Novel Indole-2-carboxamide and Cycloalkeno[1,2-*b*]indole Derivatives. Structure−Activity Relationships for High Inhibition of Human LDL Peroxidation

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Series of indole-2-carboxamide and cycloalkeno[1,2-*b*]indole derivatives were synthesized and evaluated in order to determine the necessary structural requirements for a high inhibition of human LDL copper-induced peroxidation. Various modulations were systematically performed on the indole and cycloalkeno[1,2-*b*]indole nuclei as well as on the carboxamide moiety. The best compounds (**3c**, **3e**, **7c**, **7f**, **7h**, **7g**, and **7o**) are between 5 and 30 times more active than probucol itself. Two of these compounds (**3c** and **7o**) were selected for complementary *in vitro* and *in vivo* investigations, which have shown additional properties of interest for the treatment and the prevention of atherosclerosis injuries. Compound **3c** was found to have some antiinflammatory properties while compound **7o** was proved to protect endothelial cells from the direct cytotoxicity of oxidized LDL with some additional calcium channel blocking properties.

Introduction

Oxygen-derived free radicals and hydrogen peroxide have been recognized to be essential mediators in the appearance and development of numerous human pathologies[1] with, among others, cerebral and cardiac ischemia-reperfusion injury[2−5] as well as atherosclerosis.[6] Atherosclerosis is a severe pathology which can be implicated, directly or not, in about 50% of all mortality in western countries and is considered as the main contributor to the pathogenesis of myocardial and cerebral infarction, gangrene, and loss of function of the extremities. Over the past years, evidence has accumulated to suggest that free radicals, and the lipid peroxidation they induce, could trigger most of the factors involved in the atherosclerotic vascular injuries (cytotoxicity, inflammation, formation of atheromatous plaques, ...).[6−10] Oxidative modifications of the lipoproteins, and more particularly of the low density lipoproteins (LDL), appeared to be one of the earliest phenomenon in the development of atherosclerosis pathology.[11−13] Oxidatively modified LDL (ox-LDL) are key components in endothelial injury. Indeed besides their direct cytotoxicity[14,15] they stimulate the induction of proteins responsible for the adhesion as well as chemotaxis of monocytes at the endothelial cell surface.[16] Moreover, thanks to scavenger receptors and putative ox-LDL receptors, ox-LDL are taken up in an unregulated manner by the subendothelial macrophages with, as a consequence, accumulation of cholesterol esters and formation of foam cells which accumulate in the atherosclerotic lesions leading to atheromatous plaques.[16−19]

Numerous available epidemiological, biochemical, and experimental data have led to the conclusion that antioxidant compounds able to protect lipids from peroxidation could be of value for the prevention and/or the treatment of atherosclerosis by attenuating foam−cell formation. There are several evidences that vitamin E (Figure 1), an endogenous antioxidant radical scavenger, may prevent initiation and propagation of spontaneous atherosclerosis. The epidemiological studies also suggest that humans with a high plasma level of vitamin E have a lower risk of coronary heart disease.[20] In the same way, supplementation of humans with vitamin E increases the oxidation resistance of LDL.[21]

Studies performed on Watanabe heritable hyperlipidemic rabbit showed that probucol, a potent liposoluble hydroxyl radical scavenger, prevents the progression of atherosclerosis.[22−24]

Like vitamin E and probucol, a lot of potent antioxidants have their structure based on hindered phenol or hydroxy chromane. This is the case for Trolox[25] and some of its analogues such as U-78517 F[26,27] as well as for some hydroxybenzylamine antioxidants[28] (Figure 2).

Antioxidant properties were also observed with 5-hydroxyindole and 5-hydroxytryptophan[29] and especially with 6-hydroxy-1,4-dimethylcarbazole (HDC) which proved *in vitro* to be a very powerful inhibitor of lipid peroxidation (Figure 3).[30]

In this paper, we report the synthesis and the pharmacological evaluation of a series of antioxidant indole-2-carboxamide and cycloalkeno[1,2-*b*]indole derivatives having the general formulas given in Figure 4.

Chemical modulations were systematically carried out on these two structures in order to determine the necessary structural requirements for high antioxidant properties and more particularly for high lipid peroxidation inhibition and LDL protection.

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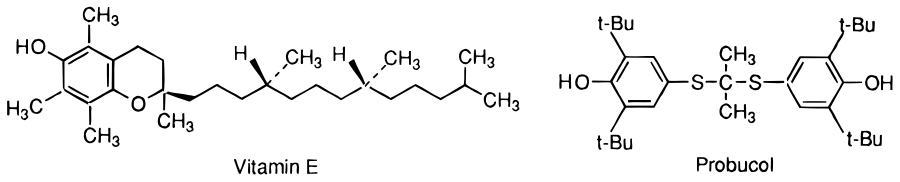


Figure 1.

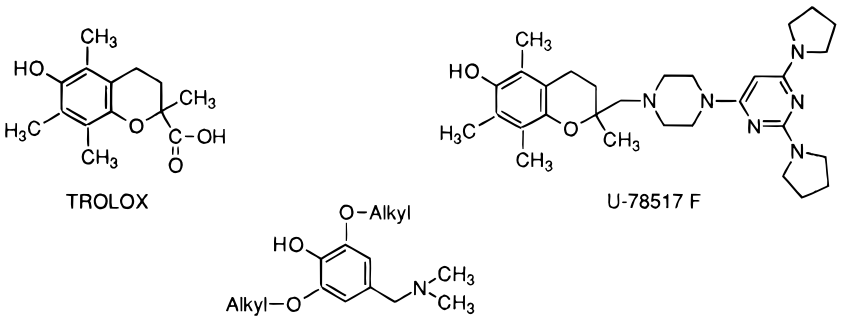


Figure 2.

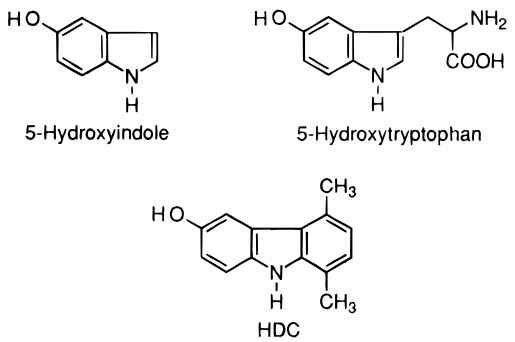


Figure 3.

