DOI: 10.17344/acsi.2023.8155 *Acta Chim. Slov.* **2023,** *70,* 440–448
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Scientific paper

Synthesis and Determination of Cerium(IV)-Reducing Antioxidant Capacity (CERAC) Assay of Some New Anthraquinones

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Received: 03-24-2023

Abstract

Novel anthraquinone-based cyclic antioxidants containing amino, thio and oxo groups were synthesized and their antioxidant capacity was determined by using the cerium(IV)-reducing antioxidant capacity (CERAC) assay. ^{1}H, ^{13}C NMR, FTIR-spectroscopy and ESI (Electrospray Ionization) mass spectrometry were used for the characterization of anthraquinone derivatives exhibiting CERAC antioxidant capacity. This study is of great importance, because the antioxidant capacity of anthraquinone compounds was analyzed for the first time by the CERAC method and CERAC-Trolox equivalent antioxidant capacity (TEAC) values were higher than that for Trolox. It should also be noted that, since all synthesized anthraquinone derivatives have the potential to find applications in terms of their biological properties due to their sulfur and nitrogen content, they will make an important contribution to the literature.

Keywords: Anthraquinone, Antioxidant, Bioactive compounds.

1. Introduction

Anthraquinones (anthracene-9,10-dione) constitute a very important class of compounds in drug production due to their high biological activities. Antioxidant, antifungal, antiviral, antimicrobial, antidiabetic are among the most interesting pharmacological activities of anthraquinone compounds; thus they have been a focus of a wide range of studies in recent years.[1–5]

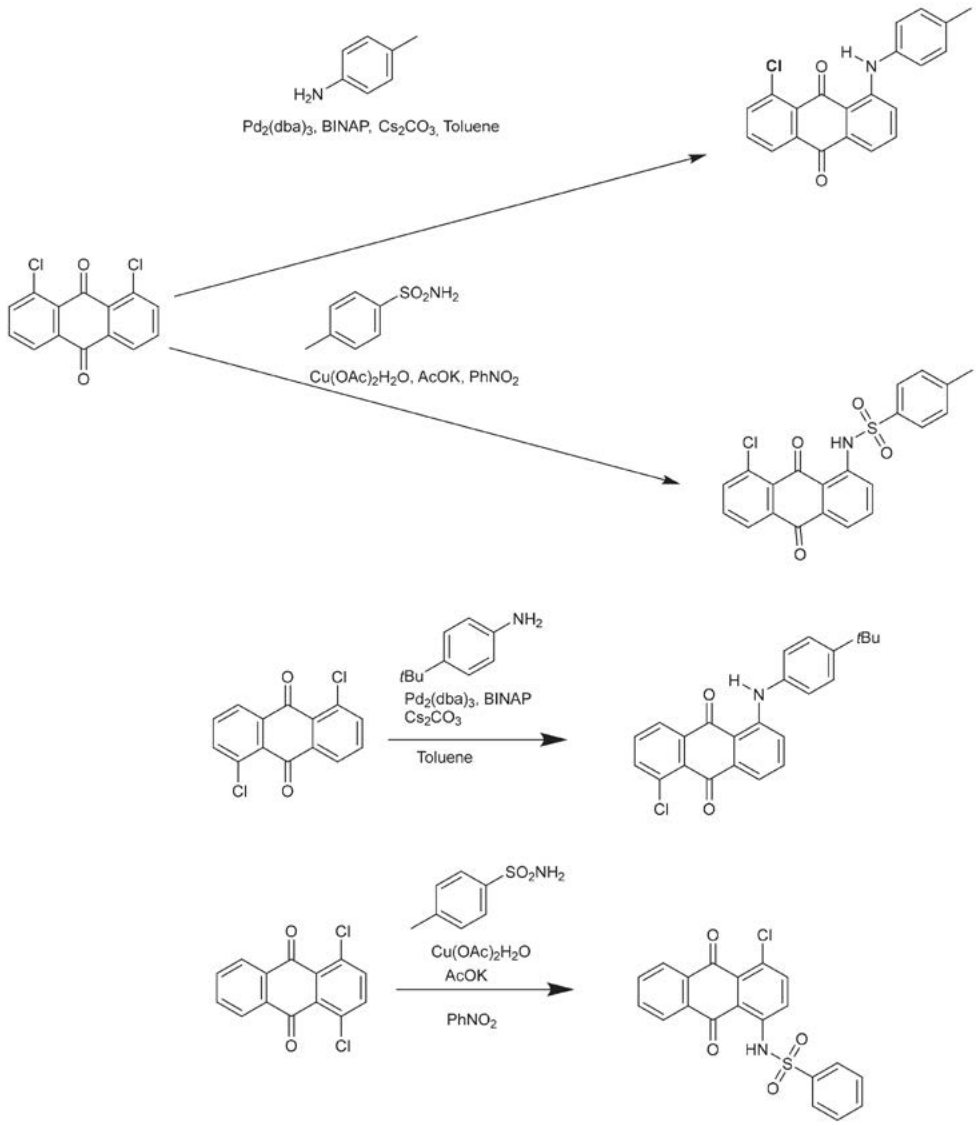
In addition to their pharmacological properties, there are many natural and synthetic anthraquinone derivatives that find application for imaging devices, in cosmetics, textile, food and paint industry products.[6–8] In all these areas of use, separation processes of pollutants with redox potential by various chemical and biochemical processes can also be added.[9,10]

