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Ferrocenyl-contained dendritic-like antioxidants with dihydropyrazole and pyrazole as the core: investigations into the role of ferrocenyl group and structure–activity relationship on scavenging radical and protecting DNA

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ABSTRACT

Eight ferrocenyl and three corresponding phenyl dendritic-like antioxidants with dihydropyrazole or pyrazole as the core were synthesized and their antioxidant abilities to scavenge 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+\bullet}$) and to protect DNA against 2,2′-azobis(2-amidinopropane hydrochloride) (AAPH)-induced oxidation were evaluated. It was found that the antioxidant abilities of almost all of the ferrocenyl dendritic-like antioxidants are greater than those of the corresponding phenyl dendritic-like antioxidants remarkably. Moreover, the structure–activity relationships of all these dendritic-like antioxidants were investigated in detail. The quantitative contributions of ferrocenyl group, hydroxyl group, and dihydro-structure in the heterocyclic core to the values of n, n_{app} and $n+n_{app}$ in scavenging $ABTS^{+\bullet}$ and the values of n in protecting DNA against AAPH-induced oxidation were also calculated.

1. Introduction

It is proved that the oxidation of lipids, DNA, membranes, and proteins caused by reactive oxygen species (ROS) incorporating free radicals in vivo is associated with a variety of chronic health problems, such as cancers, atherosclerosis,[1] neurodegenerative processes like Alzheimer's and Parkinson's diseases.[2] Free radicals are single-electron species produced in metabolism[3] or absorbed from environment,[4] which can attack many kinds of cells and tissues.[5] Therefore, supplementation with antioxidants becomes a therapeutic strategy for some diseases[6–8] as the antioxidants can provide hydrogen atoms or electrons to neutralize the single electron.[9] For this reason, exploring effective antioxidants is of importance in medicine and chemistry. Dendrimers are widely used in drug design because of their special affinities toward DNA, membranes, and other biological species.[10] In recent years, some antioxidants with analogous structures called *dendritic antioxidant* have also been synthesized and their abilities to protect DNA against 2,2′-azobis(2-amidinopropane hydrochloride) (AAPH)- and Cu^{2+}-induced oxidation were found greater than those of some polyphenols.[11] As a promising sort of dendritic antioxidants, structures with pyrazole as the core were investigated freshly.[12] Nevertheless, these pyrazoles do not possess rigid dendritic structures, which is suitable to be called dendritic-like antioxidants and their antioxidant abilities are still lower than that of our expectation.

Ferrocene, as an effective phenyl bioisostere, is becoming an applicable platform for drug design by virtue of its redox properties, high liphophilicity and three-dimensional metallocene unit, which may lead to some changes in selectivity toward biological targets compared with a phenyl or alkyl group.[13–15] A mass of drugs have possessed higher activities by introducing ferrocene moiety into molecules, such as antitumor drugs,[16] steroidal drugs,[17] antitubercular drugs,[18] etc. The same strategy was also used to develop antioxidants and the results were satisfactory.[19–21]

Therefore, such useful strategy of introducing ferrocene moiety into molecules was also used in this work to design eight ferrocenyl and three corresponding phenyl dendritic-like antioxidants with dihydropyrazole or pyrazole as the core. The aim of this work is trying to improve the antioxidant abilities of dendritic-like antioxidants with pyrazole as the core aforementioned in literature[12] and investigate the structure–activity relationship, quantitative contributions of ferrocenyl group, dihydro-structure in the heterocyclic core, and hydroxyl group to the antioxidant activities of such species of dendritic-like antioxidants in detail. The synthetic route and the names of these dendritic-like antioxidants are shown in Scheme 1.

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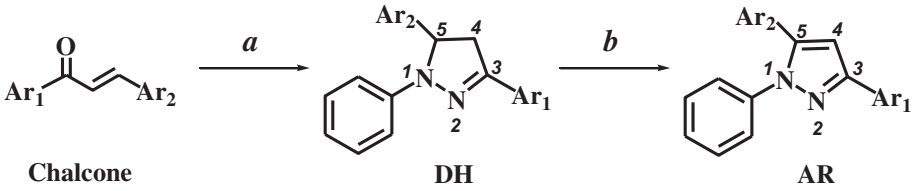
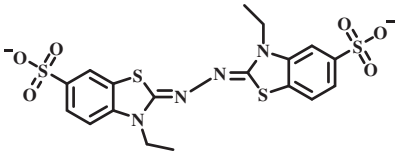


Reaction Conditions:
a) $phNHNH_2$, CH_3COOH-EtOH-H_2O, reflux.
b) The datas of **1AR** to **3AR** are used directly accroding to literatue[12], so they were not synthesized in this work; MnO_2, toluene, reflux for **4AR** and **5AR**; patial spontaneous oxidation during the reaction for **6AR** and **7AR**.