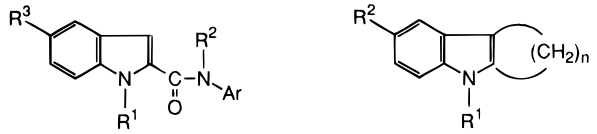


Figure 4.

Chemistry

Indoles **2** (Scheme 1) were prepared from the corresponding imines **1** by intramolecular arynic cyclization in the presence of an appropriate complex base[31] followed by quenching of the anionic intermediates with an electrophile (H_2O or Me_2SO_4). Yields varied from 60% and 88%. Treatment of **2** with $AlCl_3$ and $PhCH_2SH$, a new effective method for demethylation of methoxyindoles,[32] provided the corresponding hydroxy derivatives **3** in very good yields. The (ethylthio)indole **4b** was synthesized from **2b** using $AlCl_3-EtSH$ in large excess as reagent.[32] Indoles **5** were obtained in 50−90% yield according to Scheme 2 from the commercially available 5-methoxy-2-indolecarboxylic acid. The (ethylthio)indole **6d** was synthesized from **5d** and $AlCl_3-EtSH$ used in a large excess.[32] Hydroxyindolecarboxamides **7** were obtained with an average 70% yield by demethylation of **5** with the $AlCl_3-PhCH_2SH$ reagent. When the *N*-aryl substituent contained methoxy groups, another synthetic pathway was adopted (Scheme 3). Thus the desired amine was condensed on the commercially available (but very expensive) 5-hydroxy-2-indolecarboxylic acid via its acid chloride with an average yield of 30%. Compounds **2**−**7** were tested for their antioxidant properties.

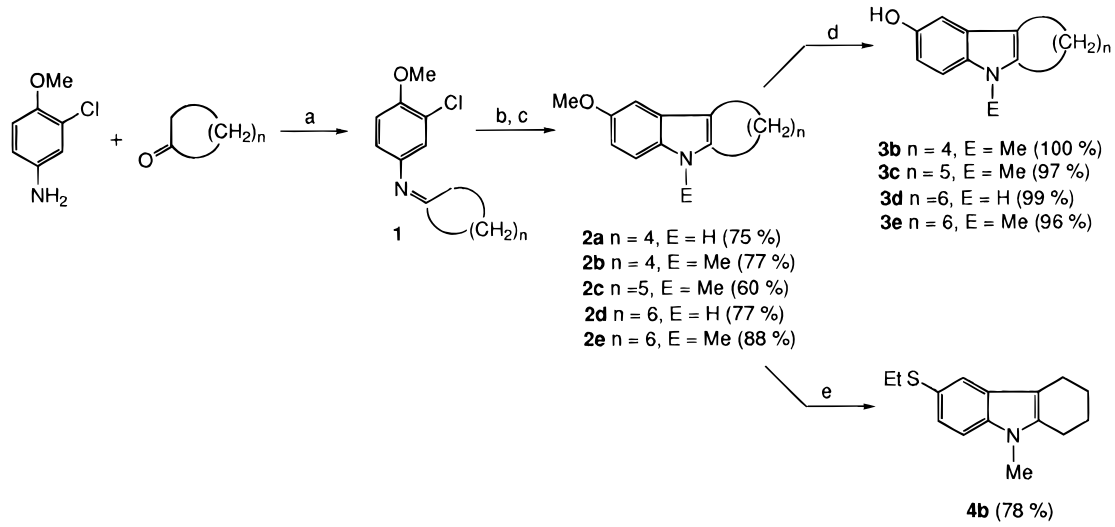
Results and Discussion

Twenty indole-2-carboxamide and six cycloalkeno[1,2-*b*]indole derivatives were synthesized and evaluated. All were prescreened *in vitro* for their ability to protect human LDL against copper-induced peroxidation. Results were expressed as IC_{50} (concentration inhibiting 50% of the copper induced lipid peroxidation) determined using the thiobarbituric acid reactive substance (TBARS) and expressed as malondialdehyde equivalent (Tables 1 and 2). To correct slight variations in response between the same evaluation procedures not performed with the same batch of human LDL, results were also expressed as an activity ratio versus probucol (*r*).

Concerning the cycloalkeno[1,2-*b*]indoles derivatives (Table 1), this prescreening procedure showed the following: (i) Methylation of the indole nucleus nitrogen results in a significant increase in activity. $r = 10$ for compound **3e** ($R^1 = CH_3$) compared to $r = 2$ for compound **3d** ($R^1 = H$). (ii) Replacement of the hydroxy substituent R^2 (**3b**, $r = 3$) with an ethylthio group (**4b**, $r = 0.1$) results in a very clear decrease in activity. (iii) The size of the cycloalkenyl ring is of a great influence on the peroxidation inhibition. Very good results are obtained with compound **3c** which is a cycloheptene derivative 30 times more efficient than probucol. The order of potency according to the size of the ring is as follows: **3c** ($n = 5$, $r = 30$) > **3e** ($n = 6$, $r = 10$) > **3b** ($n = 4$, $r = 3$).

