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Twice acting antioxidants: synthesis and antioxidant properties of selenium and sulfur-containing zingerone derivatives

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ABSTRACT

Two new organochalcogen-containing zingerone derivatives, 4-(4-hydroxy-3-methoxyphenyl)-4-(phenylseleno)-2-butanone (**2b**) and 4-(4-hydroxy-3-methoxyphenyl)-4-(phenylthio)-2-butanone (**2c**) were prepared and evaluated for their antioxidant properties. DPPH and lipid peroxidation studies show that **2b** and **2c** have significantly improved antioxidant activity over dehydrozingerone (**1**) despite having similar electron transfer capacity. We speculate that the improved activity of **2b** and **2c** is partly due to the ability of these compounds to act twice as phenolic antioxidants through a mechanism that eliminates phenylselenyl or phenylthiyl radicals.

Introduction

Dehydrozingerone (DHZ, **1**) and zingerone (**2a**) are phenolic compounds that are structurally related to curcumin (**3**) and are present as minor components in ginger, the rhizomes of *Zingiber officinale* Rosco (Fig. 1).[1] DHZ along with vanillin and ferulic acid, are formed as degradation products of curcumin at physiological pH.[2] Ginger has been widely used both as an ingredient and flavoring in foods, as well as a medicinal agent.[3] Several pharmacological studies have been reported for ginger extracts[3b] or their constituents DHZ and zingerone.[4] In particular, DHZ has been reported to have radioprotective,[3a] antimicrobial,[4a,b] pro-healing,[4c] antioxidant,[2,4a,c–j] anti-Parkinson,[4d] antimutagenic,[4k] anti-cancer[4l,m] and antidiarrheal[4n] properties.

The imbalance of oxidative metabolism has a crucial role in the progression of chronic diseases. Reactive Oxygen Species (ROS) are constantly formed in mammalian systems,[5] either as accidental products during physiological processes,[5a] or due to environmental pollutants such as ozone,[5b] heavy metal poisoning[5c] and ionizing radiation.[5d] If ROS are not controlled by cellular antioxidant defences, they can generate a state of oxidative stress.[6] The resulting ROS are responsible for the progressive and irreversible decline of various metabolic functions of the organism during aging, leading to conditions that include a decline in fertility,[7a–c] dementia[7d] and cancer.[7e]

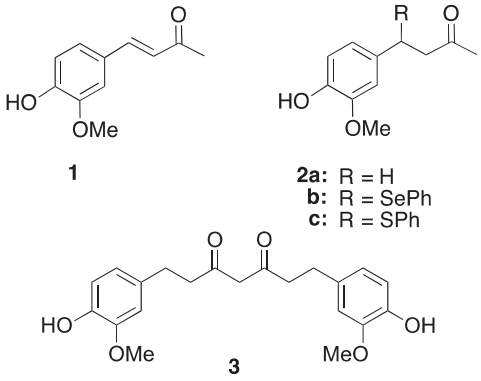

Figure 1. Dehydrozingerone (**1**), zingerone (**2a**) and related compounds.

Besides being versatile intermediates in organic synthesis,[8] organochalcogen compounds frequently exhibit biological activity, including antioxidant, antinociceptive, anticancer, antidepressant, antibacterial, and antifungal properties.[9] Novel organochalcogen

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compounds were recently synthesized and proved to be strong antioxidants.[9,10] In this context, the antioxidant properties of organoselenium compounds, such as mono- and diselenides, have been demonstrated through in vitro and in vivo model studies.[9]

The combination of two or more bioactive moieties in one molecule has been used as an effective strategy for designing new drugs and promising results with different classes of compounds have been described.[11] Based on the known bioactivities of DHZ and chalcogen-containing compounds, together with our interest in the preparation and study of the biological activities of semi-synthetic organochalcogen molecules,[12] we present herein the synthesis and the antioxidant evaluation of new derivatives of zingerone **2b–c** (Fig. 1).

The effect of chemical modifications on the antioxidant capacity of the molecules in question was examined using methods previously reported by us for this class of compound.[12] Methods employed include: 2,2-diphenyl-1-picrylhydrazyl (DPPH)-scavenging, 2,2-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid radical cation ($ABTS^{\cdot+}$)-scavenging, linoleic acid peroxidation and anti-hemolysis activity assays. These assays provide important information about the hydrogen-transfer and electron-donating abilities of the compounds in question with regard to free radicals, and their protective capacity against lipid peroxidation in homogeneous and heterogeneous environments.