Antioxidants are molecules that delay or prevent damage to the cell structure by inhibiting free radical reactions or by promoting their decomposition.[11] Most heart and cancer diseases occur as a result of low antioxidant limit.[12,13] Antioxidants protect against many genetic disorders such as asthma, cancer, eczema, aging and cataracts.[14]

Nitrogen- and sulfur-containing 9,10-anthraquinone derivatives are widely used in chemistry and technology and exhibit a wide range of biological properties such as anticancer, antimicrobial and antioxidant.[15–19]

Nucleophilic substitution reactions of dichloroanthraquinones are a highly preferred type of reaction as they allow their easy functionalization. There are many studies in the literature examining the mono- and/or di-product formation conditions as a result of the selective nucleophilic substitution reaction of 1,5-dichloroanthraquinone with various nucleophiles.[20–22]

Most dichloroanthraquinone compounds have been successfully synthesized via the Buchwald–Hartwig cross-coupling reaction or by the Ullmann coupling reaction.[23–25] For this type of coupling reaction, whether the nucleophile has terminal electron-donating alkylamino groups is important for reaction efficiency. If terminal electron donor groups are absent, the reaction will take place in higher yield. For example, in a published study, the reactions of alkylphenylamine and alkylphenylsulfonamide without terminal electron-donating alkylamino groups occurred smoothly, yielding the corresponding



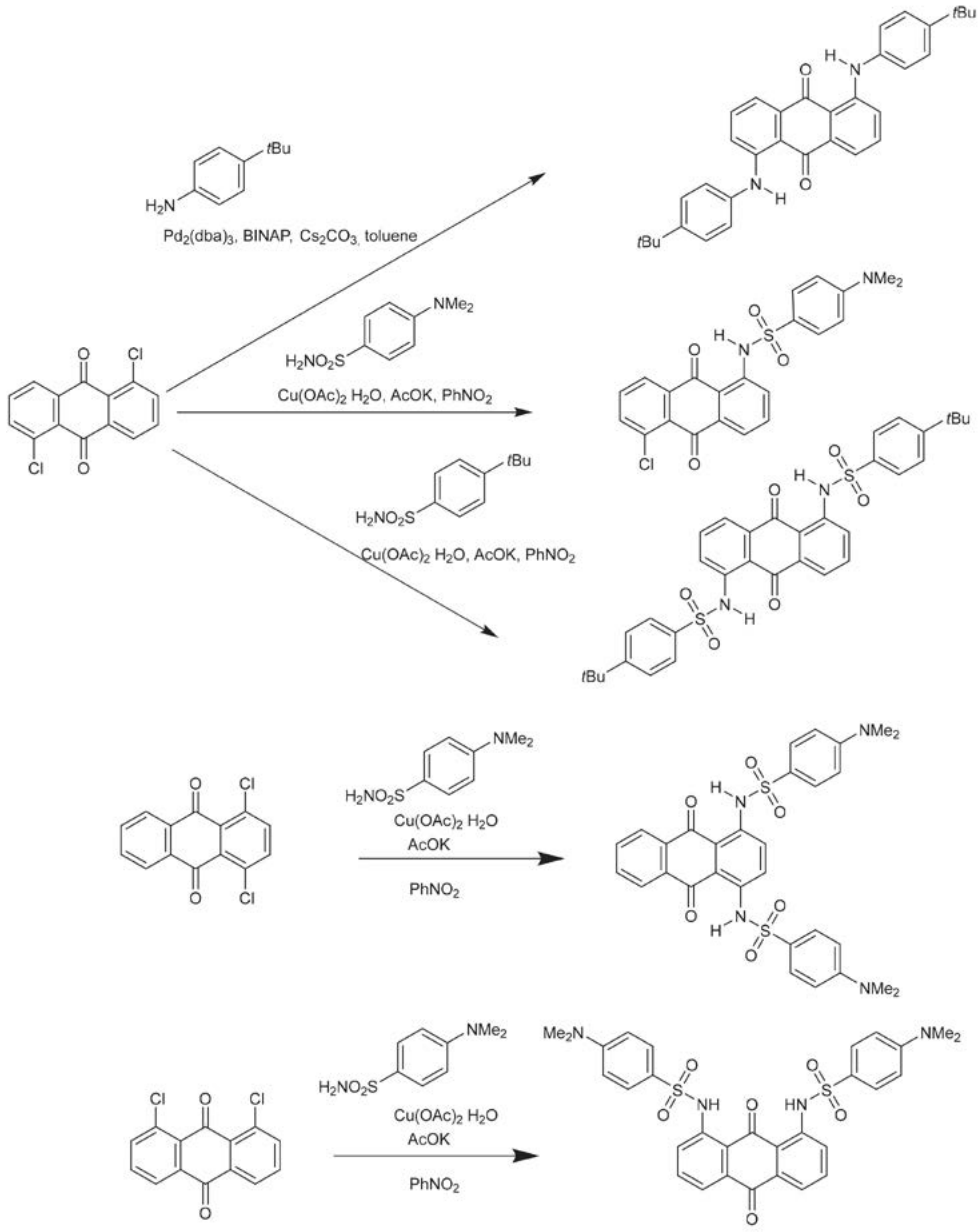
Scheme 1. Nucleophilic substitution reactions of dichloroantraquinones.

