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Heterocyclic β-keto sulfide derivatives of carvacrol: Synthesis and copper (II) ion reducing capacity

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ABSTRACT

Sixteen β-keto sulfide derivatives of carvacrol (**4–19**) incorporating phenyl or N, O and S heterocyclic moieties were synthesized in three steps. The relationships between heterocyclic structure and cupric, Cu(II), ion reducing antioxidant capacity (CUPRAC) were examined. Nine of the compounds (**8–9** and **13–19**) showed better CUPRAC activity than trolox at neutral pH, with trolox equivalent antioxidant capacity (TEAC) coefficients ranging between 1.20 and 1.75. Two derivatives (**11–12**) showed comparable reducing capacity to trolox, with TEAC values of 0.95 for **11** and 1.02 for **12**. Compounds **8–9** and **11–19** were more effective at reducing the Cu (II) ion than ascorbic acid and the parent compound, carvacrol. The most effective antioxidants were those containing an oxadiazole, thiadiazole or triazole moiety. In particular, the methyl thiadiazole derivative (**15**) had the highest Cu(II) ion reducing capacity, with a TEAC coefficient of 1.73.

Carvacrol is a monoterpenoid which is prevalent in the essential oils of plants of the mint (Lamiaceae) family, which includes oregano, thyme and savory. A diverse range of biological activities have been reported for carvacrol, such as anticancer,[1] antioxidant,[1,2] antimicrobial,[3] insecticidal,[4] tyrosinase inhibitory[5] and anti-inflammatory[6] effects. Owing to these beneficial properties, there has been much interest in the study of carvacrol derivatives, with the goal of improving biological properties relative to the parent compound. To date, many semi-synthetic derivatives of carvacrol have been prepared, and many show enhanced biological properties relative to carvcarol.[7–15]

Oxidative stress results from the overproduction of reactive oxygen species (ROS) in the body. ROS, including species such as hydroxyl radical ($OH^{\cdot}$), superoxide radical ($O_2^{-\cdot}$) and hydrogen peroxide (H_2O_2), are highly reactive. They can adversely affect biological macromolecules (e.g. protein, lipid, DNA), leading to the development of diseases such as cancer, neurodegeneration, chronic inflammation and cardiovascular disorder. Antioxidants mitigate the deleterious effects of ROS by preventing or delaying their formation by a variety of mechanisms. Thus, the discovery of new antioxidant molecules is important in combating diseases caused by oxidative stress. Although there are several *in vitro* methods for determining the antioxidant capacity of natural and synthetic compounds, most of the antioxidant studies on the semi-synthetic derivatives of carvacrol have largely been focused on the ability of these compounds to scavenge the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical. For instance, methylene bridged bis-carvacrol,[7] hydroxymethyl,[7] sulfonate,[8] bis-indole,[9] mercapto-1,3,4-thiadiazole/1,3,4-oxadiazole[10] and Schiff[11] base derivatives of carvacrol showed similar or significantly better DPPH free radical scavenging activity than the parent compound or the widely used antioxidant standard, ascorbic acid.

Transition metals such as copper and iron are also capable of generating free radicals in the body as a result of a Fenton-type reaction, which results from redox cycling of the metal ion. While carvacrol has been evaluated for its metal ion reducing/chelation capacity,[2] to our knowledge, these studies have not been extended to its semi-synthetic derivatives to a similar degree. The current study, which is focused on the synthesis and Cu(II) ion reducing capacity of a new series of heterocyclic β-keto sulfide derivatives of carvacrol, seeks to address this gap in the field.

The β-keto sulfide derivatives of carvacrol (**4–19**) were synthesized in three steps (Fig. 1). Treatment of carvacrol (**1**) with cesium carbonate and methyl iodide in DMF afforded methyl carvacrol (**2**) in 78% yield. The yield and spectroscopic data of **2** were in good agreement with literature data.[15] The chloroacetyl group was introduced by Friedel-

