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Hybrid-Increased Radical-Scavenging Activity of Resveratrol Derivatives by Incorporating a Chroman Moiety of Vitamin E

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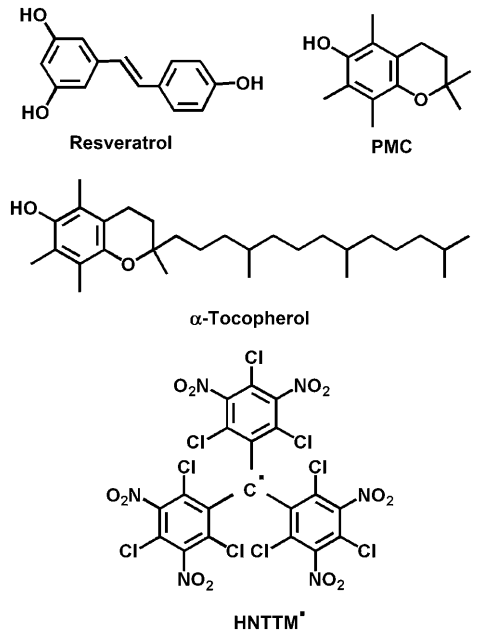
Excessive production of reactive oxygen species (ROS), oxidative stress, has been implicated as a causative mechanism in several degenerative diseases, including cancer,[1] thus using dietary antioxidants has become an attractive strategy to prevent and control cancer.[2] Of the various dietary antioxidants, resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) (Scheme 1), a natural polyphenol found in large amounts in grapes, stands out as the molecule with the most potential in cancer chemoprevention[3] and as a promising lead compound in designing more active antioxidants[4] and cancer chemopreventive agents.[5] The structure feature responsible for the antioxidant activity of resveratrol is the 4′-OH in the stilbene scaffold.[4a,6] Recently, we found that introduction of electron-donating substituents in the *ortho*- or *para*-position of the 4′-OH could significantly enhance its antioxidant activity,[7] prooxidant activity on DNA damage in the presence of Cu^{II} ions,[8] and cytotoxicity on human promeolocytic leukemia cells.[9]

The hybrid approach has recently attracted much attention in medicinal chemistry and design of hybrid molecules encompassing two pharmacophores in one molecular scaffold is a niche area in a large field of drug discovery.[10] In view of the fact that α-tocopherol (vitamin E) (Scheme 1) is known as a natural and chroman-based antioxidant of lipoproteins and biomembranes,[11] Koufaki and co-workers reported the synthesis of a trihydroxydihydrostilbene–chroman hybrid, which was proven to be a strong neuroprotectant against oxidative stress.[12] However, from an antioxidant point of view, the double bond in the stilbene scaffold is necessary to resonance stabilize the resulting phenoxyl radical. Therefore, we describe herein the synthesis of a set of novel hydroxylated resveratrol–chroman hybrids, which incorporate skeletons of two kinds of molecules (stilbene and chroman) with the aim to improve antioxidant activity and to investigate the antioxidant mechanism.



Scheme 1. Structures of resveratrol, PMC, α-tocopherol, and HNTTM•.

The overall strategy for the synthesis of hydroxylated stilbene–chroman hybrids (**11a**–**11c**) is outlined in Scheme 2. Under an inert atmosphere, the trifluoroacetic acid (TFA) catalyzed coupling of phenol **1** with 2-methylbut-3-en-2-ol followed by cyclization resulted in the formation of 2,2,5,7,8-pentamethyl-6-hydroxychroman (**2**, PMC; Scheme 1), an α-tocopherol analogue in which the polyisoprenoid chain is replaced by a methyl group. Bromination of **2** followed by protection of the phenolic OH with an acetyl group gave **4**, which was oxidized with *N*-methylmorpho-