arylamino derivatives and arylsulfonamide derivatives in good yields (62–98%) (Scheme 1).[20]

The nucleophiles used can also allow the formation of the disubstituted anthraquinones along with the mono product in the reaction. For example, in the same study, nucleophiles containing a terminal *tert*-butyl group were used to increase solubility and to carry out the reaction to form 1,5-disubstituted anthraquinone derivatives. In the reaction with *N*,*N*-dimethylaminophenylsulfonamide, 1,4- and 1,8-disubstituted anthraquinone derivatives were obtained in reasonable yield, while 1,5-disubstituted product could not be obtained under the same reaction conditions. Considering that the electron donating property of the terminal NH_2 group, which is suitable for the Buchwald–Hartwig cross-coupling reaction, is reduced due to the electron accepting neighboring sulfone unit, it is concluded that this limited reactivity is due to the limited solubility of these derivatives (Scheme 2).[20,26]

Anthraquinone derivatives that can be used as antioxidants are very good electron and hydrogen donors. However, their radical structure is relatively stable due to their resonance delocalization. Interpretation of antioxidant values of anthraquinones is quite difficult due to the existence of different types of molecular radical scavenging mechanisms and their antioxidant properties depending on the structure.[27] Although the antioxidant activity determinations of anthraquinones have been studied with most of the classical methods known before, as far as we know, they have never been investigated with the CERAC assay (Table 1).[28,29]

The basis of the CERAC method is based on electron transfer between Ce(IV) and antioxidant compound in an acidic sulfate-containing medium (i.e., H_2SO_4 and Na_2SO_4). In this redox reaction, antioxidant compounds are oxidized and Ce(IV) ions are reduced to Ce(III) ions. Meanwhile, the absorbance of Ce(IV) decreases after interacting with the antioxidant molecule.[36] The reasons for



Scheme 2. Synthesis of disubstitue anthraquinones.

using sulphate media in this method are: (i) Ce(IV)/Ce(III) reduction potential is low when sulphate ions are sufficiently present; (ii) the ability of Ce(IV) to complex with organic molecules is reduced; and (iii) Ce(IV) sulphate is of long-term stability in the solutions in the environment containing H_2SO_4.[37–39]

2. Experimental

2. 1. Chemicals and Apparatus

Unless specifically indicated, all chemicals and reagents used in this study were purchased from commercial sources and used without purification. Chemicals used for synthesis and CERAC analysis of anthraquinone derivatives were: 1,5-dichloroanthraquinone, allylamine, 3,3'-diaminodiphenylsulfone, *para*-aminobenzenesulfonamide, 2-(ethylmercapto)ethanol, ethylene glycol, Trolox (Sigma-Aldrich), $Ce(SO_4)_2{\cdot}4H_2O$ and H_2SO_4 (Merck). FTIR, ESI-MS, ^1H and ^{13}C NMR spectra were recorded with Shimadzu IR Spirit Spectrophotometer, Shimadzu LC-MS 8045 Triple Quadrupole Mass Spectrometer and Agilent VNMRS 500 MHz Nuclear Magnetic Resonance Spectrophotometer, respectively. Melting points were recorded by digital melting point equipment Büchi SMP20 (B-540). CERAC antioxidant assay studies were carried out at Istanbul University Plant and Herbal Products Application and Research Center.

