Edaravone Derivatives Containing NO-Donor Functions

Konstantin Chegaev,[†] Clara Cena,[†] Marta Giorgis,[†] Barbara Rolando,[†] Paolo Tosco,[†] Massimo Bertinaria,[†] Roberta Fruttero,[†] Pierre-Alain Carrupt,[‡] and Alberto Gasco*[,†]

Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Via Pietro Giuria 9, 10125 Torino, Italy, Unité de Pharmacochimie, Section des Sciences Pharmaceutiques, Université de Genève, Université de Lausanne, 30 Quai Ernest Ansermet, CH 1211 Genève 4, Switzerland

Received June 10, 2008

A new series of polyvalent drugs obtained by joining edaravone with NO-donor moieties is described. All compounds display high antioxidant power together with NO-dependent vasodilator properties. The analysis of a number of molecular descriptors shows that the antioxidant activity, which is tightly linked to the presence of the edaravone substructure, is principally modulated by lipophilicity. These products are potentially useful in the treatment of cardiovascular disorders in which EDRF deficiency and ROS excess are involved.

Introduction

Accumulation of LDL and ROS in the subendothelial space is one of the earliest events in the development of atherosclerosis. A consequent increase in lipidic peroxidation induces the formation of foam cells, followed by the lipid streak and ultimately by the atherosclerotic plaque. Experimental evidence in animal models of atherosclerosis supports the concept that administration of exogenous antioxidants can attenuate the negative effects of oxidative stress.[1−3] Data in humans are less consistent and less homogeneous than in animals, and further studies are necessary to conclude if antioxidants are really useful as antiatherosclerosis agents.[4] A characteristic of atherosclerotic vessels is the reduced amount of nitric oxide produced by endothelial cells (EDRF[a]). Additionally, an abnormal production of superoxyde anion ($O_2^{-\bullet}$) occurs. This anion radical traps NO to generate peroxynitrous acid/peroxynitrite (HOONO/$^-$OONO).[2,5,6] These latter species are responsible for several biological effects.[5] In particular, peroxynitrous acid may undergo homolytic cleavage to form hydroxyl radical ($OH^\bullet$) and nitrogen dioxide radical ($NO_2^\bullet$), two potent one-electron oxidants. This reaction is relevant in hydrophobic phases to initiate lipidic peroxidation. Decreased responsiveness to NO derived from endothelium is another aspect of advanced atherosclerosis. By contrast, vasodilation in response to exogenous sources of NO seems to remain largely preserved.[2,7] On these bases, we recently developed new polyvalent drugs deriving from the combination of antioxidants with appropriate NO-donor moieties.[8] This kind of hybrid drug could be an interesting tool in the treatment of a number of cardiovascular diseases that involve loss of EDRF action and abnormal production of reactive oxygen species. These disorders include chronic pathologies like atherosclerosis and a variety of associated conditions such as hypercholesterolemia, hypertension, and diabetes mellitus. Another potential application of these hybrids is the acute treatment of ischemia/reperfusion injury, which is due to a burst of ROS associated with reduced release of NO by the endothelium.[2] It is conceivable that the treatment of these different pathological processes may require different ratios of the NO-dependent and antioxidant activities of the corresponding compounds.

Edaravone (MC-186, **1**), a long-known acid pyrazoline compound,[9] has been shown to quench $OH^\bullet$ radical and display effects on $^-$OONO as well as on liposoluble peroxyl ($LOO^\bullet$) and alkoxyl ($RO^\bullet$) radicals. Edaravone and its derivatives can exist in three tautomeric forms **a**, **b**, **c** (Figure 1).[10−12] It is currently accepted that the anionic form is the most relevant in scavenging free radicals in polar media by a one-electron transfer mechanism (Figure 1, pathway A).[13] The most successful derivatives in such media are those in which the amount and the oxidation potential of the anionic form are well balanced.[12] By contrast, the mechanism of H-atom abstraction has been hypothesized to be predominant in lipidic phase (Figure 1, pathway B).[13] Edaravone was developed as a medical drug for brain ischemia[14] and has been reported to be effective for myocardial ischemia as well.[15] More recently, the drug was found to suppress oxidative stress-induced endothelial damage and early atherosclerosis.[16]