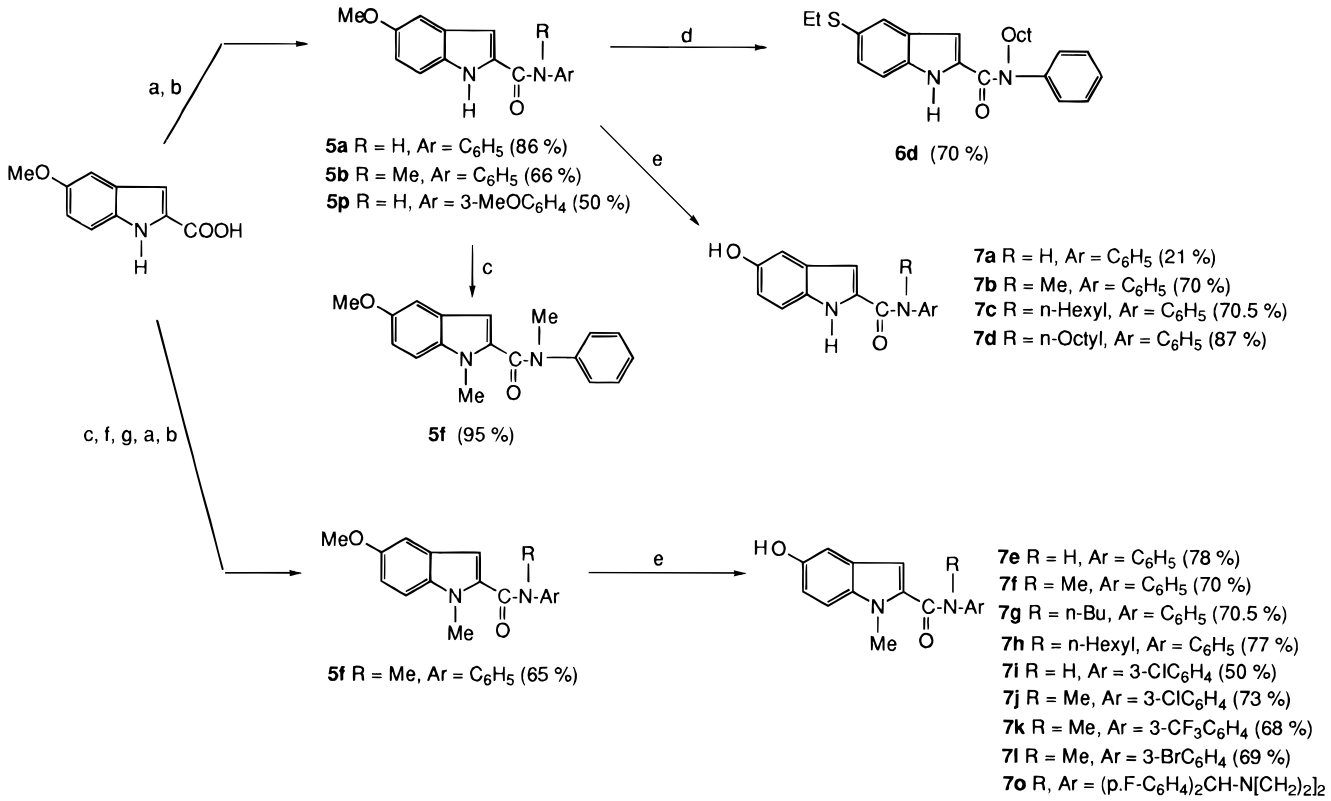
Concerning the indole-2-carboxanilides derivatives (Table 2), the following observations emerged: (i) Whatever the other substituents, R^1, R^2, and Ar, 5-methoxyindole derivatives **5** are less active than their 5-hydroxy strict analogues **7**. The difference in activity can be very low between the NH-anilides **5a** ($r = 2.2$) and **7a** ($r = 3$) or much higher for the *N*-methylanilide derivatives, **5b** ($r < 0.001$) and **5f** ($r = 0.02$), which are around 1000 times less active than their 5-hydroxy analogues **7b** ($r = 1$) and **7f** ($r = 10$) virtually inactive. (ii) Replacement of the 5-hydroxy substituent (**7d**, $r = 0.3$) by a 5-SEt group (**6d**, $r = 0.03$) clearly decreases the antioxidant properties. (iii) With the exception of **7h** which is 2 times less active than **7c**, methylation of the indole nucleus nitrogen ($R^1 = CH_3$) results generally in a moderate to clear increase of the antioxidant properties

Scheme 1[a]



[a] (a) C_6H_6, Δ; (b) $NaNH_2$−tBuONa, THF, room temperature; (c) H_2O for **2a**,**d**, 0 °C; Me_2SO_4 for **2b**,**c**,**e**, 0 °C to room temperature; (d) $AlCl_3$−$PhCH_2SH$, CH_2Cl_2, 0 °C; (e) $AlCl_3$−EtSH, CH_2Cl_2, 0 °C to room temperature.

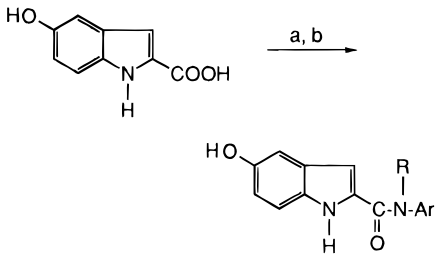
Scheme 2[a]



[a] (a) PCl_5, Et_2O, room temperature; (b) ArNHR, Et_2O/dioxane, 0 °C to room temperature; (c) NaH, Me_2SO_4, DMF, room temperature; (d)$AlCl_3$−EtSH, CH_2Cl_2, 0 °C; (e) $AlCl_3$−$PhCH_2SH$, CH_2Cl_2, 0 °C; (f) KOH, EtOH; (g) H_3O^+.

(up to 10 times for **7f** and **5f** compared to **7b** and **5b**). (iv) The influence of alkylation on the carboxamide nitrogen appears to be complex and very dependent on the other substitutions. Thus in the 5-methoxy-substituted series **5**, methylation of the amide function results in a drastic decrease in activity (more than 1000 times for **5b** compared to **5a**). In the 5-hydroxy-substituted series **7**, alkylation may result in a clear increase in activity in a dependent manner according to R^1 substituent on the indole nucleus nitrogen. When $R^1 = H$, the best results are obtained for compound **7c** (R^2 = *n*-hexyl), which is 10 times more potent than probucol itself and the order of potency is as follows: **7c** (R^2 = *n*-Hex, $r = 10$) > **7a** (R^2 = H, $r = 3$) > **7b** ($R^2 = CH_3$, $r = 1$) > **7d** (R^2 = *n*-octyl, $r = 0.3$). When $R^1 = CH_3$, the best results are obtained for compounds **7f** and **7j** ($R^2 = CH_3$) and the orders of potency are as follows: **7f** ($R^2 = CH_3$, $r = 10$) > **7h** (R^2 = *n*-Hex, $r = 5$) > **7e** (R^2 = H, $r = 0.3$) when Ar = C_6H_5 and **7j** ($R^2 = CH_3$, $r > 20$) ≫ **7i** (R^2 = H, $r = 0.8$) when Ar = 3-ClC_6H_4. (v) Concerning the substitution on the aromatic anilide moiety, compound **7j** (Ar = 3-ClC_6H_4, $r > 20$) is more active than its 3-Br (**7l**), 3-CF_3 (**7k**), or nonsubstituted (**7f**) anilides direct analogues. (vi) Replacement of the aniline moiety

Scheme 3[a]



7m R = H, Ar = 3,4,5-$(MeO)_3C_6H_2$ (30 %)

7n R, Ar = 2,3,4-$(MeO)_3C_6H_2$-CH_2-N[$(CH_2)_2$]$_2$ (33 %)

[a] (a) $SOCl_2$, C_6H_6, Δ; (b) RNHAr, Et_2O/dioxane, room temperature.

by azylpiperazines (**7n**, $r = 1$, and **7o**, $r = 5$) results in relatively active derivatives. Compound **7o** was substituted with a "flunarizine-like" fluorobenzhydrylpiperazine in the aim of providing it with some antagonistic activity on the calcium channels and consequently with additional cytoprotective potentialities.