Table 1. Antioxidant activities and mechanisms of some anthraquinones

Anthraquinone	Experimental Method	Mechanism
Purpurin	• DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging capacities.	Can be associated with 3 hydroxy groups.[30]
Alizarin	• Trolox (6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) equivalents (measure the free radical scavenging activity).	Can be associated with electron or hydrogen atom transfer.[31]
Emodin Physcion Emodin-8-*O*-β-D-idopyranoside	• DPPH radical scavenging capacities.	Can be associated with intermolecular hydrogen bridges and asidic portion's ability to donate H• and form the oxidized structure.[32]
Asphodeline anatolica *Asphodeline baytopae* *Asphodeline brevicaulis* *Asphodeline cilicica*	• Radical scavenging activities measured using DPPH radical. • Phosphomolybdenum and β-carotene bleaching methods. • ABTS (2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) radical cation were expressed as trolox equivalents. • The reducing power measured using cupric ion reducing activity (CUPRAC). • Ferric ion reducing antioxidant power (FRAP). • Metal chelating activity on ferrous ions was expressed as EDTA equivalents.	• Antioxidant molecules interact with DPPH and ABTS radicals via electron or hydrogen atom transfer, converting them to a stable structure or a non-radical species. ABTS activity can be explained as dependent on flavonoid level. • High reducing power may be attributed to high polyphenol and flavonoid content of structure.[33]
Alaternoside Physcion-8-*O*-rutinoside Rhamnocitrin	• DPPH radical scavenging capacity.	May be attributed to the higher number of hydroxyl groups.[34]
Aloe	• AAPH (2,2'-azobis(2-methylpropionamidine) dihydrochloride) were generated peroxyl radicals scavenging capacity. • CUPRAC	Reducing power may be attributed to hydrogen donating ability.[35]

2. 2. 1-Synthesis of Anthraquinone Derivatives 3a–d

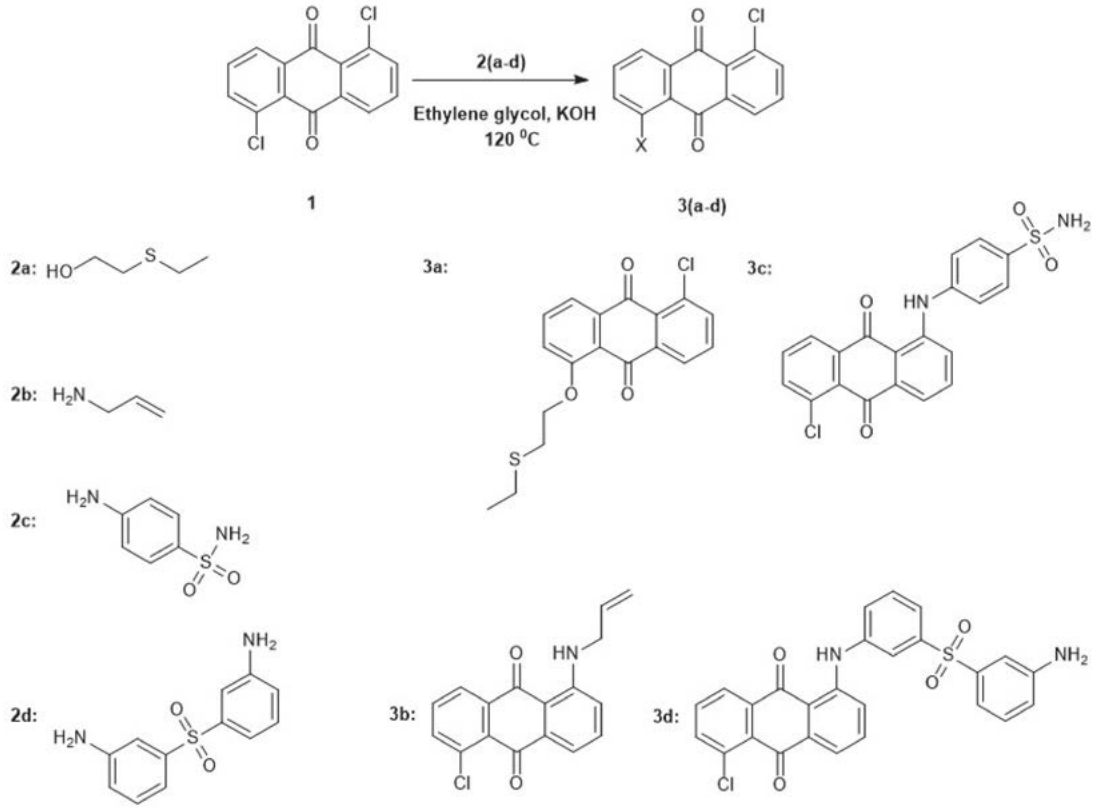
Anthraquinone derivatives were synthesized by a similar method to that in the literature (Scheme 3).[40] Based on the application of this method, after adding 25 mL of ethylene glycol to the 3.6 mmole of 1,5-dichloroanthraquinone compound, nucleophile and potassium hydroxide at an equimolar ratio were added to the mixture. Thereafter the mixture was refluxed at 110–120 °C for 48 h, the product was obtained by column chromatography, if necessary, and dried in a vacuum oven at 40 °C.