In this paper, we describe the synthesis and in vitro evaluation of antioxidant and vasodilator activities of a series of edaravone derivatives (**9a**−**g**) bearing NO-donor nitrooxy and furoxan moieties (Table 1, Scheme 1). The simple nitric ester and furoxan derivatives **3a**−**c**, **4a**−**d** (Table 1) have been used as reference compounds because they contain the same NO-donor moieties that were conjugated to edaravone. These NO-donors display widely modulated in vitro NO-dependent vasodilator properties (see Table 1). The methoxy derivative of edaravone **2**[12] was also included as a reference. Physicochemical profiling of these new edaravone derivatives, including lipophilicity (log *P*, log *D*), dissociation constants (pK_a), single electron transfer enthalpies (ΔH_{SET}) of the anionic forms, and 4−C−H bond dissociation enthalpies (ΔH_{HAT}) of tautomer **b** is also reported.

Results and Discussion

Chemistry. The edaravone derivatives studied in the present work were synthesized according to the pathway reported in Scheme 1. The *p*-benzyloxy-substituted edaravone derivative **5** was suspended in CH_2Cl_2 and treated with Boc_2O, then with DMAP to give almost exclusively the *O*-Boc-protected deriva-

* To whom correspondence should be addressed. Phone: +39-011-670-7670. Fax: +39-011-670-7286. E-mail: alberto.gasco@unito.it.

† Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino.

‡ Unité de Pharmacochimie, Section des Sciences Pharmaceutiques, Université de Genève, Université de Lausanne.

[a] Abbreviations: NO, nitric oxide; EDRF, endothelium-derived relaxing factor; ROS, reactive oxygen species; LDL, low density lipoproteins; Boc_2O, di-*tert*-butyl dicarbonate; DMAP, 4-*N*,*N*-dimethylaminopyridine; DIAD, diisopropylazodicarboxylate; Py, pyridine; TFA, trifluoroacetic acid; TFAA, trifluoroacetic acid anhydride; TBA, 2-thiobarbituric acid; TBARS, 2-thiobarbituric acid reactive substances; QSAR, quantitative structure−activity relationships; PBS, phosphate buffer solution.

10.1021/jm8007008 CCC: $40.75
Published on Web 12/29/2008

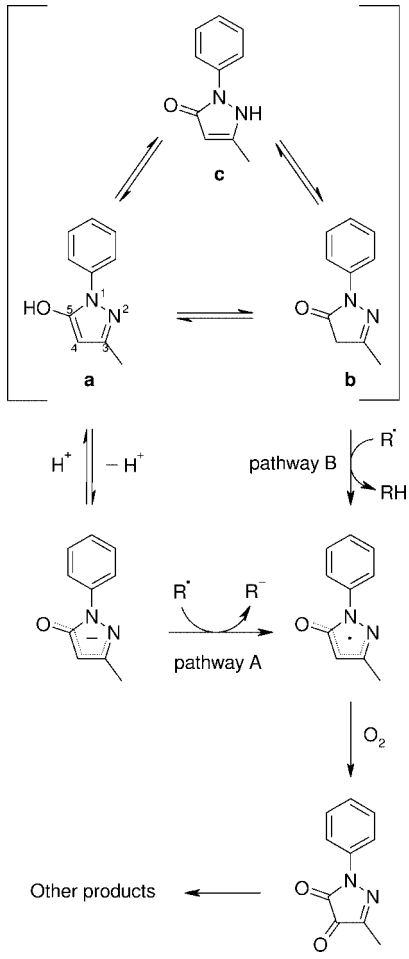


Figure 1. Tautomeric equilibrium and free radical scavenging mechanisms for edaravone **1**.

tive **6**. ^{13}C NMR and ^{1}H NMR spectra ($CDCl_3$) reveal signals at δ 95.0 ppm, attributable to the 4-C aromatic carbon, and δ 6.02 ppm, attributable to 4-CH methyne proton, confirming the assigned structure. These resonances are near the corresponding ones found in a series of esters of **1**, tautomer **a**.[17] The benzyl group was removed from **6** by catalytic hydrogenation on Pd/C in methanol to afford **7**. Compounds **8a**−**f** were synthesized under the Mitsunobu conditions,[18] namely by treating the adduct of Ph_3P and DIAD in THF solution with **7**, followed by addition of the appropriate alcohols. The cyanosubstituted furoxan derivative **8g** was obtained directly from the corresponding amide **8f** by action of TFAA and pyridine in THF. Removal of the Boc protection by TFA in CH_2Cl_2 afforded the final products **9a**−**g**. ^{1}H NMR and ^{13}C NMR spectra indicate that in $CDCl_3$ solution these compounds exist essentially as **b** tautomers, because they show typical CH_2 hydrogen[19] and carbon[20] chemical shifts in the range 3.40−3.42 and 42.9−43.0 ppm, respectively.