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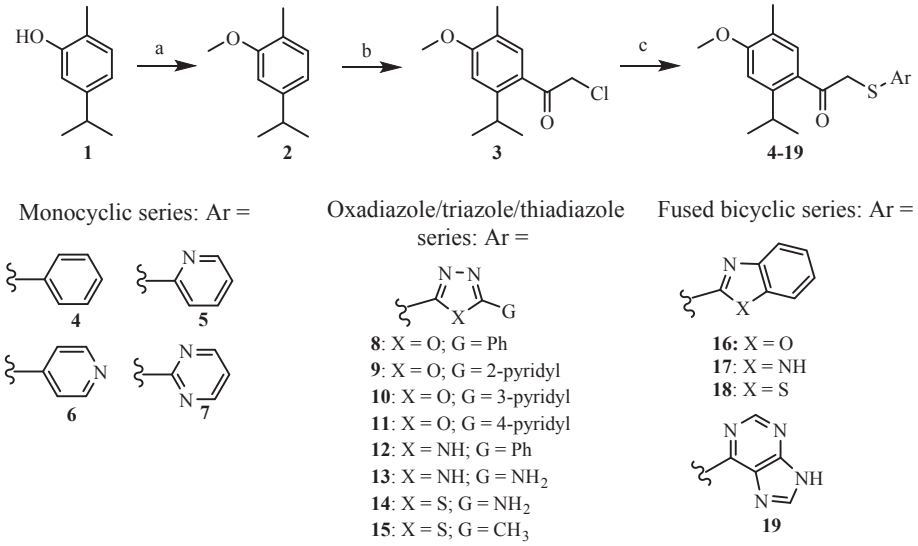


Fig. 1. Synthesis of heterocyclic β-keto sulfide derivatives of carvacrol. *Reagents and conditions:* a) Cs_2CO_3, CH_3I, dry DMF, heat, 78%; b) Chloroacetyl chloride, $AlCl_3$, dry CH_2Cl_2, 0 °C to rt, 64%; c) Ar-SH, K_2CO_3, KI, dry CH_3CN, rt, 60–96%.

Crafts acylation of the methyl carvacrol using aluminum chloride and chloroacetyl chloride in dichloromethane,[16] and the product (**3**) was obtained in 64% yield. The successful addition of the chloroacetyl group was confirmed by NMR spectra, which displayed ^{13}C signals at 193.8 ppm for the ketone, and ^{1}H and ^{13}C signals at 4.58 ppm and 48.4 ppm, respectively, for the chloromethyl group. In addition, the presence of two singlets at 7.32 ppm and 6.86 ppm in the ^{1}H NMR spectrum confirmed the placement of the chloroacetyl group para to the methoxy group. The carbonyl group was further confirmed by IR spectroscopy, which displayed a signal corresponding to a C=O stretch at 1691 cm^{-1}. For the nucleophilic substitution step, the chloro group was converted to the iodo group, a better leaving group, in the presence of KI. The displacement of the iodo group by the heterocyclic/phenyl thiolate, obtained in situ by deprotonation with K_2CO_3, was carried out in the same vessel without isolating the iodide.[17] The target compounds were obtained in 60–96% yields, after purification by silica gel column chromatography using ethyl acetate-hexane solvent mixtures. The successful formation of the carvacrol β-keto sulfides (**4–19**) was confirmed by NMR spectra, which displayed changes in the chemical shift values for the α-methylene (^{1}H and ^{13}C NMR) and carbonyl groups (^{13}C NMR) relative to the starting material, **3**. The structures were further corroborated by IR and HRMS analyses (See Supplementary data).

As depicted in Fig. 1, compounds **4–19** incorporate 3 components: *O*-methyl carvacrol moiety, β-keto sulfide group, and a monocyclic or bicyclic heterocyclic and/or phenyl group, representing a unique hybrid structure. The methoxy group was included in the design in lieu of the free hydroxy group because accessible phenol protecting groups are unstable under the acidic conditions employed in the Friedel-Crafts acylation. The sulfur atom is a component of many important biomolecules which play an antioxidant role in the body, e.g. glutathione, thioredoxin, glutaredoxin and methionine. Although many sulfur containing compounds, including thiols (e.g. cysteine, glutathione) and disulfides (e.g. cystine), have been studied for their cupric ion reducing capacity,[18] there is limited data for sulfide derivatives. Thus, the sulfide moiety was incorporated to serve as the primary Cu(II) ion reducing component. The β-keto group modifies the electron density around the sulfide, but it is not expected to be involved in neighboring group participation with the sulfur atom to a significant degree, owing to the unstable 4-membered ring arrangement. The heterocyclic structures include pyridine, pyrimidine, purine, imidazole, oxazole, thiazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole, and 1,2,4-triazole moieties, and were selected based on their presence in other molecules displaying strong antioxidant activity.[10,19–25] The compounds are divided into three groups: 1) simple monocyclic (**4–7**), 2) oxadiazole/triazole/thiadiazole (**8–15**) and fused bicyclic (**16–19**) series. The presence of these heterocyclic moieties in the carvacrol β-keto sulfides is expected to influence the Cu(II) ion reducing capacity of the target compounds to varying degrees. Therefore, correlations between the structure of the heterocycle and the Cu(II) ion reducing capacity can readily be established.