2. 3. 2-Characterization of Synthesized Compounds

1-Chloro-5-(2-(ethylthio)ethoxy)anthracene-9,10-dione (3a). Obtained by the reaction of 1,5-dichloroanthraquinone (**1**) (1 g, 3.6 mmol) and 2-(ethylmercapto)ethanol (**2a**) (0.38 g, 3.6 mmol). Product is yellow solid, 0.359 g (28.72%), R_f 0.54 (ethyl acetate), m.p. 164–165 °C. FTIR (ATR, cm^{-1}): 3100 (-$CH_{aromatic}$), 2933 (-$CH_{aliphatic}$), 1650, 1583 (C=O), 1260, 1055 (C–O). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.90–7.74 (m, 3H, -$CH_{aromatic}$), 7.60 (t, J = 7.50 Hz, 2H, -$CH_{aromatic}$), 7.27 (d, J = 8.0 Hz, H, -$CH_{aromatic}$), 4.90 (t, J = 5.40 Hz, 2H, -OCH_2), 2.48–2.40 (m, 4H, -SCH_2), 1.30–1.26 (m, 3H, -CH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 189.0, 182.0, 138.0, 136.0, 122.0, 118.0. ESI+: *m/z* 364.5 $[M+NH_4]^+$, $C_{18}H_{15}ClO_3S$ (M_A = 346.8 g/mol).

1-(Allylamino)-5-chloroanthracene-9,10-dione (3b). Obtained by the reaction of **1** (1 g, 3.6 mmol) and allylamine (**2b**) (0.21 g, 3.6 mmol). Product is orange solid, 0.196 g (18.32%), R_f 0.64 (ethyl acetate), m.p. 155–156 °C. FTIR (ATR, cm^{-1}): 3502 (-NH), 3080 (-$CH_{aromatic}$), 2949 (-$CH_{aliphatic}$), 1648, 1585 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.83–7.76 (m, 3H, -$CH_{aromatic}$), 7.62–7.58 (m, 2H, -$CH_{aromatic}$), 7.29 (dd, J_1 = 8.40 Hz, J_2 = 1.1 Hz, H, -$CH_{aromatic}$), 4.88 (bs, H, -NH), 4.17 (m, 3H, =$CH_{allylic}$, =$CH_{2allylic}$), 3.80 (t, J = 4.90 Hz, 2H, -NCH_2). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 188.0, 180.0, 160.0, 161.0, 138.0, 136.0, 133.0, 122.0. ESI+: *m/z* 298.3 $[M+H]^+$, $C_{17}H_{12}ClNO_2$ (M_A = 297.7 g/mol).

4-((5-Chloro-9,10-dioxo-9,10-dihydroanthracen-1-yl) amino)benzenesulfonamide (3c). Obtained by the reaction of **1** (1 g, 3.6 mmol) and *para*-aminobenzenesulfonamide (**2c**) (0.62 g, 3.6 mmol). Product is yellow oily substance, 0.175 g (11.7%), R_f 0.60 (ethyl acetate). FTIR (ATR, cm^{-1}): 3400, 3300 (-NH), 3091 (-$CH_{aromatic}$), 1640, 1580 (C=O),



Scheme 3. Synthesized anthraquinone compounds.

1261 (S=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.10 (bs, 1H, -NH), 7.85–7.75 (m, 4H, -$CH_{aromatic}$), 7.63–7.58 (m, 4H, -$CH_{aromatic}$), 7.29 (d, J = 8.0 Hz, 2H, -$CH_{aromatic}$), 4.87 (bs, 2H, -NH_2). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 189.0, 181.0, 160.0, 136.0, 120.0, 118.0. ESI: m/z 414.0 $[M+H]^+$, $C_{20}H_{13}ClN_2O_4S$ (M_A = 412.8 g/mol).