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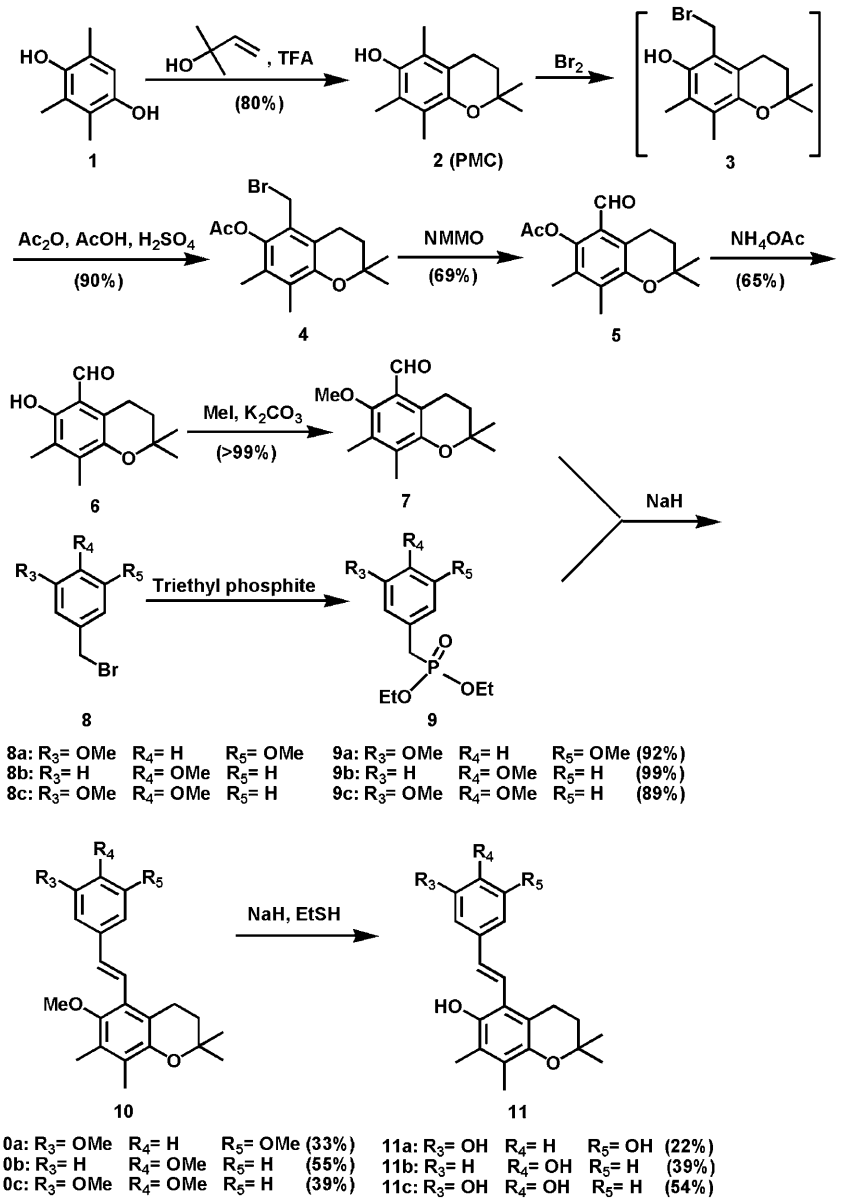


Scheme 2. Synthesis of hydroxylated stilbene–chroman hybrids (**11a–11c**).

line-*N*-oxide (NMMO), to obtain the acetyl aldehyde **5**. After deprotection of the phenolic OH with NH_4OAc, the hydroxylated aldehyde **6** was methylated with CH_3I to afford the methoxy aldehyde **7**. Wittig–Horner reaction of **7** and the corresponding phosphonate **9** in the presence of NaH in dry DMF gave exclusively the *trans*-isomers, the methoxyl hybrids **10a–10c**, followed by demethylation with a large excess of EtSNa in DMF to furnish **11a–11c**, which were characterized with HRMS (ESI) and ^1H and ^{13}C NMR spectroscopy (see the Supporting Information), and were stable in either solid or solution form under air.