The *N,N*-bidentate ligand structure in neocuproine allows for efficient coordination to Cu(I) and Cu(II) ions. The cupric, Cu(II), ion reducing antioxidant capacity (CUPRAC) assay measures the ability of antioxidant compounds to reduce Cu(II) in a bis-neocuproine-Cu(II) complex to Cu(I) by an outer sphere single electron transfer. This is a redox process, which results in concomitant oxidation of susceptible functional group(s) in the antioxidant. The extent of reduction of Cu(II) to Cu(I) by the antioxidant can be monitored by UV–visible spectroscopy because of the formation of a yellow-orange charge transfer neocuproine-Cu(I) complex, which shows absorption maximum at 450 nm.[26] Thus, increased absorbance at 450 nm indicates increased antioxidant activity. The mechanism for the CUPRAC oxidation of sulfides is thought to involve a one-electron oxidation of sulfur resulting in the formation of a radical cation, which can be further oxidized by molecular oxygen to the corresponding sulfoxide (Fig. 2).[27]

With the heterocyclic carvacrol β-keto sulfide derivatives in hand, the CUPRAC assay was performed with trolox, ascorbic acid and carvacrol as antioxidant standards. Data are reported as trolox equivalent antioxidant capacity (TEAC) coefficients (Table 1), which are expressed

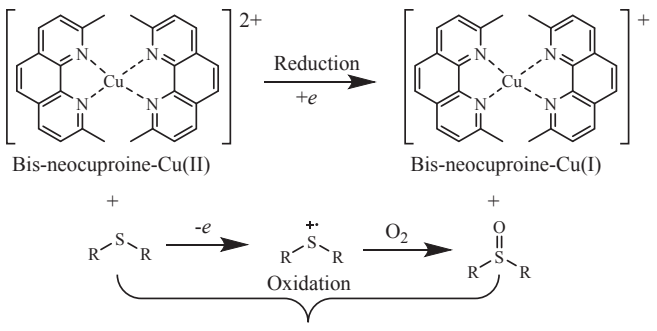
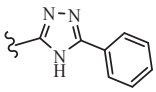
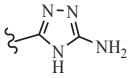
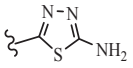
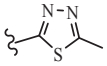
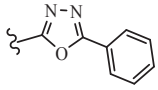
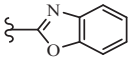
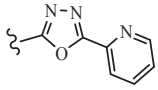
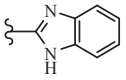
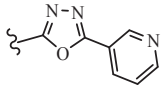
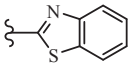
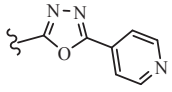
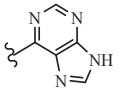


Fig. 2. Bis-neocuproine-Cu(II) reduction by β-keto sulfides.

Table 1
Trolox equivalent antioxidant capacity (TEAC) data for compounds **4–19**.

Cmpd	Ar	TEAC	Cmpd	Ar	TEAC
4		0.80	**12**		1.02
5		0.59	**13**		1.62
6		0.47	**14**		1.40
7		0.39	**15**		1.73
8		1.34	**16**		1.47
9		1.59	**17**		1.21
10		0.68	**18**		1.26
11		0.95	**19**		1.32
AA		0.85	CAR		0.87

Trolox: $\varepsilon = 16{,}100\ M^{-1}\ cm^{-1}$; $r^2 = 0.9999$.
AA: Ascorbic acid; CAR: Carvacrol.

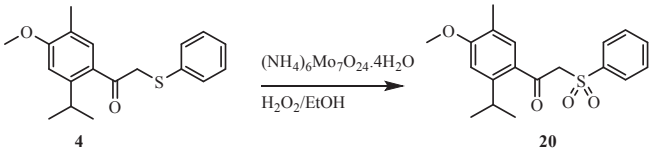


Fig. 3. Oxidation of methyl carvacrol phenyl β-keto sulfide derivative (**4**).

as the ratio of the molar absorptivity (obtained from calibration plots) of the antioxidant sample to that of trolox (TEAC = $\varepsilon_{sample}/\varepsilon_{trolox}$). The greater the TEAC value, the greater is the reducing capacity of the β-keto sulfide derivative. Although the study is primarily focused on the antioxidant effects of heterocyclic β-keto sulfide derivatives, the phenyl derivative (**4**) was included among the simple monocyclic derivatives for direct comparison with the pyridine/pyrimidine derivatives (**5–7**). Compound **4** shows comparable Cu(II) reducing capacity to ascorbic acid and carvacrol, with a TEAC value of 0.80, compared to 0.85 and 0.87 for ascorbic acid and carvacrol, respectively. In order to confirm the role of the sulfur atom in the reducing capacity of the β-keto sulfide derivatives, compound **4** was oxidized to the corresponding sulfone (**20**) by hydrogen peroxide in the presence of catalytic amounts of ammonium molybdate tetrahydrate (Fig. 3).[28] There was complete loss of reducing capacity of compound **20** in the CUPRAC assay, confirming that the unoxidized form of the sulfur atom in compound **4** is solely responsible for the compound's reducing capacity.

