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Antioxidant and acetylcholinesterase inhibition properties of novel bromophenol derivatives

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ABSTRACT

In this study, series of novel bromophenol derivatives were synthesized and investigated for their antioxidant and AChE inhibition properties. Novel brominated diarylmethanones were obtained from the acylation reactions of benzoic acids with substituted benzenes. One of the bromodiarylmethanone was synthesized from the bromination of diarylmethanone with molecular bromine. All diarylmethanones were converted into their bromophenol derivatives with BBr_3. The antioxidant activities of all synthesized compounds were elucidated by using various bioanalytical assays. Radical scavenging activities of compounds **10–24** were evaluated by means of $DPPH^{\cdot}$ and $ABTS^{\cdot+}$ scavenging activities. In addition, reducing ability of **10–24** were determined by Fe^{3+}, Cu^{2+}, and $[Fe^{3+}\text{-}(TPTZ)_2]^3$ reducing activities. α-Tocopherol, trolox, BHA, and BHT were used as positive antioxidant and radical scavenger molecules. On the other hand, IC_{50} values were calculated for $DPPH^{\cdot}$, $ABTS^{\cdot+}$ scavenging, and AChE inhibition effects of novel compounds. The results obtained from the current studies clearly show that novel bromophenol derivatives **20–24** have considerable antioxidant, antiradical, and AChE inhibition effects.

1. Introduction

Naturally occurring bromophenols are abundant in marine life [1]. They are mostly isolated from the marine algae as a very large and diverse group of eukaryotic organisms [2]. Recently, the total syntheses of these compounds have also attracted the synthetic community's attention [3], because it has been demonstrated that natural and synthetic bromophenols have diverse biological activities [4]. For instance, Vidalol A (**1**) and Vidalol B (**2**), which are isolated from the Caribbean marine red alga *Vidalia*, were shown to have anti-inflammatory properties [5]. On the other hand, bromophenols **3–5** isolated from the brown alga *Leathesia nana* showed cytotoxicity [6] and anticancer [7] activities. In another study, Wang et al. has reported the aldose reductase inhibitory activity of the natural product **6** [8]. Furthermore, radical-scavenging properties of **6** [9], antioxidant activities of **1** [10] and **6** [11] have also been investigated. Recently, the total synthesis and the biological activities of some natural bromophenols have been performed by our group [12–15]. In these studies, the human carbonic anhydrase inhibitory actions of **2** [12], **4–6** [13a,b], their synthetic derivatives [14] and paroxonase inhibitory properties [15] of some related compounds were evaluated (Fig. 1).

The oxidative stress has been a major research interest due to its implicated role in human diseases such as cancer, atherosclerosis, and brain dysfunction [16]. Free radicals, especially reactive oxygen species (ROS), such as superoxide anion radical ($O_2^{\cdot-}$), hydroxyl radical ($HO^{\cdot}$), and hydrogen peroxide (H_2O_2) generated during metabolism can damage macromolecules including fatty acids, proteins, DNA, and other macromolecules, which cause various diseases including neurodegenerative diseases, cardiovascular diseases, cancers and ageing-related disorders [17]. Many degenerative disorders are initiated by the reaction of ROS with human body cell constituents. All aerobic organisms have antioxidant defenses, including both antioxidant enzymes and antioxidant food constituents to remove or repair the damaged biomolecules [18a–c]. Antioxidants are bioactive compounds commonly used to preserve the quality of food products by protecting them against oxidative rancidity [19]. In the case of oxidative stress, the most susceptible molecules for ROS attack are lipids, proteins, and nucleic acids [20]. The most injurious effects on the viability of the cells and human health are oxidative changes in nucleic acids, which cause mutagenic processes and cancer [21]. Antioxidant compounds protect the human body from free radicals and many

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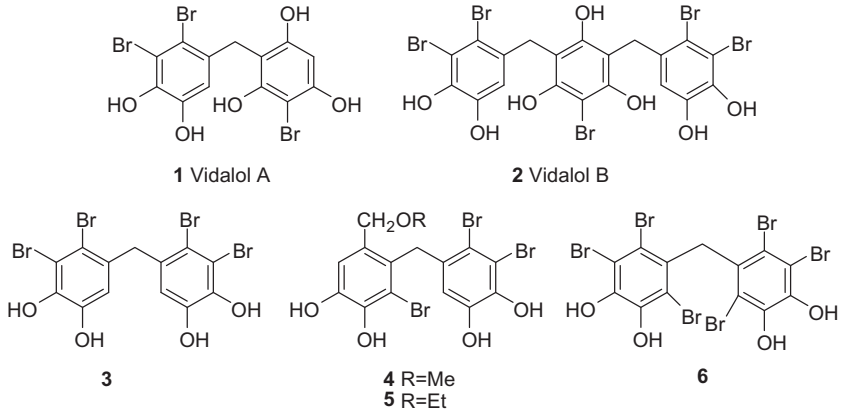

Fig. 1. Some selected natural products **1**–**6**.

chronic cardiovascular diseases, cancers, and ageing by capturing free radicals [22]. Also, these bioactive compounds can scavenge free radicals or ROS and increase shelf life by retarding the process of lipid peroxidation, which is one of the major reasons for deterioration of food and pharmaceutical products during processing and storage [23a,b]. They retard the progress of many chronic diseases as well as lipid peroxidation. Recently, there is a growing interest in safer antioxidants for food and pharmaceutical applications, and a growing trend in consumer preferences towards safer antioxidants [24a–d].