It has been admitted that the main characteristic responsible for the antioxidant activity of a phenolic compound is its ability to scavenge free radicals. Tris(2,4,6-trichloro-3,5-dinitrophenyl)methyl radical (HNTTM$^\bullet$) (Scheme 1) is a stable and unique carbon-centered radical and has been successfully applied to the evaluation of the electron-transfer ability of phenolic antioxidants by Juliá and co-workers.[13] Unlike 2,2-diphenyl-1-picrylhydrazyl radical (DPPH$^\bullet$), it cannot directly abstract hydrogen atoms from phenolic antioxidants due to the great steric hindrance.[13] The ability of HNTTM$^\bullet$ to be reduced by an electron-transfer reaction to its stable triphenylcarbanion HNTTM$^-$, as detected by spectroscopy, has made it possible to compare the electron-transfer ability of antioxidants.[13] By use of this radical, an intriguing observation that the electron-transfer capacity of catechin derivatives correlates well with cell-cycle-arrest activity and apoptosis-inducing activity in HT29 cells, was obtained.[14] Thus, HNTTM$^\bullet$ was selected to evaluate the radical-scavenging property of hydroxylated stilbene–chroman hybrids (**11a–11c**) and their corresponding parent molecules resveratrol and PMC. When **11b** was added to the chloroform/methanol solution, the rapid disappearance of the visible absorption band of HNTTM$^\bullet$ centered at 387 nm was accompanied by the appearance of a peak at 497 nm due to the formation of the corresponding anion HNTTM$^-$ (Figure 1),[13] indicating that the electron-transfer reaction from **11b** to HNTTM$^\bullet$ took place. Three possible electron-transfer reaction mechanisms of phenolic antioxidants with free radicals have been documented, that is, sequential proton loss electron transfer (SPLET mechanism, Equation (1), the electron donor is ArO^-), electron transfer then proton transfer (ETPT mechanism, Equation (2), the electron donor is ArOH), and proton-coupled electron transfer [PCET mechanism, Eq. (3)].[13d,15] The relative contribution of these processes depends not only on the nature of the solvent and acidity of the phenolic hydroxyl groups, but also on the redox potentials of the species involved.[7,13d,15a,c,f]

$$ArOH \xrightarrow{-H^+} ArO^- \xrightarrow{X^\bullet} ArO^\bullet + X^- \xrightarrow{H^+} ArO^\bullet + XH \qquad (1)$$