In conclusion to this preliminary evaluation, the chemical modulations we carried out led us to the discovery of new compounds much more potent than probucol in their ability to prevent human LDL from copper-induced peroxidation.

Pharmacology

Among the highly potent compounds selected from the prescreening procedure, compounds **3c** and **7o** were selected for complementary pharmacological evaluation.

Due to its very potent antioxidant properties, compound **3c** was investigated, *in vitro*, for its inhibiting properties on cyclooxygenase and 5-lipoxygenase. Indeed, inflammatory processes are suspected to be involved in atherosclerosis pathology. This seems to be more particularly the case for the 15-lipoxygenase pathway[33] which could be implicated in the development of atherosclerosis lesions by stimulating neovascularization[34] and also by its role in the LDL oxidation.[35]

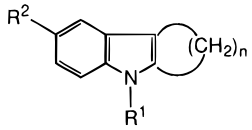
Due to its fluorobenhydrylpiperazine moiety, interactions of compound **7o** with the calcium channels were investigated. As calcium channel blockers such as nifedipine, diltiazem, and verapamil have already been proved cultured lymphoid cells against the toxicity of oxidized LDL,[36] compound **7o** was also evaluated for its direct cytoprotective properties on cultured endothelial cells exposed to oxidized LDL.

Pharmacology Results

The inhibiting properties of compound **3c** on cyclooxygenase and 5-lipoxygenase were determined *in vitro* by measuring the inhibition of the production of PGE_2 and LTB_4 from rabbit granulocytes cells stimulated by calcium ionophore A 23187.[37] Compound **3c** was found to be active in inhibiting both cyclooxygenase and 5-lipoxygenase with IC_{50} values of respectively $(4.0 \pm 0.9) \times 10^{-7}$ and $(1.2 \pm 0.3) \times 10^{-6}$ M. It also proved to be active against 15-lipoxygenase, by inhibiting, at a concentration of 10^{-5} M, 62 ± 3% of the 15-HETE production by human umbilical vein endothelial cells (HUVEC) stimulated by calcium ionophore A 23187.[38]

On another side, calcium channel blocking properties of compound **7o** were demonstrated by the ability of this compound to inhibit, with an IC_{50} of 1.5×10^{-6} M, the KCl-induced rat thoracic aorta contraction[39] (flunarizine $IC_{50} = 2.7 \times 10^{-7}$ M). In addition to its antioxidant properties, compound **7o** proved to very potently protect bovine endothelial cells against direct cytotoxicity of oxidized LDL with an IC_{50} value of $(1.4 \pm 0.4) \times 10^{-7}$ M. This compound is clearly more potent than probucol and α-tocopherol which only showed IC_{50} values of respectively $(1.5 \pm 0.4) \times 10^{-5}$ and $(2.0 \pm 0.6) \times 10^{-5}$ M in this test.

Table 1. Inhibition of Copper-Induced Lipid Peroxidation by Cycloalkeno[1,2-*b*]indole Derivatives



				inhibition of lipid peroxidation	
compd	R^1	R^2	*n*	IC_{50} (M)	r[a]
2a	H	OCH_3	4	10^{-6}	3
3b	CH_3	OH	4	6×10^{-7}	3
3c	CH_3	OH	5	10^{-7}	30
3d	H	OH	6	5×10^{-7}	2
3e	CH_3	OH	6	10^{-7}	10
4b	CH_3	SEt	4	2×10^{-5}	0,1

[a] Activity ratio versus Probucol.

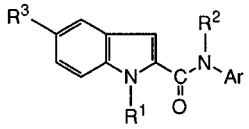
Conclusion

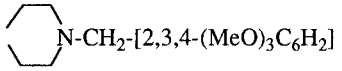
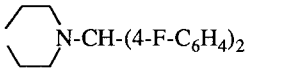
The chemical modulations performed on both indole-2-carboxamide and cycloalkeno[1,2-*b*]indole series led us to new compounds which were very efficient in preventing human LDL from copper-induced peroxidation. Among the numerous compounds more active than Probucol, compounds **3c** and **7o** were selected for complementary *in vitro* and *in vivo* investigations that showed additional properties of great interest for the treatment and for the prevention of atherosclerosis and oxidative injuries. Compound **3c** was proved to have *in vitro* inhibiting properties on cyclooxygenase and 5-lipoxygenase. This could be predictive of *in vivo* antiinflammatory activity. Compound **7o** was found to protect endothelial cells from direct cytotoxicity of oxidized LDL with additional calcium channel blocking properties. Both deserve further investigations currently under exploration.

Experimental Part

Chemistry. General Methods. Melting points were determined on a Totoli melting point apparatus and are uncorrected. ^{13}C NMR spectra were recorded with a Bruker AM 400 or a Bruker 300 MHz spectrometer (Attached Proton Test method, APT). ^1H NMR spectra were recorded on a JEOL PMX 60 at 60 MHz, or a Brucker AM 400 instrument at 400 MHz. Me_4Si was the internal standard. Infrared (IR) spectra of thin liquid films between NaCl plates or KBr pellets were recorded with a Perkin-Elmer 841 instrument. Elemental analyses were performed by CNRS Laboratory (Vernaison) and by ENSCM Microanalysis Department of Montpellier. Mass spectra were recorded on Hewlett-Packard 5971A instrument. Thin-layer chromatography (TLC) was performed with plates coated with kieselgel G (Merck). The plates were developed with petroleum ether (PE)/EtOAc or acetone/hexane as eluents. The silica gels used for column chromatography and flash chromatography were kieselgels of 0.063−0.2 and 0.04−0.063 mm particle size, respectively. A capillary HP1(6m) was used for GPC.