The pyridine and pyrimidine derivatives (**5–7**) showed lower Cu(II) reducing capacity than the phenyl derivative, implying that the nitrogen atoms reduce the electron density at the sulfur atom. The 2,6-pyrimidine (**7**), with two nitrogen atoms, has the lowest reducing capacity and the 2-pyridine derivative (**5**) has higher reducing capacity than the 4-pyridine derivative (**6**). Furthermore, given the lower reducing capacity of compounds **5–7**, it can be concluded that no *N*-oxidation occurs during the reduction of Cu(II) to Cu(I) for the simple monocyclic derivatives.

Structural modification of compounds of the simple monocyclic series (**4–7**) by incorporation of a 1,3,4-oxadiazole ring between the sulfur atom and the heterocyclic/phenyl group (**8–11**) gave TEAC coefficients that ranged from 0.68 to 1.59. Phenyl oxadiazole derivative **8** showed a 1.7-fold increase in reducing capacity over the corresponding phenyl derivative **4**. Similarly, 2-pyridyl oxadiazole derivative **9** gave a 2.7-fold increase in reducing capacity over the 2-pyridyl derivative **5**, and the 4-pyridyl oxadiazole derivative **11** had 2-fold better activity than the 4-pyridyl derivative **6**. The 3-pyridyl oxadiazole derivative **10** showed significantly lower reducing capacity than the 2-pyridyl and 4-pyridyl oxadiazole derivatives. The increase in Cu(II) reducing capacity for the oxadiazole series (**8–11**), relative to the monocyclic series (**4–7**), is not surprising, owing to the ability of the oxadiazole moiety to stabilize the sulfur radical cation intermediate by resonance effects. However, based on the trend observed for the monocyclic series, it was expected that derivative **8** would have a higher TEAC coefficient than compound **9**; the opposite was observed.

Similar to neocuproine, compound **9** incorporates a *N,N*-bidentate ligand, which should be capable of coordinating to Cu(I) and Cu(II) ions. Thus, it was hypothesized that the higher TEAC value for the 2-pyridyl oxadiazole (**9**) over the corresponding phenyl derivative (**8**), and the other pyridyl derivatives (**10–11**), may result from coordination to excess Cu(II) ions in solution. Upon reduction of Cu(II) to Cu(I), the resulting charge transfer Cu(I) complex would show a similar absorption profile to that observed for neocuproine and related compounds.[27] In order to test this theory, absorption spectra for compound **9** (12.5, 25 and 37.5 μM) were recorded in the absence (Fig. 4A) and presence (Fig. 4B) of copper (II) chloride (2.5 mM). The spectrum displayed a λ_{max} at 286 nm due to the ligand, but no peak at 450 nm that would be attributable to the formation of a charge transfer complex (Fig. 4). Additionally, there was no evidence of copper coordination after 30 min (the incubation time for the CUPRAC assay) or 1 hour, since the absorbance of compound **9** was the same in both the presence and absence of $CuCl_2$. While the exact cause of the enhanced reducing