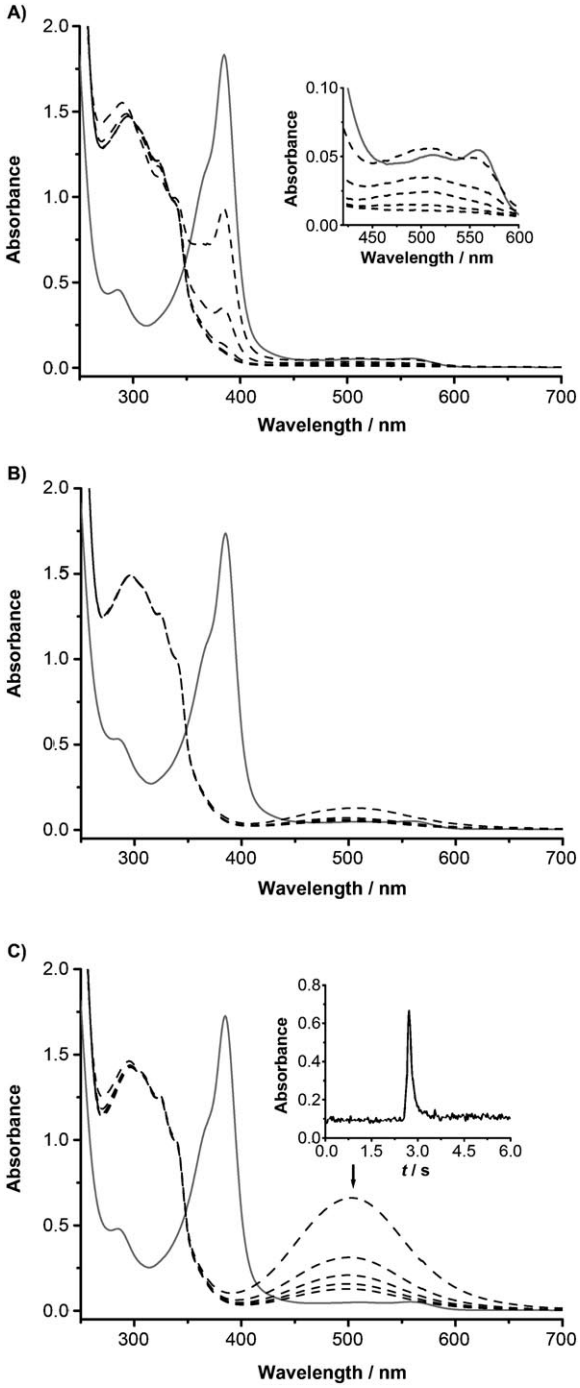


Figure 1. Spectral changes of HNTTM$^{\bullet}$ (60 μmol L^{-1}) in the absence (solid line) and presence (dashed line) of the hydroxylated hybrid **11b** (60 μmol L^{-1}) in chloroform/methanol with various volume ratios of 49:1 (A), 9:1 (B), and 4:1 (C) at 25 °C (the interval: 1 min). The inset in A shows the enlargement of absorbance in the range $\lambda = 420$–600 nm. The inset in C shows decay of HNTTM$^{\bullet}$ (30 μmol L^{-1}) at 387 nm in the presence of **11b** (30 μmol L^{-1}) in chloroform/methanol (4:1, v/v) using the stopped-flow UV/Vis spectroscopy at 25 °C.

$$ArOH + X^{\bullet} \rightarrow ArOH^{\bullet+} + X^{-} \rightarrow ArO^{\bullet} + XH \quad (2)$$

$$ArOH + X^{\bullet} \rightarrow [ArOH \cdots X^{\bullet}] \rightarrow [ArOH^{\bullet+} \cdots X^{-}] \rightarrow ArO^{\bullet} + XH \quad (3)$$

$$ArOH + CH_3OH \rightleftharpoons CH_3\overset{+}{O}H_2 + ArO^{-} \quad (4)$$

To get more of an insight into the detailed electron-transfer mechanism, the rate of HNTTM$^{\bullet}$-scavenging reaction of the hybrids and their parent molecules was measured in chloroform/methanol (with various ratios of 49:1, 9:1, and 4:1, v/v) by monitoring the decrease in absorbance of 387 nm due to HNTTM$^{\bullet}$ by using stopped-flow UV/Vis spectroscopy at 25 °C (see the inset of Figure 1C). The reaction of the hybrids and PMC obeyed second-order kinetics with the ratio of [hybrids or PMC]/[HNTTM$^{\bullet}$] being 1:1 (see the Supporting Information), and their second-order rate constants (k_2) are summarized in Table 1. The activity order is

Table 1. Observed rate constants and $n_{HNTTM^{\bullet}}$ values for the reactions of the hydroxylated hybrids with HNTTM$^{\bullet}$ in chloroform/methanol at 25 °C.

ArOH	k_2 [L mol^{-1} s^{-1}][a] chloroform/methanol (v/v)			$n_{HNTTM^{\bullet}}$[a,b]
	4:1	9:1	49:1	
11a	$(9.8\pm0.74)\times10^4$	$(1.9\pm0.05)\times10^3$	$(1.3\pm0.04)\times10^2$	1.81
11b	$(5.1\pm0.19)\times10^5$	$(8.4\pm0.55)\times10^4$	$(5.8\pm0.30)\times10^2$	2.37
11c	$(4.6\pm0.09)\times10^5$	$(8.1\pm0.50)\times10^4$	$(4.9\pm0.18)\times10^2$	4.29
2 (PMC)	$(6.2\pm0.19)\times10^4$	$(1.6\pm0.04)\times10^2$	$(2.4\pm0.01)\times10^1$	2.42
resveratrol	–[c]	–[c]	–[c]	–[c]

[a] Data are expressed as the mean ±SD for three determinations. [b] $n_{HNTTM^{\bullet}}$ values were measured in chloroform/methanol (2:1, v/v). [c] Resveratrol is inactive in the reaction.

11b > **11c** > **11a** > PMC. It is worth noting that the HNTTM$^{\bullet}$-scavenging activity of the hybrids is significantly higher than that of the parent molecule PMC, an α-tocopherol analogue, which exhibits more effective antioxidant activity than α-tocopherol in some reaction system,[16] whereas the other parent molecule resveratrol is inactive. In particular, the k_2 value (8.4×10^4 L mol^{-1}s^{-1}) of **11b** in chloroform/methanol (9:1, v/v) is about 500-fold larger than that of PMC (1.6×10^2 L mol^{-1}s^{-1}), which clearly indicates that the hybrid approach is feasible in antioxidant drug design. The present observations that the reaction rates of the hybrids increase with increasing the content of methanol (Table 1), and that the increase of methanol ratio makes the peak of HNTTM^{-} more obvious (Figure 1), suggest that in ionizable methanol, the phenolic hybrid (ArOH) is partially ionized to the corresponding anion (ArO^{-}) [Eq. (4)], which is a much stronger electron donor than the parent molecule (ArOH). The increase of ArO^{-} concentration with the increase of methanol ratio facilitates electron-transfer reaction with HNTTM$^{\bullet}$ (SPLET reaction) and thus leads to a faster reaction rate. Furthermore, the anodic potentials of the hybrids and PMC, and their corresponding anion, as well as the cathodic peak potential of HNTTM$^{\bullet}$ in chloroform/methanol (9:1, v/v) were determined using cyclic voltammetry (Table 2). It is seen that the anodic peak potentials of hybrids **11a**–**11c** and PMC are higher than the cathodic peak potential of HNTTM$^{\bullet}$ (0.50 V vs. SCE), demonstrating that the electron-transfer reaction between the parent molecule