Table 2. Inhibition of Copper-Induced Lipid Peroxidation by Indole-2-carboxamide Derivatives



					Inhibition of lipid peroxidation	
	R^1	Ar	R^2	R^3	IC_{50} (M)	r[a]
7a	H	C_6H_5	H	OH	10^{-6}	3
7b	H	C_6H_5	CH_3	OH	10^{-6}	1
7c	H	C_6H_5	n-Hexyl	OH	10^{-7}	10
7d	H	C_6H_5	n-Octyl	OH	10^{-5}	0.3
7e	CH_3	C_6H_5	H	OH	9×10^{-7}	3.3
7f	CH_3	C_6H_5	CH_3	OH	2×10^{-7}	10
7g	CH_3	C_6H_5	n-Butyl	OH	10^{-6}	3
7h	CH_3	C_6H_5	n-Hexyl	OH	2×10^{-7}	5
7i	CH_3	3-Cl-C_6H_4	H	OH	10^{-6}	0.8
7j	CH_3	3-Cl-C_6H_4	CH_3	OH	$< 10^{-7}$	> 20
7k	CH_3	3-CF_3-C_6H_4	CH_3	OH	10^{-6}	0.5
7l	CH_3	3-Br-C_6H_4	CH_3	OH	8×10^{-7}	2.5
7m	H	3,4,5-$(MeO)_3C_6H_2$	H	OH	8×10^{-7}	3.8
7n	H			OH	5×10^{-6}	1
7o	CH_3			OH	6×10^{-7}	5
5a	H	C_6H_5	H	OCH_3	9×10^{-7}	2.2
5b	H	C_6H_5	CH_3	OCH_3	$> 10^{-3}$	< 0.001
5f	CH_3	C_6H_5	CH_3	OCH_3	9×10^{-5}	0.02
5p	CH_3	3-CH_3O-C_6H_4	CH_3	OCH_3	2×10^{-4}	0.01
6d	H	C_6H_5	n-Octyl	SEt	10^{-4}	0.03
Probucol	-	-	-	-	5×10^{-6} - 5×10^{-7}	-

[a]Activity ratio versus Probucol

Imines **1** were classically obtained in yields varying from 40% to 75% by azeotropic dehydration of an equimolar amount of amine and ketone. They were either purified by fast distillation under vacuum or used as crude product after classical workup without other purification.

Arynic Synthesis: General Procedure for the Preparation of Indoles 2. To a stirred suspension of 7 equiv of $NaNH_2$ in THF (1 mL/7 mmol) was slowly added at 0 °C 2 equiv of *t*-BuOH in the minimum amount of THF. The stirred reaction mixture was then warmed to 42 °C for 2 h. The complex base thus obtained was cooled to 0 °C, and a solution of the imine **1** in THF (3 mL/1 mmole) was dropwise added. The stirred reaction mixture was then allowed to warm to room temperature for 24 h, and a quenching with various electrophiles was done.

(1) Quenching with $E^+ = H_2O$. The reaction mixture was poured into ice and extracted with Et_2O, the organic phase was dried on $MgSO_4$, and the solvent was removed under vacuum. Indoles were isolated by flash chromatography with AcOEt/PE as eluents.

1,2,3,4-Tetrahydro-6-methoxycarbazole (2a) was obtained with AcOEt/PE (10/90) as eluent. IR (NaCl): 3395 (NH), 2916−2852 (C−H). ^{1}H NMR ($CDCl_3$): δ 6.50−7.55 (4H, m, arom H + NH), 3.80 (3H, s, OMe), 2.90−2.50 (4H, m, 2 × CH_2), 2.15−1.60 (4H, m, 2 × CH_2). ^{13}C NMR ($CDCl_3$): δ 153.7 (arom *C*OMe), 135.1 (arom C), 130.7 (arom C), 128.1 (arom C), 110.9 (arom CH), 110.4 (arom CH), 109.8 (arom C), 100.2 (arom CH), 55.9 (OMe), 23.2 (CH_2), 23.1 (CH_2), 20.9 (2 × CH_2). Mp: 84−87 °C. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.57; H, 7.51; N, 6.95. Found: C, 77.04; H, 7.66; N, 6.90.

2-Methoxy-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole (2d) was obtained with AcOEt/PE (10/90) as eluent. IR (NaCl): 3405 (NH), 2922−2848 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.90−6.50 (4H, m, arom H + NH), 3.86 (3H, s, OMe), 3.00−2.50 (4H m, 2 × CH_2), 2.00−1.20 (8H, m, 4 × CH_2). ^{13}C NMR ($CDCl_3$): δ 153.5 (arom *C*OMe), 136.7 (arom C), 130.1 (arom C), 128.8 (arom C), 111.2 (arom C), 110.9 (arom CH), 110.0 (arom CH), 99.9 (arom CH), 55.8 (OMe), 29.4 (CH_2), 29.4 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 22.1 (CH_2). Mp: 100−104 °C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.65; H, 8.43; N, 6.10.

(2) Quenching with $E^+ = Me_2SO_4$. The reaction mixture was decanted, and the supernatant liquid was transferred into a flask containing a stirred solution of 3 equiv of Me_2SO_4 in THF at 0 °C. After the mixture was stirred at room temperature, the reaction, monitored by TLC (AcOEt/PE as eluent) or CPG, was stopped when the unsubstituted indole had desappeared. The reaction mixture was then poured into ice/NH_4OH (10%) and extracted with Et_2O. The organic phase was washed three times with H_2O and dried on $MgSO_4$ and the solvent removed under vacuum. Indoles were isolated by flash chromatography with AcOEt/PE as eluent.

1,2,3,4-Tetrahydro-6-methoxy-9-methylcarbazole (2b) was obtained with AcOEt/PE (5/95) as eluent. IR (NaCl): 2993, 2930, 2833 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.50−6.60 (3H, m, arom H), 3.80 (3H, s, OMe), 3.55 (NMe), 3.10−2.50 (4H, m, 2 × CH_2), 2.30−1.70 (4H, m, 2 × CH_2). ^{13}C NMR ($CDCl_3$): δ 153.5 (arom *C*OMe), 136.3 (arom C), 132.0 (arom C), 127.2 (arom C), 109.9 (arom CH), 108.9 (arom CH), 108.7 (arom C), 100.1 (arom CH), 55.9 (OMe), 28.8 (NMe), 23.1 (2 × CH_2), 22.0 (CH_2), 21.0 (CH_2). Mp: 70−72 °C. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.50. Found: C, 78.37; H, 8.10; N, 6.44.

