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Spectroscopic and structural aspects of the reactions of 1,4-quinones with sulfur and nitrogen nucleophiles

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ABSTRACT

A series of 1,4-benzoquinone derivatives from 2,5-dichloro-3,6-diethoxy-1,4-benzoquinone and 2,6-dichloro-3,5-diethoxy-1,4-benzoquinone were prepared by nucleophilic substitution reactions of sulfur and nitrogen nucleophiles. Spectral techniques (^{1}H NMR, ^{13}C NMR, FT–IR, and LC–MS) were employed to structurally characterize the reaction products of alkoxy, chloro substituted-1,4-benzoquinones with thiols and amines in the presence of sodium carbonate in ethanol at room temperature. The orientations and the regioselectivity of the reactions of alkoxy, chloro substituted-1,4-benzoquinones with various thiol and amine nucleophiles are discussed.

1. Introduction

Quinones are prevalent structural components in various natural products, which are associated with diverse biological activities, including antibacterial, antimalarial, antifungal, antitumor activities [1–5]. The biological activity of the quinones originates from the redox chemistry of the quinone system [6]. A great deal of research has been conducted in recent years on the charge transfer complexes of quinones because of their wide applications ranging from chemistry, medicine to biology [7,8]. Despite the fact that natural products are important sources of new biologically active molecules for drug discovery, their structural complexity and poor availability make greatly difficult natural product-based drug discovery. The discovery of new synthetic methodologies for the preparation of organic compounds is a prime focus of the researches in the field of current organic, bioorganic, and medicinal chemistry [9–12]. In recent years, the concept of privileged medicinal structures or scaffolds that commonly consist of quinone moiety, which contains heteroatoms as substituents, has emerged as one of the guiding principles of drug discovery process [3,13]. Quinone derivatives have been widely investigated for cancer therapy and many drugs containing a quinone moiety, such as anthracyclines, daunorubicin, mitomycin, and saintopin have received clinical approval for cancer treatment [13–16].

Structure–activity relationship of quinone compounds showed that the ring number, the position, and number of heteroatoms in the side chain or inside the ring with various substituents are very crucial to affect the biological activities [17]. Especially, we have known incorporation of a heteroatom such as a sulfur or nitrogen atom into the ring of the quinone skeleton can change the physicochemical properties and create a new pharmacophore with a different biological profile [17]. Chemical structures of biologically important compounds that include the benzoquinone core and sulfur or nitrogen atoms in the side chain or inside the ring with various substituents are shown in Fig. 1 [1,3,11,18–20]. The interesting biological profile resulting from the presence of a heteroatom, sulfur

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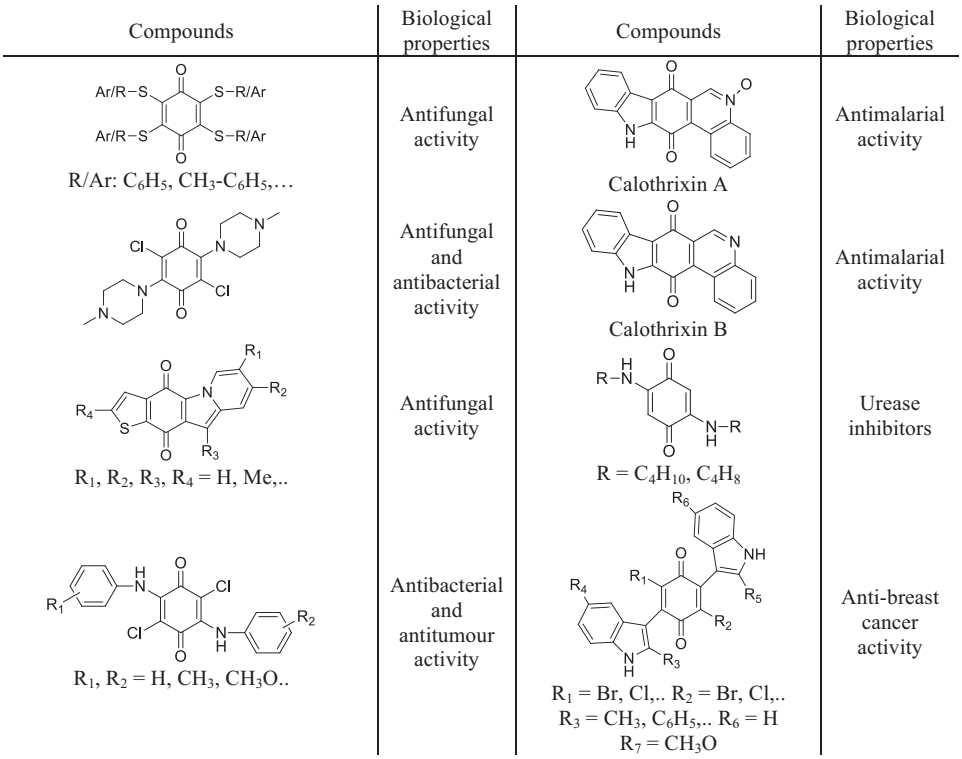