Computed Descriptors of Reactivity. Hydrogen atom transfer (HAT) enthalpies relative to edaravone were calculated according to the following eq 1:

$$\Delta H_{\mathrm{HAT}} = \Delta H_f(\text{edaravone-H}) + \Delta H_f(\mathrm{R}^{\bullet}) - \Delta H_f(\text{edaravone}^{\bullet}) - \Delta H_f(\text{R-H}) \quad (1)$$

where RH are the edaravone derivatives studied in the present work and R$^{\bullet}$ the related radicals. All the radicals were built by H-atom abstraction from the 4-position of the tautomeric form **b**, as suggested by previous investigators.[13,21] The ΔH_{HAT} enthalpy values were very similar among them, ranging from −0.79 to +0.48 kcal mol^{-1}. Single electron transfer (SET) enthalpies relative to edaravone were computed according to eq 2:

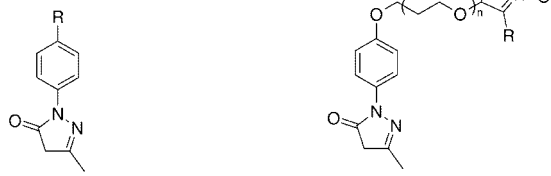
$$\Delta H_{\mathrm{SET}} = \Delta H_f(\text{edaravone}^{-}) + \Delta H_f(\mathrm{R}^{\bullet}) - \Delta H_f(\text{edaravone}^{\bullet}) - \Delta H_f(R^{-}) \quad (2)$$

where edaravone$^-$ and R$^-$ are the conjugated anions of the edaravone derivatives. Also ΔH_{SET} enthalpies lied in a close range, from −2.62 to 1.21 kcal mol^{-1}. This suggests that these compounds should display similar behavior as antioxidants in lipidic phase, where the radical intermediates would be largely produced by direct hydrogen abstraction from the neutral forms, and also in aqueous medium, where the anions would be the main active species in scavenging free radicals by a one-electron transfer mechanism.

Dissociation Constants (pK_as) and Lipophilicity Descriptors. The ionization constants of the compounds were determined by potentiometric titration. In the case of edaravone **1** and of his methoxy derivative **2**, the pK_as were obtained by aqueous titration, while for all the other compounds, they were measured in methanol−water mixtures because of low aqueous solubility. In the latter case, aqueous pK_a values were calculated by extrapolation at 0% methanol using the Yasuda−Shedlovsky procedure.[22] Distribution coefficients (log $D^{7.4}$), partition coefficients of neutral forms (log P^{N}), and partition coefficients of the ionized forms (log P^{I}) between *n*-octanol and water were obtained by potentiometric titration and by shake-flask technique. Analysis of the results (Table 1) shows that all the NO-donor edaravone derivatives have similar dissociation constants, near that of the simple *p*-methoxy derivative **2** and just a little higher than the one of the lead **1**. Consequently, at physiological pH (7.4), the anionic forms of these compounds are present in almost the same amount. By contrast, the lipophilicities are quite different across the series. The log P^{N} values lie in the range 0.92−4.04. The distribution coefficients at pH 7.4 are lower (0.48−3.56), in keeping with the partial ionization of the products at this pH. The log P^{I} values are in keeping with the general assumption of a 3-unit difference between the log *P* of neutral and ionic forms (*diff* log $P^{\mathrm{N-I}}$).