1-((3-((3-Aminophenyl)sulfonyl)phenyl)amino)-5-chloroanthracene-9,10-dione (3d). Obtained by the reaction of **1** (1 g, 3.6 mmol) and 3,3'-diaminodiphenylsulfone (**2d**) (0.89 g, 3.6 mmol). Product is yellow solid, 0.136 g (7.7%), R_f 0.56 (ethyl acetate), m.p. 173–174 °C. FTIR (ATR, cm^{-1}): 3360, 3290 (-NH), 3100 (-$CH_{aromatic}$), 1740, 1680 (C=O), 1295 (S=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.10 (bs, H, -NH), 7.80–7.73 (m, 4H, -$CH_{aromatic}$), 7.61–7.56 (m, 5H, -$CH_{aromatic}$), 7.27 (d, J = 8.30 Hz, 5H, -$CH_{aromatic}$), 4.89 (bs, 2H, -NH_2). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 188.0, 181.0, 162.0, 160.0, 138.0, 136.0, 124.0, 116.0. ESI+: m/z 489.9 $[M+H]^+$, $C_{26}H_{17}ClN_2O_4S$ (M_A = 488.9 g/mol).

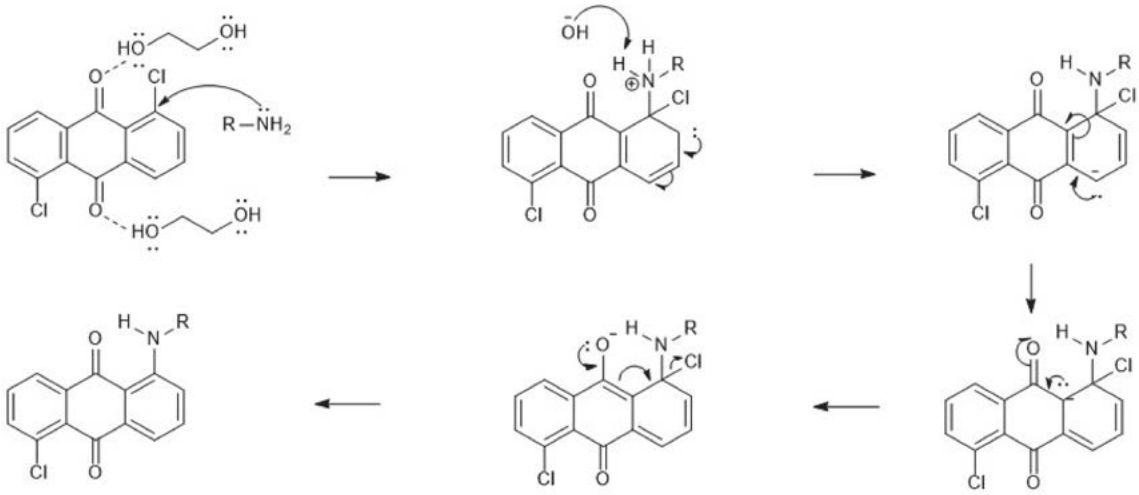
2. 4. 3-CERAC (Cerium(IV) Reduction Antioxidant Capacity) Method

The Trolox equivalent antioxidant capacity of an antioxidant molecule is the millimolar (mM) concentration of the Trolox solution, which has the same reducing power as 1 mM antioxidant solution under the same conditions. Furthermore, the measure of total antioxidant capacity (TAC) refers to the cumulative effect of all antioxidants present in the compound.[36,41]

In the laboratory study to determine the CERAC antioxidant activities of anthraquinone compounds, $Ce(SO_4)_2$ solution was added to anthraquinone solution prepared in DMSO at certain concentrations in an acidic sulfate-containing medium. After the reaction mixture was left for 30 min at room temperature, absorbance measurements were made at 320 nm, which is the maximum absorption wavelength of Ce(IV). Since the initial absorption of Ce(IV) decreases after interacting with antioxidant molecules, the ratio of the antioxidant molar absorptivity coefficient obtained from the measured absorbance values to the molar absorptivity coefficient obtained from the concentration–absorbance plot of Trolox gives the TEAC (Trolox equivalent antioxidant capacity) value.