2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (2c) was obtained with AcOEt/PE (5/95) as eluent. IR (NaCl): 2990, 2920, 2845 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.30−6.50 (3H, m, arom H), 3.80 (3H, s, OMe), 3.00−2.50 (4H, m, 2 × CH_2), 2.00−1.50 (6 H, m, 3 × CH_2). ^{13}C NMR ($CDCl_3$): δ 153.6 (arom *C*OMe), 139.7 (arom C), 139.7 (arom C), 131.2 (arom C), 127.7 (arom C), 113.0 (arom C), 109.9 (arom CH), 108.9 (arom CH), 99.8 (arom CH), 55.9 (OMe), 31.5 (CH_2), 29.3 (NMe), 28.4 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 24.3 (CH_2). Mp: 47−49 °C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.41; H, 8.51; N, 6.26.

2-Methoxy-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole (2e) was obtained with AcOEt/PE (5/95) as eluent. IR (NaCl): 2921−2848 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.10−6.50 (3H, m, arom H), 3.78 (3H, s, OMe), 3.68 (3H, s, NMe), 3.00−2.60 (4H, m, 2 × CH_2), 1.90−1.20 (8H, m, 4 × CH_2). ^{13}C NMR ($CDCl_3$): δ 153.5 (arom *C*OMe), 137.7 (arom C), 131.9 (arom C), 127.4 (arom C), 111.1 (arom C), 109.7 (arom CH), 109.1 (arom CH), 99.9 (arom CH), 55.9 (OMe), 30.4 (CH_2), 29.2 (NMe), 28.7 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 22.9 (2 × CH_2). Mp: 53−55 °C. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.96; H, 8.69; N, 5.75. Found: C, 78.90; H, 8.52; N, 5.82.

Demethylation of Methoxyindoles 2: Typical Procedure for the Preparation of 1,2,3,4-Tetrahydro-6-hydroxy-9-methylcarbazole (3b). To a suspension of 20 equiv of $PhCH_2SH$ (10.9 mL) and 1.5 equiv of $AlCl_3$ (930 mg) at 0 °C was slowly added a solution of 1 equiv of **2b** (1 g) in CH_2Cl_2 (25 mL). The reaction mixture was stirred for 0.5 h at 0 °C, and 20 equiv of $PhCH_2SH$ (10.9 mL) and 1.5 equiv of $AlCl_3$ (930 mg) were added. After the mixture was stirred for 5 h at 0 °C, acid hydrolysis with HCl (10%) (50 mL) was done at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was successively washed with H_2O (100 mL) and brine (100 mL) and dried over Na_2SO_4. The solvents were removed under vacuum and 1,2,3,4-tetrahydro-6-hydroxy-9-methylcarbazole **3b** isolated by flash chromatography with AcOEt/PE (15/85) as eluent. IR (NaCl): 3356 (OH), 2930−2839 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.00−6.46 (3H, m, arom H), 6.00 (1H, s, OH), 3.30 (3H, s, NMe), 2.83−2.16 (4H, m, 2 × CH_2), 2.00−1.46 (4H, m, 2 × CH_2). ^{13}C NMR ($CDCl_3$): δ 148.5 (arom COH), 136.4 (arom C), 132.0 (arom C), 127.4 (arom C), 109.7 (arom CH), 108.7 (arom CH), 108.2 (arom C), 102.7 (arom CH), 23.0 (2 × CH_2), 21.8 (CH_2), 20.8 (CH_2), 28.6 (NMe). Mp: 91−93 °C. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.57; H, 7.51; N, 6.95. Found: C, 77.45; H, 7.51; N, 6.86.

2-Hydroxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (3c) was obtained after a reaction time of 3.5 h and isolated with AcOEt/PE (15/85) as eluent. IR (NaCl): 3349 (OH), 2920−2845 (C−H). ^{1}H NMR ($CDCl_3$): δ 6.5−7.3 (3H, m, arom H), 5.2 (1H, s, OH), 3.6 (3H, s, NMe), 2.5−3.0 (4H, m, 2 × CH_2), 1.5−2.0 (6H, m, 3 × CH_2). ^{13}C NMR ($CDCl_3$): δ 148.8 (arom COH), 140.0 (arom C), 131.3 (arom C), 128.1 (arom C), 112.6 (arom C), 109.7 (arom CH), 109.2 (arom CH), 102.4 (arom CH), 31.4 (CH_2), 29.4 (NMe), 28.3 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 24.3 (CH_2). Mp: 101−103 °C. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.50. Found: C, 77.69; H, 7.85; N, 6.52.

2-Hydroxy-6,7,8,9,10,11-hexahydro-5*H*-cyclooct[*b*]indole (3d) was obtained after a reaction time of 1.5 h and isolated with AcOEt/PE (15/85) as eluent. IR (NaCl): 3404 (OH + NH), 2922−2849 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H, NH), 6.90−6.25 (3H, m, arom H), 5.45 (1H, s, OH), 2.70−2.25 (4H, m, 2 × CH_2), 1.90−1.00 (8H, m, 4 × CH_2). ^{13}C NMR ($CDCl_3$): δ 148.88 (arom COH), 137.06 (arom C), 132.24 (arom C), 129.20 (arom C), 111.03 (arom C), 110.81 (arom CH), 109.92 (arom CH), 102.52 (arom CH), 29.44 (CH_2), 29.38 (CH_2), 25.91 (CH_2), 25.78 (CH_2), 25.72 (CH_2), 22.08 (CH_2). Mp: 90−94 °C. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.50. Found: C, 77.57; H, 7.94; N, 6.58.

2-Hydroxy-5-methyl-6,7,8,9,10,11-heptahydro-5*H*-cyclooct[*b*]indole (3e) was obtained after a reaction time of 1.5 h and isolated with AcOEt/PE (15/85) as eluent. IR (NaCl): 3368 (OH), 2925−2847 (C−H). ^{1}H NMR ($CDCl_3$) δ ppm: 7.00−6.35 (3H, m, arom H), 5.55 (1H, s, OH), 3.50 (3H, s, NMe), 3.00−2.50 (4H, m, 2 × CH_2), 1.90−1.00 (8H, m, 4 × CH_2). ^{13}C NMR ($CDCl_3$): δ 148.7 (arom COH), 138.0 (arom C), 132.0 (arom C), 127.7 (arom C), 110.8 (arom C), 109.5 (arom CH), 109.0 (arom CH), 102.4 (arom CH), 30.4 (CH_2), 29.2 (NMe), 28.6 (CH_2), 25.8 (2 × CH_2), 22.9 (2 × CH_2). Mp: 97−99 °C. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.12. Found: C, 78.07; H, 8.30; N, 6.12.

