Novel Potent Inhibitors of Lipid Peroxidation with Protective Effects against Reperfusion Arrhythmias

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A series of new compounds that contain lipoic acid and trolox connected through spacers were synthesized and examined for their antioxidant activity and their protective effects against reperfusion arrhythmias in isolated heart preparations. All compounds tested are strong inhibitors of lipid peroxidation in rat liver microsomal membranes induced by ferrous ions and ascorbate. N-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)-*N*′-(1,2-dithiolane-3-pentanoyl)-1,2-phenylenediamine (**13**) exhibits anti-lipid peroxidation activity at the nanomolar range. *N*-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)-N′-(1,2-dithiolane-3-pentanoyl)ethylenediamine (**10**) and **13** totally suppressed reperfusion arrhythmias.

Introduction

Reactive oxygen species (ROS) are believed to be involved in several pathological conditions. Endogenous antioxidant defenses are inadequate in many of these disorders. Oxidative damage and disease progression may be retarded by administering natural antioxidants (enzymes and vitamins) or synthetic agents.[1]

Tocopherol (vitamin E) is the most important and widely studied natural, lipid-soluble, chain-breaking antioxidant. Recent studies provide evidence of protective effects of vitamin E against atherosclerosis[2] and reperfusion injury.[3]

Lipoic acid is an antioxidant that is found endogenously as lipoamide in five proteins in eukaryotes where it is covalently bound to a lysyl residue. Exogenously supplied lipoic acid is taken up readily by a variety of cells and tissues where it is reduced rapidly to dihydrolipoic acid (DHLA).[4,5]

There is a growing interest in these natural antioxidants as a protective strategy against myocardial ischemia−reperfusion damage. Thürich et al.[6] compared the cardioprotective effects of DHLA and vitamin E during the reoxygenation of hypoxic hearts. The results showed that the mechanism of action of these two antioxidants is different, and thus a combined treatment of lipoic acid and tocopherol could result in improved mitochondrial function. In other studies in which rodents were fed a high vitamin E diet and DHLA was added to the myocardial perfusion medium, it was reported that the combination improved cardiac performance and reduced myocardial lipid peroxidation.[7] Recently, Coombes et al. showed that dietary supplementation of tocopherol and α-lipoic acid decreased lipid peroxidation during in vivo ischemia−reperfusion in young adult rats. However, the combination did not influence cardiac performance.[8]

On the basis of the promising synergistic results of the combined use of lipoic acid and vitamin E in the protection of the hypoxic reoxygenated heart,[6−8] we set out to synthesize hybrids of these two compounds and to study their cardioprotective activity. We opted to use trolox amides since this type of compounds exhibit improved results in the ischemia−reperfusion model.[9] The aim of this study is to probe the necessary structural requirements of the linkers for the best cardioprotective results. The issue of stereochemistry is not addressed in the new compounds since its does not seem to influence the antioxidant activity either of trolox amides[10] or of lipoic acid.[11]

Chemistry

The synthesis of the novel compounds is shown in Schemes 1−3. The aminoamides **1** and **2** were synthesized by heating trolox methyl ester with ethylenediamine or hexamethylenediamine, respectively.[12] Activation of trolox with 1,1′-carbonyldiimidazole (CDI) and subsequent coupling to piperazine or aromatic diamines afforded **3**−**8**. *N*-(1,2-Dithiolane-3-pentanoyl)-1,2-phenylenediamine (**9**) was prepared from lipoic acid and *o*-phenylenediamine after activation with CDI. The synthesis of the final diamides **10**−**17** involves the reaction of the aminoamides **1**−**8** with lipoic acid chloride in THF/H_2O. Lipoic acid chloride was prepared following the procedure described by Wagner et al.[13] with minor modifications. Reduction of **10** and **13** using $NaBH_4$ gave the DHLA analogues **18** and **19**, respectively. Finally, the carbocyclic analogue of diamide **10**, compound **22**, was synthesized via the corresponding acid **21** as shown in Scheme 3.