3. Results and Discussion

In this study, we prepared systematically a series of arylaminoanthraquinone derivatives containing electron accepting sulfone units and electron donating dialkylami-



Scheme 4. Possible mechanism of nucleophilic substitution reaction.

no or oxo units, by refluxing 1,5-dichloroanthraquinone compound with amino, thio and oxo nucleophile in basic KOH medium in ethylene glycol at 110–120 °C. This synthesis method, besides being economical and practical, is a one-step (one pot synthesis) reaction and makes it possible to obtain pure products without the need for hard-to-find and expensive catalysts.[40]

Reaction between nucleophiles and 1,5-dichloroanthraquinones is driven by the S_NAr mechanism (aromatic nucleophilic substitution reaction). The hydrogen bond between the ethylene glycol and the oxygen of the carbonyl group increases the electrophilicity of the anthraquinone, facilitating the attack of the nucleophile (Scheme 4.)

Amino- and sulfur-containing derivatives of 9,10-anthraquinones have received great attention for their beneficial antioxidant properties.[16] In this context, based on this bioactivity, we preferred amino-, sulpho- and sulfur-containing nucleophiles, which can significantly affect the antioxidant properties of anthraquinones, in order to develop new and powerful biological agents of synthetic origin.

FTIR spectra of compounds **3b–d** showed clear absorption bands at 3500–3290 cm^{-1}, 1740–1580 cm^{-1} and 1583–1520 cm^{-1} belonging to υ(NH) amine, υ(C=O) and υ(C=C) aromatic, respectively. Furthermore, υ(C–O) band of **3a** and υ(S=O) bands of compound **3c–d** appeared at 1055 cm^{-1} and 1261–1295 cm^{-1}, respectively.

For compounds **3a–d**, the aromatic protons of the anthraquinone moiety gave resonance signals in ^1H NMR spectra between 7.90–7.27 ppm as multiplets, doublets and triplets. The $-OCH_2$ and $-SCH_2$ protons of compound **3a** showed resonance signals at 4.90 and 2.48–2.40 ppm, respectively. The signal of the -NH proton for compound **3b** was observed at 4.88 ppm, while it was around 8.10 ppm for both **3c** and **3d**. In addition, the $-NH_2$ proton signals for compounds **3c** and **3d** were observed at about 4.87 ppm. The carbon atom resonance signal of the carbonyl group of anthraquinone derivatives **3a–d** in ^{13}C NMR was observed in the range of 189.0–180.0 ppm. The ^1H, ^{13}C NMR and FTIR spectroscopic data of the obtained compounds are in agreement with similar anthraquinone derivatives described in the literature.[19,20,42]

The presence of an electron accepting sulpho unit between amino and aryl units, the terminal group containing an electron donating amino unit, the number and position of nitrogen and sulfur atoms in the structure contributed significantly to the decrease of yield and antioxidant activity. Since mercaptoethanol and allylamine nucleophiles do not contain terminal electron-donating alkyl amino groups, their reactions proceeded more smoothly, producing the corresponding **3a** and **3b** anthraquinone derivatives in higher yields than **3c** and **3d**. Because of the fact that, 3,3'-diaminodiphenylsulfone and *para*-aminobenzenesulfonamide contain strong electron donating alkylamino terminal groups, their reactions with 1,5-dichloroanthraquinone have not progressed completely. On the other hand, during the synthesis of **3b** not only the monoproduct (**3b**), but also the disubstituted anthraquinone derivative was formed with the removal of both chlorines as a result of the nucleophilic substitution reaction. When the synthesis of **3b** was terminated, it was observed that the amount of 1,5-dichloroanthraquinone compound still present in the reaction medium was higher than the amount of unreacted anthraquinone in the synthesis of **3c** and **3d**.

In the nucleophilic substitution reactions of **2a** and **2c** as nucleophiles reacting with 1,5-dichloroanthraquinone, it can be thought that further reactivity of the monoproduct is more suppressed due to the fact that the electron withdrawing properties of the monochloroanthraquinone derivatives (**3a** and **3c**) formed in the reaction are more reduced compared to **3b** and **3d** by the addition of electron donating nucleophiles to the anthraquinone.[20]