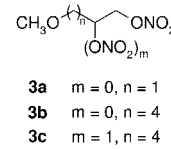
Antioxidant Properties. TBARS Assay. All the NO-donor compounds were assayed as inhibitors of ferrous salt/ascorbate-induced lipidic peroxidation of membrane lipids of rat hepatocytes. Edaravone **1**, its *p*-methoxy derivative **2**, and the NO-donor reference compounds were also considered for comparison. The TBA assay was used to follow the progress of the autoxidation. This procedure involves the detection of the final metabolites of the lipidic autoxidation, namely TBARS, by visible spectroscopy.[23] All NO-donor edaravone derivatives were able to inhibit autoxidation in a dose-dependent manner; their antioxidant potencies expressed as IC_{50}, that is the molar concentration able to reduce the autoxidation by 50%, are collected in Table 1. By contrast, none of the simple NO-donors **3a**−**c**, **4a**−**d** showed any antioxidant activity per se in the concentration range at which the related hybrids were tested (0.5−15 μM). Therefore, it can be concluded that the NO-donor portion of the corresponding hybrids only modulates the antioxidant activity of the edaravone moiety. Analysis of the data collected in Table 1 shows that all the NO-donor derivatives of **1** are more potent than both the lead and its *p*-methoxy analogue **2**. The most active product of the series is the highly lipophilic phenylfuroxan derivative **9d**, while the hydrophilic carbamoylfuroxan derivative **9f** is the least active. These two derivatives are about 13 times and 2 times more potent than **1**,

Table 1. Dissociation Constants, Lipophilicity, Antioxidant, and Vasodilator Activity for References **1**, **2**, **3a**−**c**, **4a**−**d**, and for Target Compounds **9a**−**g**