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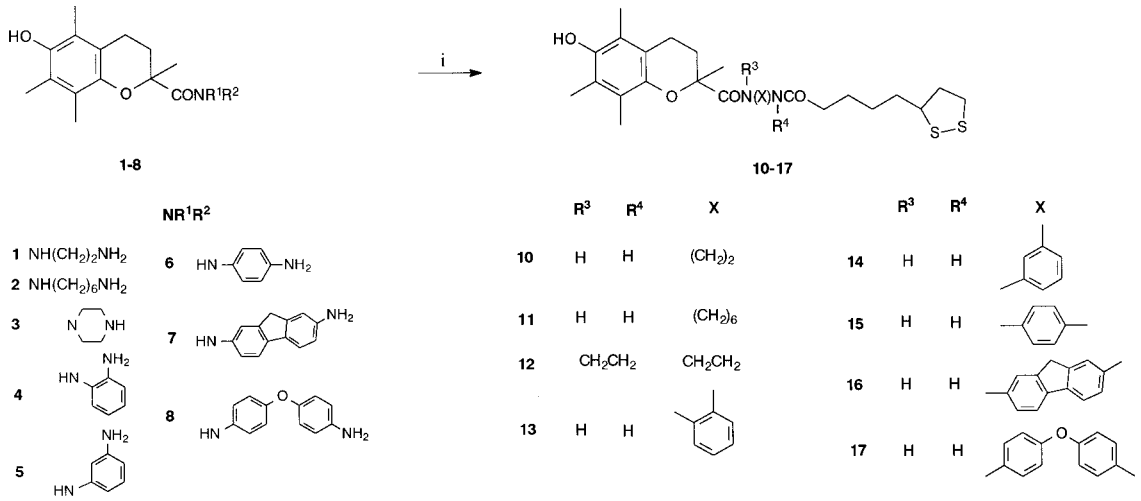
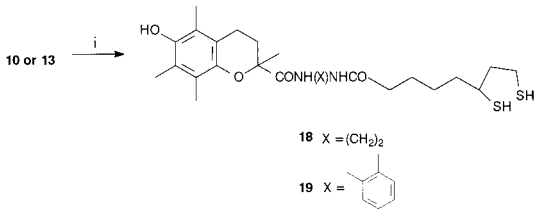
Scheme 1[a]



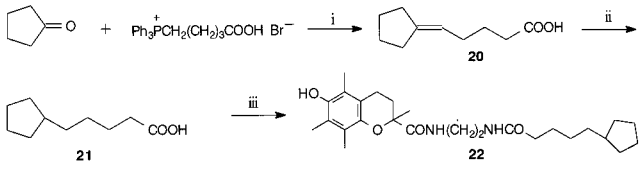
[a] Reagents and conditions: (i) lipoic acid cloride, THF/H_2O, room temperature.

Scheme 2[a]



[a] Reagents and conditions: (i) $NaBH_4$, MeOH, room temperature.

Scheme 3[a]



[a] Reagents and conditions: (i) $KNSi_2(CH_3)_6$, THF, room temperature; (ii) H_2, 10% Pd/C, 10 psi, (iii) CDI, THF, **1**.

Table 1. Inhibition of In Vitro Peroxidation (LP) of Rat Hepatic Microsomal Membrane Lipids[a]

compd	LP IC_{50} (μM)	DPPH IC_{50} (mM)	ClogP
lipoic	>1000	>0.4	2.39
trolox	24.8 ± 1.0	0.045	3.19
1	2.49 ± 0.14	0.057	2.50
6	1.63 ± 0.32	0.034	3.37
9	61.0 ± 4.5	>0.4	2.51
10	0.34 ± 0.05	0.044	4.96
11	1.04 ± 0.03	nd	5.67
12	0.35 ± 0.05	0.050	5.90
13	0.06 ± 0.01	0.053	5.99
14	0.62 ± 0.05	nd	6.20
15	0.53 ± 0.04	0.033	6.20
16	2.58 ± 0.49	0.020	8.13
17	1.22 ± 0.29	0.055	8.50
18	0.29 ± 0.10	0.028	4.18
19	0.69 ± 0.02	0.066	5.20
22	0.73 ± 0.05	0.158	5.96

[a] Results are expressed as mean ± SEM, $n = 3$. Interaction of compounds with 0.2 mM of the stable free radical DPPH. nd, not determined. Calculated lipophilicity of compounds is expressed as ClogP values.

Results and Discussion

The interaction of the new compounds at 30 min with 0.2 mM stable free radical DPPH expressed as IC_{50} values is shown in Table 1. All the analogues tested possess similar IC_{50} values ranging from 0.02 to 0.07 mM. Lipoic acid and the aminoamide **9** are inactive while diamide **22**, which does not contain lipoic acid, exhibits an IC_{50} of 0.158 mM.