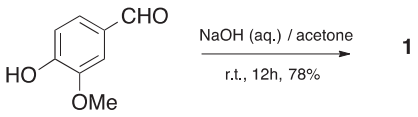
Results and discussion

Synthesis of dehydrozingerone analogues

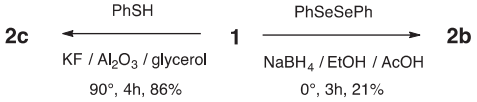
The overall strategy for the synthesis of the DHZ analogues (**2b–c**) is outlined in Schemes 1 and 2. Compound **1** was prepared by aldol condensation of vanillin with acetone (Scheme 1).[4i]

The conjugate addition of an organochalcogen group to α,β-unsaturated carbonyl compounds is an efficient strategy for C–S and C–Se bond formation.[13] Traditional methods for thia-Michael addition require Lewis acid activation of the acceptor olefin or deprotonation of the thiol.[14] To prepare selenium-Michael adducts, benzeneselenol is frequently generated in situ from diphenyl diselenide in acidic media,[15a] or by using the $(PhSe)_2/NaBH_4$/PEG-400 system.[15b] Alternatively, the nucleophilic 1,4-addition of $C_6H_5SeZnCl$ in water has been successfully employed to prepare β-phenylseleno ketones.[15c]

Accordingly, treatment of dehydrozingerone (**1**) with benzeneselenol that was generated in situ from diphenyl diselenide and sodium borohydride in ethanol and acetic acid[15a,16] afforded 4-(4-hydroxy-3-methoxyphenyl)-4-(phenylseleno)-2-butanone (4-(phenylseleno)zingerone, **2b**) in 21% yield (Scheme 2). Attempts to improve the yield of **2b** from **1** using alternative methods for the generation of PhSeH failed.[15b,c,17] This indicated that the addition of acid was crucial to minimize reduction of the carbonyl group in **1**. Decomposition of **2b** to zingerone (**1**) and diphenyl diselenide during workup and/or competitive reduction of the carbonyl group contributed to the modest yield of **2b**. Due to this instability, **2b** was purified by flash chromatography or preparative TLC and used immediately in the antioxidant assays (vide infra). Similarly, 4-(phenylthio)zingerone (**2c**) was prepared by the Michael addition of benzenethiol to DHZ in 86% yield, using solid-supported KF in glycerol as the solvent (Scheme 2).[14c,18]



Scheme 1.



Scheme 2.

Radical scavenging activity

A series of in vitro antioxidant screening methods were used to explore the antioxidant potential of compounds **1** (control) and **2b–c**. Initial experiments were carried out in order to evaluate the ability of these compounds to scavenge 2,2-diphenyl-1-picrylhydrazyl radicals (DPPH) and provides information about the ability of these compounds to donate hydrogen atoms to *N*-centered radicals. While details of this assay are provided elsewhere,[12] it is important to note that assay is not affected by metal ion chelation or enzyme inhibition.[19]

Based on the calculated IC_{50} values, the DPPH radical-scavenging activity follows the order: **2b** = **2c** > **1**. To our surprise, the data in Table 1 show that the DHZ derivatives **2b–c** are approximately twice as effective at scavenging DPPH when compared with DHZ (**1**). This observation is consistent with the mechanism depicted in Scheme 3, and the observation that **2b** is unstable, affording **1** and diphenyl diselenide upon workup (vide supra). Accordingly, we propose that DHZ derivatives **2b–c** 'act twice', firstly through direct hydrogen atom transfer (HAT) to DPPH, and secondly through HAT from DHZ (**1**) which is produced through ε-scission of the intermediate radical **4** followed by tautomerism (Scheme 3).

We next examined the interaction of these compounds with the radical cation derived from 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\cdot+}$) which provides information on the ability of these compounds to become involved in electron-transfer chemistry. This would serve as a measure of the effectiveness of compounds to reduce radicals by electron transfer.[12,20] As shown by the IC_{50} data in Table 2, all compounds (**1**, **2b,** and **2c**) show similar potency in this assay as expected due to the commonly substituted aromatic π-systems of these compounds.

The ability of antioxidants to inhibit lipid peroxidation is important since this is implicated in cardiovascular disease.[21] Consequently, the ability of **1** and **2b–c** to inhibit direct lipid oxidation was evaluated in a linoleic acid emulsion. Linoleic acid oxidation generates lipid peroxides and hydroperoxides, that decompose to secondary oxidation products such as malondialdehydes (MDA). The thiobarbituric acid-reactive substances (TBARS) assay was used to evaluate the possible effects of **1** and its analogues in decreasing lipid peroxidation.[12] Table 3 illustrates the effect of different concentrations of these compounds against linoleic acid peroxidation induced by sodium nitroprusside (SNP).[22]

Compounds **2b–c** demonstrate a clear capacity to reduce lipid peroxidation by more than 50%, with **2b** showing the best antioxidant capacity (IC_{50} = 66.3 ± 3.6 μM). Based on these results, it can be concluded that the addition of the Se-aryl group results in a

Table 1
Radical scavenging activity of DHZ (**1**) and derivatives (**2b–c**) toward DPPH

Compound	I_{max}	IC_{50} (μM)	*n*
1	82.4 ± 3.6	57.0 ± 2.5	0.4
2b	96.6 ± 3.0	27.7 ± 9.6	0.9
2c	96.3 ± 3.3	33.3 ± 3.5	0.7

Data are expressed as mean ± standard error (SE) of % maximal inhibition (I_{max}) and concentration required to scavenge 50% of DPPH (IC_{50}); *n* = stoichiometric factor (equivalents of radicals quenched by 1 equiv of substrate).