Alzheimer's disease (AD) is a fatal and chronic neurodegenerative disease that usually starts slowly and gets worse over time. It was reported that the disease process is associated with tangles and plaques in the brain. There were 35 million people worldwide with AD, and there has been no effective treatment developed for this disease up to now. The use of acetylcholinesterase inhibitors (AChEIs) to block the cholinergic degradation of acetylcholine (Ach) is therefore considered to be a promising approach for the treatment of AD [25a–c]. At the present, the main clinical treatment strategy for AD is the use of AChEIs such as Donepezil, Rivastigmine, and Galantamine. These drugs modestly improve the memory and cognitive function but do not prevent progressive neurodegenerative effects because of the complexity of AD pathogenesis. Based on these discoveries, many different approaches to treat AD have been developed. In particular, the use of AChEIs for this multifaceted disease has received much attraction [25a–c].

As it can be seen from the brief description given above, bromophenols show useful biological activities. In our previous studies, we synthesized bromophenols containing polybromides in their structures. The synthesis and biological evaluation of novel bromophenols having only a single bromine atom will be important for synthetic and biological features. In this context, here we report the synthesis and determination of antioxidant, antiradical and AChE inhibition effects of five novel bromophenols.

2. Results and discussion

2.1. Chemistry

The reactions of acids or alcohols with benzene related compounds in the presence of polyphosphoric acid (PPA) afford diarylmethanones [26a,b]. It is obvious from the structure of **9** that an electrophilic aromatic substitution carried out on this compound can lead to two different products. However, methoxy group has more steric hindrance than a bromine atom. For this reason, an electrophilic aromatic substitution of these kinds of compounds react at the *ortho*- position of –Br substituent and at the *para*- position of an –OMe group [26b]. Therefore, benzoic acids **7** and **8** were reacted with commercially available 3-bromoanisole (**9**) in the presence of PPA to give diarylmethanons **10** and **11** in moderate yields. On the other hand, 2-substituted 1,4-dimethoxy benzenes (especially Br or Me substituted ones) undergo electrophilic aromatic substitution at the *ortho*- position of the OMe group and the *para*- position of the substituent [27]. Similarly, the reactions of acids **12** and **13** with a known 2-bromo-1, 4-dimethoxy benzene (**14**) [28] afforded diarylmethanones **15** and **16** [29] in 76% and 50% yield, as expected (Scheme 1).

Again the reaction of carboxylic acid **12** with 1,3-dimethoxy benzene (**17**) in the presence of PPA produced the compound **18** [30]. Selective bromination of aromatic compounds is an important route for the synthesis of novel target compounds. There are several reagents used for this purpose. Molecular bromine (Br_2) is one of these reagents mostly used for the bromination of activated aromatic compounds [31]. To extend our research on the synthesis of another mono brominated compound, the bromination of **18** with 1.01 equiv. of Br_2 at room temperature (rt) for 12 h (h) afforded mono brominated diarylmethanone **19** with a yield of 62% (Scheme 2).

Demethylation of aryl methyl ethers is one of the most convenient methods for the synthesis of biologically active phenolic compounds [32a,b]. BBr_3 is one of the most widely-used reagents for the *O*-demethylation of aryl methyl ethers [33]. Hence, demethylation reactions of diarylmethanones **10**, **11**, **15**, **16**, and **19** with BBr_3 at 0–25 °C under N_2 for 24 h furnished novel bromophenols **20**–**24** in 91%, 80%, 92%, 93%, and 83% yields, respectively (Scheme 3).

The structures of the synthesized compounds were elucidated with ^1H, ^{13}C NMR, IR and elemental analysis.

2.2. Biochemistry

2.2.1. Antioxidant properties

Lipid peroxidation in foods has become a major concern with the increased use of polyunsaturated vegetable, fish, or microbial oils for health benefits. It not only produces undesirable off-flavours, but also decreases the nutritional quality and safety of food products [34a,b], which are unacceptable to consumers. Among the methods employed to retard or inhibit oxidation of lipids, addition of antioxidants is the most effective way [35a,b]. On the other hand, phenolic compounds have attracted wide range of interest because of their health benefits, biological features and impact on multiple sensory attributes of food including colour, flavour and astringency of foods [36a,b]. They are thought to be an integral part of both human and animal diets and frequently used for