether they are derived from ω-carboxyalkylamines or simple alkylamines. Such lacks of GPx-like activity let us quantitatively relate the GPx-like activities of the congeners of the above 3 series with their hydrophobicity (ClogP), which showed satisfactory correlations in each series. The molecular hydrophobicity was then extensively applied to diverse known aromatic selenium GPx mimics including diaryl diselenides and ebselen derivatives to explain their GPx-like activities in comparably quantitative mode, which could be helpful in designing new improved GPx mimic analogues in each series.

Keywords: Organoselenium compound, Antioxidant, Glutathione peroxidase-like activity, Partition Coefficient, Hydrophobicity, QSAR

1. Introduction

Selenium, an essential trace element for human health [1], has been of great significance in pathogenesis of many fatal diseases such as Keshan disease [2], cancer [3], etc. Selenium is incorporated into selenocysteine which functions as a re-dox active site of many selenoenzymes [4] including GPx. GPx is one of the most important antioxidant enzymes in mammals, which catalyses reduction of hydrogen peroxide and lipid peroxide, using glutathione (GSH) as a reductant [5,6]. During several decades, a variety of organoselenium compounds have been appeared as possible GPx mimics, but there are only a few leads superior to ebselen, a "standard" of organoselenium GPx mimics [7].

We have previously synthesized a new 5-seleninic anhydride of salicyloylglycine (**1** in Fig. 1) which exhibited higher GPx-like activity than ebselen and inhibited plant and mammalian 12/15-lipoxygenase (LOX) [8]. Further synthesized 5-selenized salicylic acid derivatives showed not only selective inhibition against 5-LOX but also GPx-like activities superior or similar to the lead compound (**1**) [9]. Interestingly, only one derivative (**2**) with a long side chain showed no detectable GPx-like activity [9].

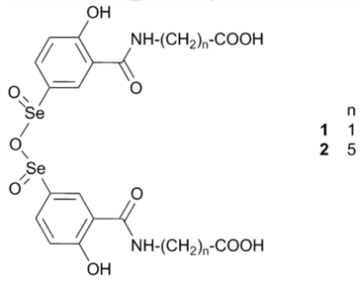

Fig. 1 5-seleninic anhydrides of *N*-salicyloyl ω-carboxyalkylamines published earlier.

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To our knowledge of structure-activity relationship in a series of homologues, elongation of a side chain might result in steric and hydrophobic effect on certain biological activity. Steric effects of substituents in aromatic selenium GPx mimics have been discussed mainly in the cases of *ortho*-substituted analogues [7], but the effect of molecular hydrophobicity has not been mentioned yet. Because the elongation of substituents in our salicyloyl-derived GPx mimics occurs in *meta*-position to seleninic acid, their catalytic reactions might not be affected by steric hindrance of substituents. Actually, molecular hydrophobicity does not directly influence on GPx-like reaction mechanism, but the reaction rate could depend on it as the catalytic assay runs in certain solvents (e.g. phosphate buffer solution or CH_2Cl_2/MeOH). We, therefore, continued to synthesize 19 new derivatives with carbon side chains of different lengths to relate their hydrophobicity with their GPx-like activities.

The result that not the simple side chain elongation but the change in molecular hydrophobicity could affect the catalytic reactivity of our GPx mimics has encouraged us to apply this hydrophobic effect to some of known aromatic selenium GPx mimics, including diaryl diselenides and ebselen derivatives.

2. Experimental

2.1. Chemicals and instruments

Some starting reagents such as methyl salicylate, phenyl salicylate (salol), salicylamide, salicylanilide and $SeCl_4$ were purchased from Merck and Sigma-Aldrich and commercially unavailable reagents were synthesized by the reaction of methyl salicylate with corresponding amines. All the solvents were of extra pure grade from Roth (Germany). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Biospin AV 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) by using d_6-DMSO as a solvent. For **3m** and **4m**, d_6-D_2O+KOH was used as a solvent because of its getting dark in d_6-DMSO. Chemical shift values (δ) are reported in ppm downfield from