Synthesis of 6-(Ethylthio)-1,2,3,4-tetrahydro-9-methylcarbazole (4b). To a suspension of 20 equiv of EtSH (6.9 mL) and 1.5 equiv of $AlCl_3$ (930 mg) at 0 °C was slowly added a solution of 1 equiv of indole **2b** (1 g) in CH_2Cl_2 (25 mL). The reaction mixture was stirred for 0.5 h at 0 °C, and 20 equiv of EtSH (6.9 mL) and 1.5 equiv of $AlCl_3$ (930 mg) were added. After the mixture was stirred for 0.5 h at 0 °C, a third identical portion of each reagent was added. After 2 h at 0 °C and 48 h at room temperature, an acid hydrolysis with HCl (10%) (50 mL) was done at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was successively washed with H_2O (100 mL) and a saturated solution of NaCl (100 mL) and dried over Na_2SO_4. The solvents were removed under vacuum, and 6-(ethylthio)-1,2,3,4-tetrahydro-9-methylcarbazole (**4b**) was isolated by flash chromatography with AcOEt/PE (10/90) as eluent: Yield: 78%. IR (NaCl): 3408 (NH), 2925−2840 (C−H). ^{1}H NMR ($CDCl_3$): δ 7.70−6.80 (4H, m, arom H + NH), 3.10−2.30 (6H, m + q, SCH_2 + 2 × CH_2), 2.20−1.50 (4H, m, 2 × CH_2), 1.50−1.00 (3H, t, CH_3). ^{13}C NMR ($CDCl_3$): δ 134.9 (arom CS), 134.8 (arom C), 128.4 (arom C), 125.5 (arom CH), 124.2 (arom C), 122.1 (arom CH), 110.6 (arom CH), 109.88 (arom C), 30.5 (SCH_2), 23.1 (CH_2), 23.0 (2 × CH_2), 20.72 (CH_2), 14.7 (CH_3). Mp: 58−61 °C. Anal. Calcd for $C_{14}H_{17}SN$: C, 72.67; H, 7.40; N, 6.05; S, 13.85. Found: C, 72.40; H, 7.54; N, 6.15; S, 13.59.

Synthesis of Indoles 5 (Scheme 2): Typical Procedure for the Preparation of *N*-Phenyl-5-methoxyindole-2-carboxamide (5a). To a suspension of 1 equiv of 5-methoxy-2-indolecarboxylic acid (1 g) in anhydrous Et_2O (60 mL) was slowly added 1.5 equiv of PCl_5 (1.64 g) at room temperature. When the solution became clear, the solvent was removed under vacuum. The crude solid was dissolved in $CHCl_3$, the solvent was removed under vacuum, and this operation was repeated twice. The solid thus obtained was then dissolved in anhydrous Et_2O (50 mL), and a solution of 2 equiv of aniline (975 mg) in solution in dioxane (in such amount that Et_2O/dioxane = 3/1) was added at 0 °C. The reaction mixture was then allowed to warm to room temperature and maintained

under stirring for 12 h. After acidification with 1 N HCl (50 mL) and extraction with $CHCl_3$ (3 × 50 mL), the organic phase was washed with H_2O (3 × 100 mL) and dried over $MgSO_4$. The solvent was removed under vacuum. *N*-Phenyl-5-methoxyindole-2-carboxamide (**5a**) was obtained in 86% yield after washing with Et_2O. IR (KBr): 3424 (NH), 3295 (NH), 1649 (CO). ^{1}H NMR ($CDCl_3$): δ 8.00−6.90 (11H, m, arom H + 2 × NH), 3.80 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$/DMSO): δ 158.0 (CO), 152.2 (arom *C*OMe), 138.0 (arom C), 130.5 (arom C), 130.2 (arom C), 126.7 (2 × arom CH), 125.7 (arom C), 121.6 (3 × arom CH), 113.3 (arom CH), 111.4 (arom CH), 102.0 (arom CH), 100.2 (arom CH), 53.5 (OCH_3). Mp: 190−192 °C. Anal. Calcd for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.29; N, 10.52; O, 12.01. Found: C, 71.90; H, 5.44; N, 10.55; O, 12.46.

***N*-Methyl-*N*-phenyl-5-methoxyindole-2-carboxamide (5b).** Yield: 66%. IR (NaCl/Nujol): 3268 (NH), 1616 (CO). ^{1}H NMR ($CDCl_3$): δ 7.60−6.60 (9H, m, arom H + NH), 5.10 (1H, s, arom H2), 3.70 (3H, s, OCH_3), 3.45 (3H, s, NCH_3). ^{13}C NMR ($CDCl_3$): δ 159.4 (CO), 151.6 (arom *C*OMe), 142.3 (arom C), 128.9 (arom C), 128.3 (arom C), 127.7 (2 × arom CH), 125.9 (2 × arom CH), 125.8 (arom CH), 125.0 (arom C), 113.0 (arom CH), 111.0 (arom CH), 103.4 (arom CH), 99.5 (arom CH), 53.1 (OCH_3), 36.5 (NCH_3). Mp: 193−195 °C. Anal. Calcd for $C_{17}H_{16}O_2N_2$: C, 72.83; H, 5.75; N, 9.99; O, 11.41. Found: C, 72.66; H, 5.89; N, 9.85; O, 11.16.