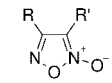


1 R = H
2 R = OCH_3
9a R = $O(CH_2)_3ONO_2$
9b R = $O(CH_2)_6ONO_2$
9c R = $O(CH_2)_4CHCH_2ONO_2$ (with ONO_2)

9d n = 1, R = Ph
9e n = 1, R = SO_2Ph
9f n = 0, R = $CONH_2$
9g n = 0, R = CN



3a m = 0, n = 1
3b m = 0, n = 4
3c m = 1, n = 4

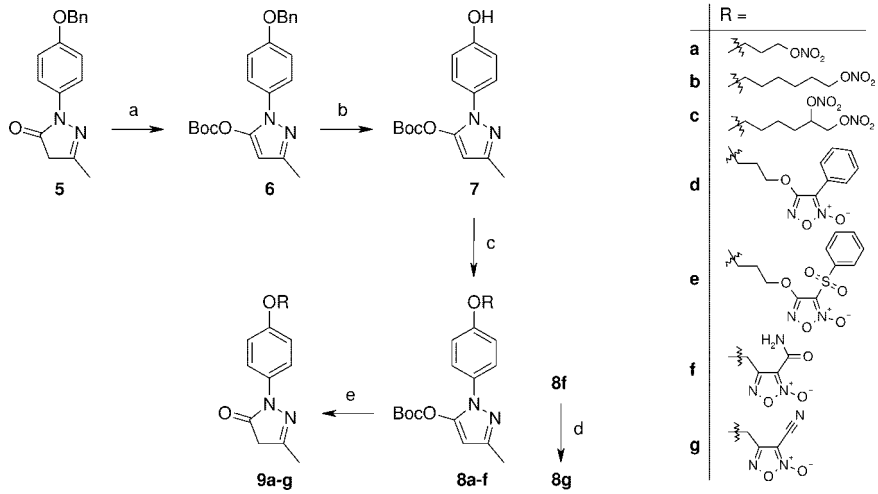


4a R = OCH_3, R' = Ph
4b R = OC_2H_5, R' = SO_2Ph
4c R = CH_2OCH_3, R' = $CONH_2$
4d R = CH_2OCH_3, R' = CN

		lipophilicity			antioxidant activity			vasodilator activity
compd	pK_a [a]	log P^N	log $D^{7.4}$ [b]	log P^I [b]	IC_{50} (μM, CL 95%) [c]	Δt_{lag} (min) ± SEM [d]	R (nmol min^{-1} mg^{-1} LDL prot) ± SEM [d]	EC_{50} (μM) ± SEM
1	6.90	1.28[e]	0.78	ND	17 (15−18)	3 ± 1	6.2 ± 0.5	inactive
2	7.06	1.19[e]	0.77	ND	20 (18−23)	10 ± 3	5.1 ± 0.4	inactive
3a		1.01[f]			*g*	0	9.1 ± 1.5	9.6 ± 1.2
3b		2.23[f]			*g*	0	8.4 ± 2.6	1.4 ± 0.4
3c		1.71[f]			*g*	0	8.2 ± 2.4	0.66 ± 0.06
4a		2.47[b]			*g*	0	10.6 ± 0.1	5.6 ± 0.5
4b		3.15[b]			*g*	0	9.4 ± 1.4	0.012 ± 0.002
4c		0.14[b]			*g*	0	9.2 ± 1.7	3.9 ± 0.4
4d		0.83[b]			*g*	0	11.1 ± 0.1	0.0095 ± 0.0002
9a	7.11[h]	1.90[e]	1.59	−1.07	3.4 (2.8−4.2)	102 ± 12	4.6 ± 0.3	1.1 ± 0.2
9b	7.12[h]	3.34[e]	2.67	0.15	2.1 (1.7−2.4)	186 ± 7	3.8 ± 0.3	0.98 ± 0.20
9c	7.15[h]	3.10[e]	2.54	0.05	2.9 (2.6−3.1)	138 ± 14	4.2 ± 0.6	0.68 ± 0.07
9d	7.09[h]	4.04[e]	3.56[i]	0.85	1.3 (1.2−1.5)	118 ± 3	4.4 ± 0.7	14 ± 3
9e	7.12[h]	3.62[e]	3.16[i]	0.40	3.8 (3.5−4.2)	114 ± 10	3.7 ± 0.3	0.077 ± 0.008
9f	7.08[h]	0.92[e]	0.48	ND	7.9 (7.3−8.5)	0	5.3 ± 0.1	2.8 ± 0.6
9g	7.06[h]	1.72[e]	1.28	−0.99	5.8 (5.5−6.1)	44 ± 4	4.2 ± 0.2	0.023 ± 0.004

[a] Determined by potentiometric titration with GlpKa apparatus; $n \geq 4$, SD < 0.03. [b] Determined by shake-flask technique; $n \geq 6$, SD < 0.08. [c] Obtained by $FeSO_4$/ascorbate-induced lipid peroxidation assay on rat hepatic microsomal membranes. [d] Obtained by $CuSO_4$-induced human LDL oxidation assay at 10 μM. R values were calculated from ΔA_{234} as a function of time, using $\varepsilon_{234} = 29500\ M^{-1}\ cm^{-1}$ for conjugated lipid peroxides. For control LDL samples $R = 10.7 \pm 0.4$ nmol min^{-1} mg^{-1} LDL prot. [e] Determined by potentiometric titration with GlpKa apparatus and validated by shake-flask technique; $n \geq 6$, SD < 0.03. [f] Calculated log P value (Bio-Loom for Windows v. 1.5, BioByte Corp., Claremont, CA). [g] No activity in the tested concentration range (0.5−15 μM). [h] pK_as obtained by extrapolation at 0% methanol using Yasuda−Shedlovsky procedure.[22] [i] Calculated according to the equation $\log D = \log [P^N/(1 + 10^{pKa-pH}) + P^I \times 10^{pKa-pH}/(1 + 10^{pKa-pH})]$.

Scheme 1[a]



[a] Reagents: (a) Boc_2O, DMAP, CH_2Cl_2, rt; (b) H_2, Pd/C, MeOH, rt; (c) ROH, Ph_3P, DIAD, THF, −15 °C → rt; (d) TFAA, Py, THF, 0 °C → rt; (e) TFA, CH_2Cl_2, rt.

respectively. The limited number of analogues considered does not allow to build a robust QSAR model. However, because all compounds display similar pK_a, ΔH_{HAT}, and ΔH_{SET} values, a qualitative analysis of the data collected in Table 1 suggests that the differences in antioxidant potencies among compounds **9a**−**g** can be principally ascribed to their different lipophilic−hydrophilic balance. This is in keeping with a previous finding that lipophilic substituents are beneficial to the lipidic peroxi-

dation inhibitory activity of edaravone in the TBARS assay.[24] In summary, these NO-donor edaravone derivatives are capable of protecting membranes from autoxidation in a manner proportional to their ability to partition into the lipidic bilayer. This statement is supported also by the results we obtained working with other series of NO-donor antioxidants.[8]

LDL Oxidation. All compounds were also assessed for their ability to suppress conjugated diene formation during copper-mediated LDL oxidation.[25] LDL isolated from human blood were incubated in PBS with the tested compounds. The autoxidation, initiated by addition of $CuSO_4$, was followed spectrophotometrically by detecting the formation of conjugated dienes at 234 nm. At 10 μM, all target compounds, with the sole exception of the furoxancarboxamide derivative **9f**, were able to increase the lag time of the oxidation (Δt_{lag}) with respect to the control (Table 1; Supporting Information, Figure 1), while all references were almost ineffective. In both the nitrooxy and the furoxan series, this activity is influenced by the degree of lipophilicity. On the other hand, target compounds and references **1**, **2** only slightly reduced the propagation rate of the oxidation (*R*, Table 1) with respect to the control. However, when the assay was performed at a higher concentration (20 μM), this parameter was significantly reduced (data not shown). All simple NO-donors had no effect on *R*.