The activity of the new analogues on the in vitro peroxidation of rat hepatic microsomal membrane lipids is expressed as the concentration of compound that inhibited lipid peroxidation by 50% after 45 min of incubation (IC_{50} values) and is shown in Table 1. All compounds tested exhibited very potent antioxidant activities. The most active of the series is the *o*-phenylenediamine-substituted analogue **13** with 400-fold higher antioxidant activity as compared to trolox. The activity of all other compounds tested was 10−125-fold higher than that of trolox.

Amide or amine analogues of trolox have been reported to inhibit microsomal lipid peroxidation with IC_{50} values ranging from 1 to 10 μM.[10,14] Our intermediate aminoamides **1** and **6** also exhibit better antioxidant activity on lipid peroxidation than trolox, as expected. However, the final trolox−lipoic acid diamides **10** and **15** are stronger inhibitors than the corresponding intermediate aminoamides. It seems that the presence of lipoic acid results in increased activity, which is dependent on the nature of the spacer (IC_{50} ranged from 0.06 to 2.58 μM). Despite the fact that lipoic acid is inactive on iron-induced lipid peroxidation, its aminoamide analogue **9**, bearing 1,2-phenylenediamine, was found to be a weak inhibitor ($IC_{50} = 61$ μM).

Diamide **18**, which is the DHLA analogue of **10**, has similar activity in the lipid peroxidation bioassay ($IC_{50} = 0.29$ μM vs 0.34 μM) while the DHLA analogue of **13** is less active ($IC_{50} = 0.70$ μM vs 0.06 μM). On the basis of these data and the fact that the DHLA analogues are less stable, there does not seem to be an obvious advantage in using the reduced analogues as potential therapeutic agents, at least for this class of compounds.

Although in many cases there is a correlation between antioxidant activity and lipophilicity, this is not applicable for these compounds. However, we can deduce an optimum ClogP range of 4.18−6.20 for these series

Table 2. Effects of Selected Compounds on In Vitro Myocardial Electrical Activity and Accumulation of MDA Derivatives

compd (5 μM)	arrhythmia score	MDA
none	15 ± 3.4	2.11 ± 0.3
lipoic acid	6.3 ± 2.1[a]	1.03 ± 0.02[b]
trolox	3.15 ± 1.7[a]	1.07 ± 0.05[b]
10	0	1.10 ± 0.1[b]
12	16 ± 4.1	1.19 ± 0.09[b]
13	0	0.99 ± 0.06[b]
9	10.25 ± 2.34	1.13 ± 0.08[b]
6	10.98 ± 4.1	1.27 ± 0.06[c]
22	6.98 ± 3.12[a]	1.41 ± 0.15 [c]

[a] $p < 0.001$ vs control. [b] $p < 0.001$ vs control. [c] $p < 0.05$ vs control; $n = 2-4$.

of compounds for improved antioxidant capacity. Higher or lower values result in decreased activity as shown in Table 1.

The most active of the final diamides (**10**, **12**, and **13**) as well as the intermediate aminoamide analogue of trolox **6** and the aminoamide analogue of lipoic acid **9** were evaluated for their antiarrhythmic and antioxidant activity on isolated heart preparations using the Krebs perfused Langerdorff model (Table 2). The tissue MDA levels reflect the antioxidant capacity of the analogues under study. As shown in Table 2, the MDA content in hearts perfused in the absence of test compounds is 2.11 ± 0.3 μmol/g of tissue. All the compounds tested induced a statistically significant decrease of MDA content ($p < 0.001$ or 0.05) approximately to the same extent, including trolox and lipoic acid.

Arrhythmia scores were calculated for the first 15 min of reperfusion. The arrhythmic score of controls was 15 ± 3.4 and was mainly due to premature beats and nonsustained ventricular fibrillation. The experiments were performed using a 5 μM concentration for each compound. Both lipoic acid and trolox reduced the arrhythmias induced by reoxygenation during reperfusion (6.3 ± 2.1 and 3.15 ± 1.7, respectively; $p < 0.001$). The arrhythmias observed in the presence of these compounds were due to premature beats and were not accompanied by ventricular fibrillations. It should be noted, however, that bradycardia was observed in the presence of both compounds. In hearts treated with the test compounds, a total suppression of arrhythmias was observed in the presence of **10** and **13**, whereas **12**, **9**, and **6** did not reduce the arrhythmia score. **10**, **12**, and **13** are trolox−lipoic acid hybrids and exhibit similar microsomal and myocardial anti-lipid peroxidation activity and lipophilicity. The striking difference in antiarrhythmic activity of these compounds could be attributed to the presence of the secondary diamine in analogue **12** whereas **10** and **13** are primary amine analogues. However, further investigations are required to clarify this point.