Table 2. Cyclic voltammetry parameters for the oxidation of the hybrids and PMC and for the reduction of HNTTM• in chloroform/methanol (9:1, v/v).[a]

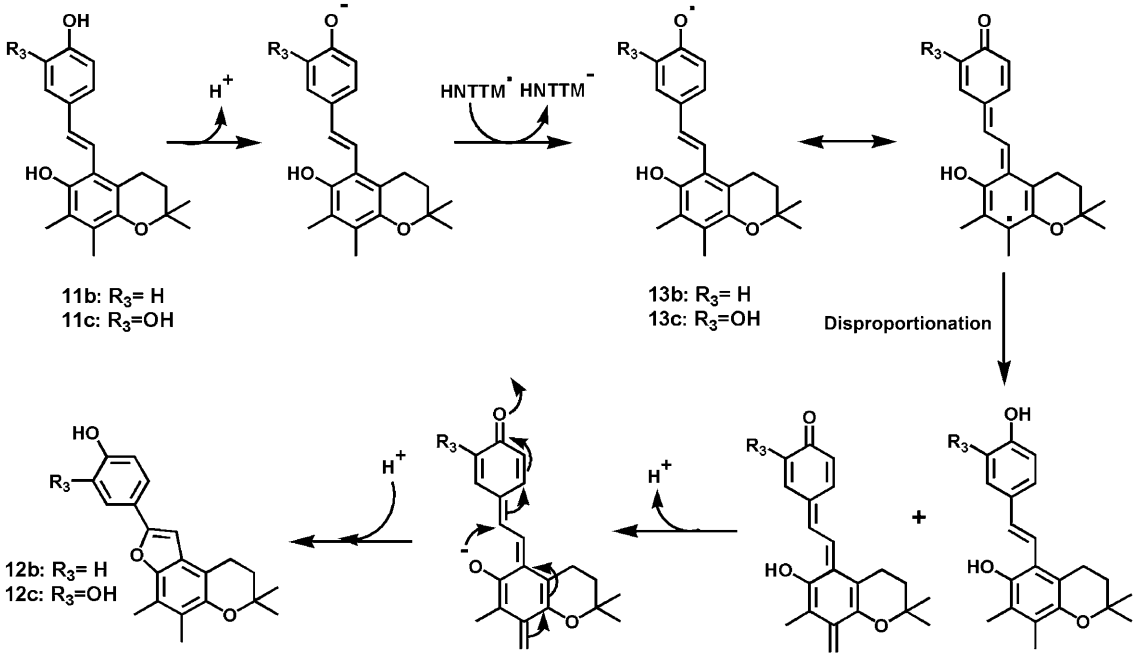
	E_p [V][b] (E_p [V][c], anion)	E^o [V][d] (E_p [V][e])
HNTTM		0.55 (0.50)
2 (PMC)	0.81 (0.50)	
11a	0.79 (–)[f]	
11b	0.73 (0.20)	
11c	0.59 (0.16)	

[a] The potential was measured versus a saturated calomel electrode (SCE). [b] Anodic peak potentials. [c] Anodic peak potentials of PMC, **11b** and **11c** with an excess of tetrabutylammonium hydroxide of 2, 4, and 4 mmol L^{-1}, respectively. [d] Standard redox potentials. [e] Cathodic peak potentials. [f] The anodic peak potential of the phenolate anion for **11a** could not be determined probably due to the quick and irreversible side reactions in the alkaline condition (see the Supporting Information).

and HNTTM• is not thermodynamically feasible. However, the anodic peak potentials of the phenolate anion for **11b** and **11c** (0.20 and 0.16 V, respectively) are much lower than the cathodic peak potential of HNTTM•, providing unambiguous evidence that the actual electron donor is the phenolate anion instead of the parent molecule, and a SPLET mechanism [Eq. (1)] does operate in chloroform/methanol.