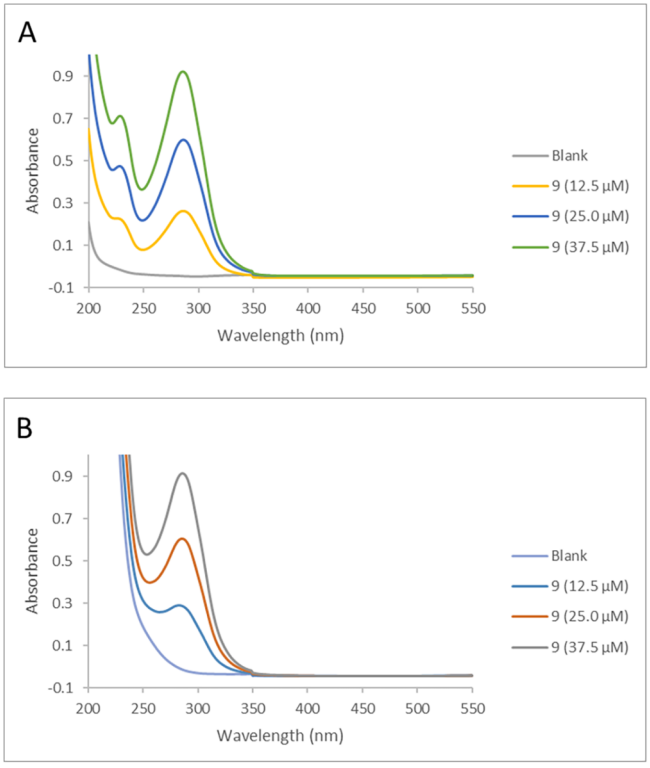


Fig. 4. Absorption spectra of **9** (12.5, 25.0, 37.5 μM) after 1 h; A: without $CuCl_2$; B: with $CuCl_2$ (2.5 mM).

capacity of **9** is unknown, it is possible that *N*-oxidation of the 2-pyridyl ring occurs as a result of the presence of the oxadiazole moiety, which was not observed for the monocyclic 2-pyridyl derivative, **5**.

Isosteric substitution of the oxygen in the oxadiazole ring of compound **8** with NH to form the corresponding phenyl triazole derivative (**12**) led to a significant decrease in Cu(II) reducing capacity, with the triazole having a TEAC value of 1.02. Conversely, replacement of the phenyl group in derivative **12** with an amino group to give amino triazole (**13**) lead to a dramatic increase in Cu(II) reducing capacity, with a TEAC value of 1.62, which approximates to that of the 2-pyridyl oxadiazole derivative (**9**). This enhancement in activity can be attributed to the electron-donating nature of the amino group; partial oxidation of the NH_2 group is also possible.

Replacement of the nitrogen atom in the triazole ring of compound **13** with a sulfur atom to form the corresponding thiadiazole (**14**) lead to a moderate decrease in Cu(II) reducing capacity, with a TEAC value of 1.40. The methyl thiadiazole derivative (**15**) had superior reducing capacity relative to the amino thiadiazole (**14**), and displayed the highest Cu(II) reducing capacity of all the compounds tested, with a TEAC coefficient of 1.73. The amino group is a better electron donor than the methyl group, and thus, **15** was expected to show a lower reducing capacity than **14**. There are many examples in the literature of copper (II) catalyzed benzylic oxidation of alkyl groups to the corresponding carbonyl compound.[29] However, we did not detect evidence of oxidation of the methyl group in the assay mixture.

The fused bicyclic derivatives (**16–18**) showed better antioxidant activities than trolox, with TEAC values ranging from 1.21 to 1.47. The benzoxazole derivative (**16**) had higher Cu(II) reducing capacity than the benzimidazole (**17**) and benzothiazole (**18**) derivatives, which had similar reducing capacities. The trend for the benzoxazole and benzimidazole derivatives is similar to that observed for phenyl oxadiazole (**8**) and phenyl triazole (**12**) derivatives, with the oxygen containing heterocycle having a greater Cu(II) reducing capacity. Since the phenyl thiadiazole derivative was not included in this study, because of unavailability of the starting material, no direct comparison can be made for the benzothiazole derivative. Purine derivative (**19**), with a TEAC value of 1.32, showed comparable reducing capacity to that of the phenyl oxadiazole (**8**). Since the sulfur atom in **19** is not directly connected to the imidazole ring, it is not possible to make a direct comparison between compounds **17** and **19**. However, given the low reducing capacity of the pyrimidine derivative **7**, it can be inferred that the imidazole ring of purine **19** plays a significant role in its reducing capacity.

In summary, sixteen new phenyl and/or heterocyclic β-keto sulfide derivatives of carvacrol (**4–19**) have been synthesized in three steps, and evaluated for their ability to reduce Cu(II) to Cu(I) using the CUPRAC assay. Nine of the compounds (**8–9** and **13–19**) showed an augmentation of Cu(II) reducing capacity relative to trolox, and two compounds (**11–12**) exhibited comparable activity. Our studies demonstrate an original approach to the development of transition metal ion reducing agents, and reveal that the structure of the heterocyclic moiety has an influence on the reducing capacity of carvacrol-based β-keto sulfides. In general, the oxadiazole/triazole/thiadiazole class of derivatives displayed the highest Cu(II) reducing ability. Based on these results, it can be concluded that heterocyclic β-keto sulfides are effective Cu(II) reducing agents that could serve as potential lead compounds against diseases caused by oxidative stress. Further studies will be focused on the evaluation of antioxidant effects of hybrid molecules incorporating the heterocyclic β-keto sulfide moiety and other biologically active monoterpenes similar to carvacrol.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2019.126636.

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