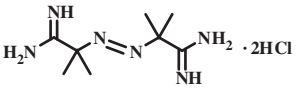
Ar_1	Ar_2	Chalcone	DH	AR
		1	1DH	1AR
HO		2	2DH	2AR
	HO	3	3DH	3AR
	Fe	4	4DH	4AR
Fe		5	5DH	5AR
HO	Fe	6	6DH	6AR
Fe	HO	7	7DH	7AR

Scheme 1. The synthetic route and the structures of the dendritic-like antioxidants with dihydropyrazole and pyrazole as the core.

Their antioxidant abilities were evaluated via scavenging 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+\bullet}$), which is an oxidant-type radical commonly used to test the redox capacities of antioxidants,[22] and protecting DNA against AAPH-induced oxidation, which is commonly used to mimic the oxidation of DNA caused by peroxyl radicals ($ROO^{\bullet}$) in vivo.[23] The structures of $ABTS^{+\bullet}$ and AAPH are shown in Scheme 2.



2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) (**ABTS**)



2,2'-azobis(2-amidinopropane hydrochloride) (**AAPH**)

Scheme 2. Structures of AAPH and $ABTS^{+\bullet}$ used in this work.

2. Results

2.1. Radical-scavenging ability

The radical-scavenging ability is commonly regarded as the basic property of an antioxidant[24] and evaluated by trapping $ABTS^{+\bullet}$ in this work. As shown in Fig. 1, the absorbance of $ABTS^{+\bullet}$ decreases in the presence of dendritic-like antioxidants.

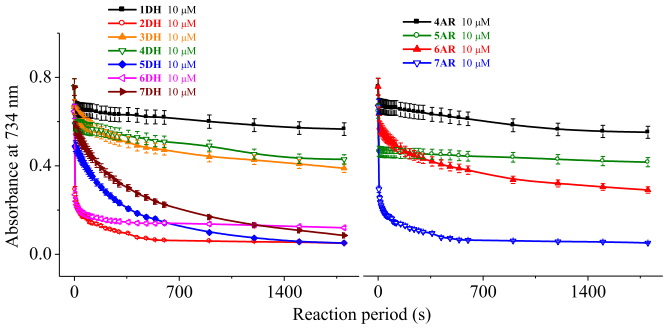


Fig. 1. The decrease in the absorbance of $ABTS^{+\bullet}$ (734 nm) in the presence of 10.0 μM dihydropyrazole and pyrazole derivatives.

The decay of the absorbance of $ABTS^{+\bullet}$ in the presence of an antioxidant was studied by means of chemical kinetics expressed by two equations eventually.[25] The difference between the concentration of $ABTS^{+\bullet}$ at the beginning ($[ABTS^{+\bullet}]_0$) and the end ($[ABTS^{+\bullet}]_\infty$) of the reaction is divided by the concentration of the antioxidant to express the number of $ABTS^{+\bullet}$ (n) trapped by the antioxidant in the primary period, as shown in Eq. 1.

$$n = \frac{[ABTS^{+\bullet}]_0 - [ABTS^{+\bullet}]_\infty}{[\text{antioxidant}]_0} \quad (1)$$

If the oxidized product of the antioxidant can also trap $ABTS^{+\bullet}$, the reaction between the antioxidant and $ABTS^{+\bullet}$ will undergo the secondary stage. Thus, the decay of the concentration of $ABTS^{+\bullet}$ can be expressed by the Eq. 2, which shows the relationship between $[ABTS^{+\bullet}]$ and the corresponding reaction time (t). In this equation, $a=n_{app}[\text{antioxidant}]_0$ and $b=1/(k_{app}[\text{antioxidant}]_0)$.