Generally speaking, the molecules with a catechol moiety possess higher activity than those with no such moiety due to the intramolecular hydrogen-bonding interaction of the oxidative intermediate, the *ortho*-hydroxy phenoxyl radical.[17] Although the k_2 value of **11b** is slightly larger than the catechol derivative **11c** in the various solvent mixtures, their values are very close and fall within the error range of 10%. The possible reason is that the anodic peak potentials of the phenolate anions for **11b** and **11c** are very close (0.20 and 0.16 V, respectively). Furthermore, the total number of HNTTM• reduced per molecule of the hybrids or PMC, that is, the stoichiometric factor ($n_{HNTTM•}$) was determined with a large excess of HNTTM• by UV/Vis spectroscopy. Excellent linear correlations of concentration versus absorbance were obtained for all the compounds tested (see the Supporting Information). The $n_{HNTTM•}$ values can be obtained from the slope of the straight line (Table 1). Indeed, the catechol derivative **11c** has the highest $n_{HNTTM•}$ value among the compounds tested, and hence possesses the highest HNTTM•-scavenging ability.

The SPLET mechanism was also supported by identifying the oxidation products of the hybrids in chloroform/methanol (2:1, v/v) at room temperature. It was found that HNTTM• completely converted **11b** and **11c** to the corresponding benzofuran derivatives **12b** and **12c** (Scheme 3) by characterization with HRMS (ESI) and 1D and 2D NMR spectroscopy (see the Supporting Information). The formation of **12** can be easily rationalized by sequential proton loss from the 4′-OH and electron transfer between the phenolate anion and HNTTM•, giving the phenoxyl radical **13**, followed by disproportionation and intramolecular nucleophilic attack to give **12** with restoration of aromaticity as the driving force of the reaction as exemplified in Scheme 3. Notably, the oxidative products, **12b** and **12c** were obtained with 1.5 equivalent of HNTTM•. If a large excess of HNTTM• was used, the oxidative product would further contribute to the HNTTM•-scavenging reaction, the end result being that the $n_{HNTTM•}$ values of **11b** and **11c** would be larger than **2**. In the case of the catechol derivative **11c**, the $n_{HNTTM•}$ value is 4.29 and is larger than the available number of hydroxyl groups. This could be due to further reaction products, such as dimers and quinones.[18] On the other hand, a protic solvent, such as the alcohol molecule, can re-



Scheme 3. The HNTTM•-scavenging reaction mechanism by **11b** or **11c** in chloroform/methanol.

generate the catechol structure of the phenol by a nucleophilic attack to the corresponding *o*-quinone,[18c] which can further enlarge the stoichiometry.

In summary, resveratrol derivatives containing a chroman moiety of vitamin E were synthesized, and exhibited remarkably higher HNTTM•-scavenging activity than the parent molecules (resveratrol and PMC). The detailed mechanism was also elucidated by kinetic and oxidative product analyses of the HNTTM•-scavenging reaction and redox potential determination. It should be pointed out in this context that a chain-breaking antioxidant (ArOH) should have high reactivity towards the lipid peroxy radical (ROO•), a chain-carrying species in lipid peroxidation, and the produced antioxidant radical (ArO•) should not propagate the oxidation chain. Thus, we investigated the antioxidant activities of the hybrids and the parent molecules against 2,2′-azobis(2-amidinopropane) hydrochloride (AAPH)-induced peroxidation of linoleic acid in *tert*-butyl alcohol/water (3:1, v/v) solution by measuring the oxygen consumption (see the Supporting Information). Preliminary studies showed that all of the hybrids almost completely inhibited the oxygen absorption until the antioxidant was exhausted, and were more effective chain-breaking antioxidants than the parent molecules in the above experimental system (see the Supporting Information). Further investigations into the biological activities of the hybrids including antioxidant activities in biological systems, cytotoxic and apoptosis-inducing activities against cancer cells, are currently underway in our laboratory.

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