Fig. 1. Chemical structures of biologically active 1,4-benzoquinones.

or nitrogen, prompted us to synthesize quinone derivatives possessing nitrogen and sulfur atoms.

There have been new studies about charge transfer complexes of a number of quinones with a variety of donors [21–23] and the mechanism behind the interaction of quinone with drugs. In recent years, the spectral, thermodynamic, and kinetic aspects of the interaction of 1,4-benzoquinones with variable alkyl chain of alkoxy groups such as 2,3,5-trichloro-6-methoxycyclohexa-2,5-diene-1,4-dione, 2,3,5-trichloro-6-ethoxycyclohexa-2,5-diene-1,4-dione, and 2,3,5-trichloro-6-butoxycyclohexa-2,5-diene-1,4-dione with sulfamethoxazole drug were investigated for understanding the mechanism of the interaction and to characterize the structures of the products formed in these interactions [24].

The reactivity of quinones towards nucleophiles is dependent to a large degree on the π-acceptor character and electron affinity of the quinones. To the best of our knowledge, LCAO-MO calculations for 1,4-benzoquinone have shown that the distribution of π-electron density is very changeable. This class of compounds has a diverse range of activities because of a wide variation in the electron density of quinones [25]. Possible variations in substitution models on the quinone ring affect its capability to accept electrons and so its capacity to reconcile biological reactions [26,27]. As shown in Fig. 2, electron affinity can be increased by appropriate substitution of the quinone. The electron affinity of unsubstituted 1,4-benzoquinone, which has a low value (1.91 eV), can be changed by replacement of hydrogen by other atoms [28].

We aimed to synthesize new 1,4-benzoquinone compounds, which not only may give promising candidates with respect to biological activity but also may be potent receptors for interaction with drugs. Although there were a lot of studies investigating features and reactions of quinones, there is a notable lack of information about the structural aspects on the nucleophilic substitution reactions of 1,4-quinone derivatives. Additionally, we have focused on nucleophilic reactions of 1,4-quinones and spectroscopic, structural aspects of the reactions of quinones with sulfur and nitrogen nucleophiles. We also observed the behavior of the two isomers of alkoxy, chloro substituted-1,4-benzoquinones on nucleophilic reactions.

2. Results and discussion

1,4-Benzoquinones are known to be easily reacted with various nucleophiles in different conditions [29,30]. Earlier studies show that when chloranil (**1**) reacts with thiol in the presence of Na_2CO_3 and ethanol, alcohol can act as a nucleophile along with thiol, and replace chloro atoms [31]. We have observed this situation in the reaction of chloranil (**1**) with *n*-octylthiol in the presence of Na_2CO_3 and ethanol (Scheme 1).

In the beginning of our studies, we studied the chloranil compound to obtain new quinone derivatives but due to high reactivity of chlorine atoms in the structure, a lot of by-products were obtained. This situation suffers from the low yields and serious difficulties in purification. We decided to assist *p*-chloranil by two ethoxy groups to