To evaluate the influence of lipoic acid on the antiarrhythmic activity of the new compounds, we synthesized **22** in which the dithiolane ring is replaced by a cyclopentane ring. The carbocyclic analogue **22** was slightly less potent than the corresponding lipoic acid analogue **10** in inhibiting in vitro microsomal lipid peroxidation ($IC_{50} = 0.73$ μM vs 0.34 μM, $p < 0.005$) and reacts less with the DPPH radical ($IC_{50} = 0.158$ mM vs 0.044 mM). In contrast to the corresponding lipoic acid analogue **10**, which totally suppressed the reperfusion arrhythmias, **22** induced a decrease of arrhythmias (6.98 ± 3.12, $p < 0.001$ as compared to the control), and the arrhythmias observed were due to both premature beats and nonsustained ventricular fibrillations.

The lack of correlation between the protective effects of the new compounds against myocardial lipid peroxidation and suppression of the arrhythmias has been previously observed.[15] Concerning our compounds, the observed cardioprotective activity is probably due in part to their antioxidant potency. In addition, we measure total MDA production, and we cannot distinguish between local MDA production differences.

In conclusion, we have synthesized new trolox−lipoic acid hybrids that possess potent anti-lipid peroxidation activity on rat liver microsomal membranes and exhibit protective effects against reperfusion damage on isolated heart preparations. The IC_{50} values against microsomal lipid peroxidation ranged from 0.06 to 2.58 μM. All the compounds tested were equipotent in reducing total MDA production during reoxygenation of the heart tissue. Trolox amides **6** and **22**, even though they possessed good antioxidant activity, did not reduce reperfusion arrhythmias effectively. Trolox−lipoic acid hybrids **10** and **13** that were very potent antioxidants in microsomal lipid peroxidation totally suppressed arrhythmias during reoxygenation. Since the ischemia−reperfusion injury is of multifactorial nature, identification of specific events contributing to myocardial damage in relation to the class of compounds described herein is necessary for the design of more effective cardioprotective agents.

Experimental Section

General Procedure for the Preparation of the Aminoamides 1 and 2. A mixture of trolox methyl ester (500 mg, 1.9 mmol) and 5 mL of the appropriate diamine was heated at 110 °C for 4 h. The reaction mixture was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo.

***N*-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)ethylenediamine (1).** Trituration with Et_2O to afford a white solid (350 mg, 78%), mp 164−165 °C. ^{1}H NMR (δ): 6.76 (bs, 1H), 3.40−3.15 (m, 2H), 2.70−2.55 (m, 4H), 2.40−2.30 (m, 1H), 2.16 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H), 1.90−1.80 (m, 1H), 1.51 (s, 3H). Anal. ($C_{16}H_{24}N_2O_3$) C, H, N.

General Procedure for the Preparation of the Aminoamides 3−8. A solution of trolox (500 mg, 2 mmol) and 1,1′-carbonyldiimidazole (350 mg, 2.2 mmol) in 25 mL of anhydrous THF was stirred at ambient temperature under nitrogen for 1 h. The appropriate diamine (4 mmol) was added to the solution, and stirring was continued overnight. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic extracts were combined, washed with brine, and dried (Na_2SO_4), and the solvent was evaporated in vacuo.

***N*-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)-1,2-phenylenediamine (4).** Purified by flash column chromatography using CH_2Cl_2−MeOH (98:2) as an eluent. Yield 490 mg (72%), yellowish solid, mp 150−153 °C. ^{1}H NMR (δ): 8.02 (s, 1H), 7.33 (m, 1H), 6.98 (m, 1H), 6.80−6.68 (m, 2H), 4.34 (s, 1H), 2.64 (t, $J = 5.5$ Hz, 2H), 2.56−2.49 (m, 1H), 2.24 (s, 3H), 2.18 (s, 3H), 2.08 (s, 3H), 1.95−1.90 (m, 1H), 1.66 (s, 3H).

***N*-(1,2-Dithiolane-3-pentanoyl)-1,2-phenylenediamine (9).** Prepared from lipoic acid and 1,2-phenylenediamine as described in the general procedure above. Purified by flash column chromatography using petroleum ether−acetone (70:30) as an eluent. Yield 75%, yellow solid, mp 74−76 °C. ^{1}H NMR (δ): 7.15−6.56 (m, 5H), 3.85 (bs, 2H), 3.70−

3.55 (m, 1H), 3.20−3.05 (m, 2H), 2.48−2.30 (m, 3H), 1.95−1.50 (m, 7H). Anal. ($C_{14}H_{20}N_2OS_2$) C, H, N.