Vasodilator Properties. The NO-donor edaravone derivatives were assayed for their vasodilator properties on rat aorta strips precontracted with 1 μM phenylephrine. All compounds were able to relax the contracted tissues in a concentration-dependent manner. Their EC_{50} values, namely the concentration able to induce half-maximal vasodilation, basically parallel those of the related simple NO-donors (Table 1). As expected, in the nitrooxy series, the most active compound was the dinitrooxy-substituted derivative **9c**, while in the furoxan series, the cyano-substituted furoxan derivative **9g** gave the best results. The vasorelaxant properties of all tested compounds proved to be cGMP-dependent because ODQ (1*H*-[1,2,4]-oxadiazolo[4,3-*a*]quinoxalin-1-one, a well-known inhibitor of soluble guanylate cyclase) caused a significant reduction in the vasodilating potencies (data not shown). This is in keeping with the involvement of NO in the vasodilator action. Analysis of the data reported in Table 1 shows that **9g** ($IC_{50}/EC_{50} = 251$) and **9e** ($IC_{50}/EC_{50} = 49$) behave principally as vasodilators, **9d** ($IC_{50}/EC_{50} = 0.09$) as antioxidant, and finally **9a**−**c**, **9f** ($IC_{50}/EC_{50} = 2.1-4.2$) as relatively balanced hybrids.

Conclusions

We were successful in designing a new series of NO-donor edaravone derivatives that display varying degrees of balance between in vitro antioxidant and vasodilator activities. This feature makes these compounds potential tools for the treatment of cardiovascular diseases in which EDRF deficiency and ROS excess are involved. The vasodilator activities of the hybrids parallel those of the corresponding reference simple NO-donors. The antioxidant activity is due to the edaravone substructure and it seems to be principally modulated by the lipophilicity of the molecule as a whole.

Experimental Section

Chemistry. References for literature compounds **4a**, **4b**, **5**, as well as full experimental details and structural characterization for compounds **3a**−**c**, **4c**, **4d**, **6**, **7**, **8a**−**g**, **9a**−**g** are reported in the Supporting Information.

General Procedure for the Preparation of Protected Derivatives 8a−**g.** To a solution of Ph_3P (0.60 g, 2.3 mmol) in dry THF, kept at −15 °C under positive N_2 pressure, DIAD (0.46 mL, 2.4 mmol) was added in one portion. The reaction mixture was stirred at −15 °C for 30 min, then **7** (0.55 g, 1.9 mmol) was added, followed, after 15 min, by the appropriate alcohol[8c] (1.9 mmol). The reaction was stirred at rt for a further 3 h, and then the solvent was removed under reduced pressure. Purification by flash chromatography gave the title products as oils in yields ranging from 40 to 83%. Compound **8g** (white solid, yield 92%) was obtained from **8f** (1.0 g, 2.4 mmol) by dehydration (dry THF, 0 °C, N_2 atmosphere) with pyridine (0.40 mL, 5.0 mmol) and TFAA (0.50 mL, 3.6 mmol).

General Procedure for the Preparation of Compounds 9a−**g.** To the solution of protected derivatives **8a**−**g** (1.2 mmol) in CH_2Cl_2 (10 mL) TFA (1 mL) was added, an then the reaction was stirred at rt until all starting material was consumed (TLC control). The reaction mixture was diluted with AcOEt (30 mL), and then the organic phase was washed with H_2O, brine, dried, and evaporated. Pure products were obtained by recrystallization, or flash chromatography for oils, in yields ranging from 67 to 96%.