TEAC and TAC values of compound **1** and its syn-

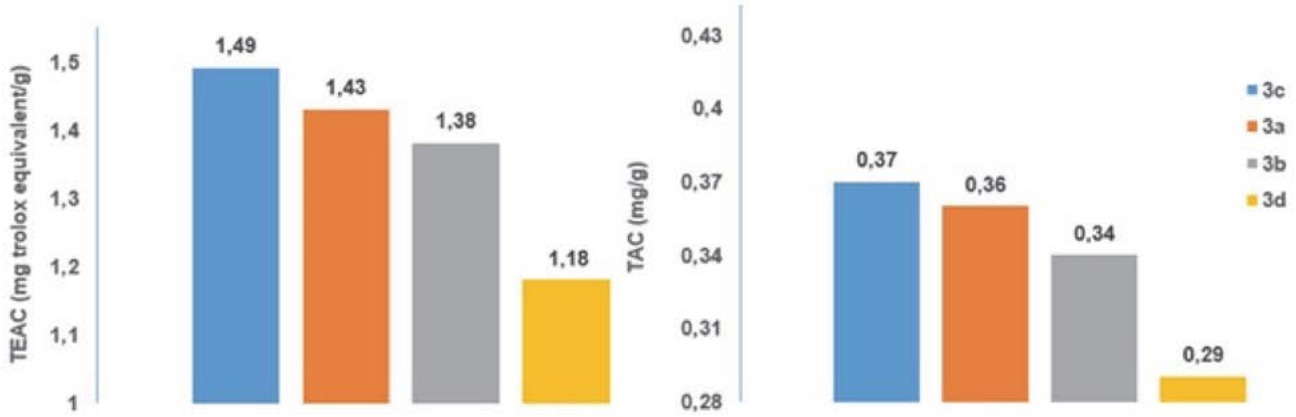


Figure 1. TEAC and TAC values of synthesized anthraquinones: blue (**3c**), orange (**3a**), grey (**3b**) and yellow (**3d**).

thesized derivatives **3a**–**d** determined by CERAC method are shown in the Figure 1.

It is difficult to interpret the antioxidant activity properties of anthraquinone compounds. Because the antioxidant effect, the radical capture molecule mechanism, may differ in terms of structure-dependent characteristics and environmental effects.[43]

Anthraquinones are good electron and proton donors. In addition, radical structures show relative stability due to the resonance delocalization.[44] In the CERAC method, electron transfer takes place.[36] According to the results of the CERAC analysis, starting 1,5-anthraquinone compound (**1**) did not exhibit antioxidant activity unlike its derivatives; this can be explained by the fact that it does not contain nitrogen and sulfur atoms in its structure.

Among the analyzed samples, compound **3c** showed the highest TEAC and TAC values determined by CERAC assay. It can be interpreted that it originates from the sulpho (O=S=O) group and -N atom in its structure. In addition, the increased stability as a result of the increase in electron density on the carbon atom to which the sulpho group is attached, through delocalization caused by the unshared electron pair in the -NH atom in this compound, may have affected the activity. Considering the free structure effects of atoms on the antioxidant activity, it can be commented that the low number of bonds of the sulfur atom in compound **3a** may have contributed to high antioxidant activity compared to **3d**.

4. Conclusıons

A simple metal-free alternative procedure for Ullmann type C–N coupling reactions has been carried out by allowing dichloroanthraquinones to react with a variety of nucleophiles in the presence of ethylene glycol. In conclusion, we have successfully developed a simple, moderate, economical and environmentally friendly procedure for the synthesis of N- and O-aryl anthraquinone derivatives under metal-free conditions.[40] The fact that the derivatives of 1,5-anthraquinone containing similar groups to those introduced by our nucleophiles have not been studied much, increases the importance of the study.[20,45,46]

In addition to what we said, the reason why the CERAC method was preferred for the determination of antioxidant activity is that it is easy, does not require a very high level of equipment, and as far as we know, the antioxidant activities of anthraquinones have never been studied with this method before. According to the results of the analysis, while the 1,5-dichloroanthraquinone starting compound (**1**) did not exhibit CERAC antioxidant activity, all the synthesized derivatives responded to the CERAC method.

Acknowledgements

We would like to thank Istanbul University Plant and Herbal Products Application and Research Center for their CERAC assay studies.

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Povzetek

Povzetek. Sintetizirali smo nove ciklične antioksidante, ki temeljijo na antrakinonu, in vsebujejo aminsko, tiolno in okso skupine ter določili njihovo antioksidativno kapaciteto s pomočjo CERAC testa (antioksidativna kapaciteta glede na redukcijo cerijevih(IV) ionov). Za karakterizacijo pripravljenih antrakinonskih derivatov, ki so izkazovali CERAC antioksidativno kapaciteto, smo uporabili ^{1}H, ^{13}C NMR in FTIR spektroskopijo ter ESI (ionizacija z razprševanjem v električnem polju) masno spektrometrijo. Ta študija je pomembna, saj je bila antioksidativna kapaciteta antrakinonskih derivatov prvič določena s pomočjo CERAC metode in na osnovi vrednosti CERAC-Trolox ekvivalentne antioksidativne kapacitete (TEAC); poleg tega so bile vrednosti za preučevane spojine večje kot za sam Trolox. Pomembno je tudi poudariti, da imajo pripravljene spojine potencialno biološko uporabnost, saj vsebujejo žveplove in dušikove atome, vse skupaj pa se odslikuje v pomembnosti te objave v literaturi.

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