General Procedure for the Preparation of the Diamides 10−17. To a mixture of THF (3 mL) and H_2O (2 mL) were sequentially added the appropriate aminoamide (0.3 mmol), lipoic acid chloride (135 mg, 0.6 mmol), and $NaHCO_3$ (100 mg, 1.2 mmol); the mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic extracts were combined, washed with saturated aqueous NaCl, and dried (Na_2SO_4), and the solvent was evaporated in vacuo.

***N*-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)-N′-(1,2-dithiolane-3-pentanoyl)-1,2-phenylenediamine (13).** Purified by flash column chromatography using petroleum ether−acetone (70:30) as an eluent. Yield 65 mg (41%), yellowish solid, mp 80−82 °C. ^{1}H NMR (δ): 8.52 (s, 1H), 8.02 (s, 1H), 7.58−7.55 (m, 1H), 7.21−7.13 (m, 3H), 4.53 (s, 1H), 3.53−3.50 (m, 1H), 3.19−3.08 (m, 2H), 2.73−2.55 (m, 2H), 2.43−2.28 (m, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H), 2.00−1.80 (m, 3H), 1.70−1.60 (m, 4H), 1.62 (s, 3H), 1.47−1.35 (m, 2H). ^{13}C NMR (δ): 174.1, 171.6, 145.9, 143.9, 130.9, 129.3, 126.7, 125.9, 125.6, 125.1, 122.2, 121.8, 119.1, 117.6, 78.4, 56.3, 40.2, 38.5, 36.7, 34.6, 29.6, 29.2, 28.9, 25.3, 24.3, 24.2, 20.5, 12.4, 12.1, 11.4. Anal. ($C_{28}H_{36}N_2O_4S_2$) C, H, N.

***N*-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)-N′-(6,8-dimercaptooctanoyl)ethylenediamine (18).** $NaBH_4$ (90 mg, 0.8 mmol) was added to a solution of **10** (120 mg, 0.2 mmol) in MeOH (3 mL) at 0 °C, and the mixture was stirred at ambient temperature for 4 h. Yield 120 mg (100%) yellowish oil. ^{1}H NMR (δ): 6.74 (bs, 1H), 5.81 (bs, 1H), 4.50 (s, 1H), 3.45−3.25 (m, 4H), 2.95−2.90 (m, 1H), 2.70−2.55 (m, 4H), 2.40−2.30 (m, 1H), 2.17(s, 6H), 2.08 (s, 3H), 2.07 (m, 1H), 1.85−1.70 (m, 2H), 1.65−1.50 (m, 4H), 1.51 (s, 3H), 1.45−1.35 (m, 2H). ^{13}C NMR δ 175.8, 173.4, 145.8, 144.1, 122, 121.9, 119.2, 117.8, 78.2, 42.7, 40.1, 39.3, 39.1, 38.7, 36.2, 29.6, 26.6, 25.2, 24.4, 22.3, 20.6, 12.4, 12.1, 11.5. Anal. ($C_{24}H_{38}N_2O_4S_2$) C, H, N.

***N*-(3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonyl)-N′-(cyclopentyl-5-pentanoyl)ethylenediamine (22).** Prepared from **1** (175 mg, 0.6 mmol) and **21** (100 mg, 0.6 mmol) as described for **3**−**8**. Yield 50 mg (20%), gummy solid. ^{1}H NMR (δ): 6.77 (bs, 1H), 5.85 (bs, 1H), 3.40−3.30 (m, 4H), 2.70−2.50 (m, 3H), 2.40−2.30 (m, 1H), 2.17 (s, 6H), 2.08 (s, 3H), 2.1−2.01 (m, 1H), 1.90−1.76 (m, 1H), 1.75−1.24 (m, 19H). Anal. ($C_{26}H_{40}N_2O_4$) C, H, N.

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Supporting Information Available: Detailed experimental procedures for the synthesis of compounds **2**, **5**−**8**, **10**−**12**, **14**−**17**, and **19**−**21**, analytical data for all compounds presented in Table 1, and experimental details for in vitro lipid peroxidation, interaction of test compounds with DPPH, ClogP, isolated heart preparation, and MDA measurements, with corresponding references. This material is available free of charge via the Internet at http://pubs.acs.org.

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