Theoretical ΔH_{HAT} and ΔH_{SET} Calculations. All molecular models were constructed using standard bond lengths and angles with the MOE software package.[26] The radicals $R^{\bullet}$ were built by H-atom abstraction from position 4, as suggested by previous investigators.[13,21] ΔH_{HAT} and ΔH_{SET} values were obtained from the enthalpies of formation (ΔH_f) of the different species involved in the respective isodesmic reactions (see Results and Discussion). The ΔH_f values were calculated by ab initio quantum mechanics (QM) with the GAMESS-US software package;[27] full details are reported in the Supporting Information. All computations were performed on a Linux cluster (Pentium IV/Xeon CPUs, 24 cores overall).

Ionization Constants and Lipophilicity Descriptors. The ionization constants and lipophilicity descriptors of compounds were determined by potentiometric titration with the GlpKa apparatus (Sirius Analytical Instruments Ltd, Forest, Row, East Sussex, UK). Ionization constants of **1**[28] and **2** were obtained by aqueous titrations. Because of the low aqueous solubility, ionization constant measurement of all the other compounds was performed in different methanol−water mixtures; aqueous pK_a values were obtained by extrapolation at 0% methanol using the Yasuda−Shedlovsky procedure.[22]

To obtain lipophilicity data, at least four separate titrations of the compounds were carried out using various volumes of *n*-octanol. In the presence of *n*-octanol, a new ionization constant (p_oK_a) was determined. In the dual solvent mixture, the pK_a value shifts as a consequence of the partitioning of the substance into the organic phase and the shifts in the pK_a are used to determine log P^N, the logarithm of the partition coefficient of the neutral form. The details of the method have been previously reported.[22,29] Log P^N and log $D^{7.4}$ between *n*-octanol and water were also obtained by shake-flask technique; each log *P* and log *D* value is an average of at least six measurements. Further details are included in the Supporting Information.

Antioxidant Activity. Hepatic microsomal membranes preparation from male Wistar rats and lipid peroxidation assays were performed as previously described.[8a] The antioxidant activity of tested compounds was evaluated as the percent inhibition of TBARS production with respect to control samples, using the values obtained after 30 min of incubation. IC_{50} values were calculated by nonlinear regression analysis.

LDL Isolation and Oxidation. Human plasma from healthy donors was provided by Blood Bank (A.O. San Giovanni Battista, Torino, Italy) and added with 0.1% EDTA. The LDL fraction was isolated by ultracentrifugation through NaCl discontinuous gradients and collected as the fraction floating at a density of 1.019−1.063 g mL^{-1}. EDTA was removed by rapid filtration through disposable desalting columns Econo-Pac 10 DG (Bio-Rad). Filtered LDL were diluted with PBS (10 mM phosphate, pH 7.4) to give a final concentration of 50 μg LDL protein mL^{-1} and transferred to a 1 cm cuvette with 10 μL of DMSO alone or 10 μL of the tested compound solution in DMSO at a final concentration of 10 μM. The formation of conjugated dienes was measured spectrophoto-

metrically in a Varian Cary 50 Bio spectrophotometer, equipped with a thermostatic control (37 °C) and an automatically exchangeable multiposition cuvette holder, operating at 234 nm. Oxidation was initiated by the addition to the LDL suspension of $CuSO_4$ at a final concentration of 2.5 μM. The determination of the lag phase (t_{lag}) and of the propagation rate (R) was carried out as previously described.[25]

Vasodilator Activity. Thoracic aortas were isolated from male Wistar rats weighing 180−200 g. As few animals as possible were used. The purposes and the protocols of our studies have been approved by the Ministero della Salute, Rome, Italy. Experiments were performed according to procedures previously described.[8a] Results are expressed as $EC_{50} \pm$ SEM (μM). Responses were recorded by an isometric transducer connected to the MacLab System PowerLab (ADInstruments, Bella Vista, Australia). Addition of the drug vehicle (DMSO) had no appreciable effect on contraction level.

Acknowledgment. This work was supported by a grant from Italian Ministry for University and Research (MIUR), Studi e Ricerche Finalizzate 40% Roma (COFIN 2005), and Regione Piemonte Ricerca Scientifica Applicata, CIPE 2004. We gratefully acknowledge the ShareGrid management team for the computing power provided through the ShareGrid distributed platform.[30]

Supporting Information Available: Synthesis of intermediates **6** and **7**, full experimental procedures and physicochemical characterization for all compounds, elemental analyses for **9a**−**g**, details on theoretical ΔH_{HAT} and ΔH_{SET} calculations, on dissociation constant assessment, lipophilicity determination, LDL oxidation kinetics. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM8007008