***N*-(3-Methoxyphenyl)-5-methoxyindole-2-carboxamide (5p).** Yield: 50%. IR (KBr): 3348 (NH), 3277 (NH), 1650 (CO). ^{1}H NMR ($CDCl_3$): δ 7.70−6.50 (10H, m, arom H + 2 × NH), 3.80 (6H, s, 2 × CH_3). ^{13}C NMR ($CDCl_3$/DMSO): δ 157.8 (CO), 157.5 (arom *C*OMe), 152.01 (arom *C*OMe), 138.2 (arom C), 130.3 (arom C), 129.8 (arom C), 127.5 (arom CH), 125.4 (arom C), 113.2 (arom CH), 111.3 (arom CH), 110.5 (arom CH), 106.8 (arom CH), 104.1 (arom CH), 101.7 (arom CH), 100.1 (arom CH), 53.5 (OMe), 53.2 (OMe). Mp: 182−184 °C. Structure established during an X-ray diffraction study.[40]

Typical Procedure for the Preparation of *N*-Methyl-*N*-phenyl-5-(methoxymethyl)indole-2-carboxamide (5f). (1) From *N*-Phenyl-5-methoxyindole-2-carboxamide (5a). To 4 equiv of NaH (15 mmol) was slowly added, at 0 °C, a solution of 1 equiv of **5a** (1 g) in DMF (10 mL). When the addition was complete, the reaction mixture was allowed to warm to room temperature and 3 equiv of Me_2SO_4 (1 mL) was added. The reaction was monitored by TLC. After completion of the reaction, the mixture was hydrolyzed with a solution of NH_4OH (50 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with H_2O (4 × 100 mL) and dried over $MgSO_4$. The solvents were removed under vacuum, and *N*-methyl-*N*-phenyl-5-(methoxymethyl)indole-2-carboxamide (**5f**) was isolated by flash chromatography with AcOEt/PE (15/85) as eluent. Yield: 95%.

(2) From 5-Methoxy 2-indolecarboxylic Acid. The 5-methoxy-2-indolecarboxylic acid was methylated using the same procedure as (1). The crude methyl 5-methoxy-*N*-methyl-2-indolecarboxylate was isolated with 98% yield and the corresponding acid obtained by a KOH/EtOH saponification. Yield: 94%. Mp: 215 °C (lit.[41] mp 215 °C). The desired amide was obtained by the condensation of *N*-methylaniline using the same procedure as described above for indole **5a**. Yield: 65%/5-methoxy-2-indolecarboxylic acid. IR (NaCl): 2941−2832 (C−H), 1638 (CO). ^{1}H NMR ($CDCl_3$): δ 7.40−6.80 (8H, m, arom H), 5.80 (1H, s, arom H2), 3.90 (3H, s, NCH_3), 3.70 (3H, s, OCH_3), 3.50 (1H, s, NCH_3). ^{13}C NMR ($CDCl_3$): δ 163.5 (CO), 154.1 (arom *C*OMe), 144.9 (arom C), 133.2 (arom C), 132.2 (arom C), 129.2 (2 × arom CH), 126.7 (2 × arom CH), 126.5 (arom CH), 126.2 (arom C), 114.5 (arom CH), 110.5 (arom CH), 106.7 (arom CH), 102.3 (arom CH), 55.5 (OCH_3), 38.0 (NCH_3), 31.5 (NCH_3). Mp: 93−95 °C. Anal. Calcd for $C_{18}H_{18}O_2N_2$: C, 73.44; H, 6.16; N, 9.51. Found: C, 73.39; H, 6.21; N, 9.45.

Synthesis of *N*-Octyl-*N*-phenyl-5-(ethylthio)indole-2-carboxamide (6d). To a suspension of 20 equiv of EtSH (3.9 mL) and 1.5 equiv of $AlCl_3$ (530 mg) was slowly added a solution of 1 equiv of *N*-octyl-*N*-phenyl-5-methoxyindole-2-carboxamide (1 g) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 0.5 h at 0 °C, and 20 equiv of EtSH (3.9 mL) and 1.5 equiv of $AlCl_3$ (530 mg) were added. After the mixture was stirred for 0.5 h at 0 °C, a third identical portion of each reagent was added. After 2 h at 0 °C, an acid hydrolysis with HCl (10%) (50 mL) was done at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was successively washed with H_2O (100 mL) and brine (100 mL) and dried over Na_2SO_4. The solvents were removed under vacuum, and *N*-octyl-*N*-phenyl-5-(ethylthio)indole-2-carboxamide (**6d**) was isolated by flash chromatography with AcOEt/PE (15/85) as eluent. Yield: 70%. IR (NaCl): 3277 (NH), 1952, 2930, 2853 (C−H), 1615 (CO). ^{1}H NMR ($CDCl_3$): δ 10.20 (1H, s, NH), 7.90−6.90 (8H, m, arom H), 5.20 (1H, s, arom H2), 4.20−3.70 (2H, m, NCH_2), 3.10−2.60 (2H, q, SCH_2), 2.20−0.70 (18H, m + t, 6 × CH_2 + 2 × CH_3). ^{13}C NMR ($CDCl_3$): δ 161.5 (CO), 142.6 (arom C), 134.6 (arom C), 130.4 (arom C), 129.7 (arom CH), 128.8 (arom CH), 128.4 (arom CH), 128.2 (arom C), 125.9 (arom C), 125.5 (arom CH), 112.1 (arom CH), 106.3 (arom CH), 51.1 (NCH_2), 31.7 (CH_2), 29.9 (SCH_2), 29.3 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 26.9 (CH_2), 22.5 (2 × CH_2), 14.5 (SCH_2CH_3), 13.9 (CH_3). Mp: 86−88 °C. Anal. Calcd for $C_{25}H_{32}SN_2O$: C, 73.48; H, 7.89; N, 6.85; S, 7.84. Found: C, 73.23; H, 7.83; N, 6.89; S, 8.09.

Demethylation of Methoxyindolecarboxamides 5: Same Typical Procedure as for the Demethylation of Methoxyindoles 2. *N*-Phenyl-5-hydroxyindole-2-carboxamide (7a) was obtained after a reaction time of 1.5 h and isolated with AcOEt/PE (35/65) as eluent. IR (NaCl): 3297 (OH + NH), 2961−2932 (C−H), 1655 (CO). ^{1}H NMR ($CDCl_3$): δ 10.00 (1H, s, NH), 8.70 (1H, s, NH), 8.00−6.60 (10H, m, arom H + OH). ^{13}C NMR ($CDCl_3$): δ 158.3 (CO), 149.6 (arom COH), 137.4 (arom C), 130.3 (arom C), 126.3 (arom C), 126.9 (2 × arom CH), 121.8 (2 × arom CH), 118.6 (arom CH), 113.6 (arom CH), 111.2 (arom CH), 103.0 (arom CH), 101.6 (arom CH). Mp: 225−228 °C. Anal. Calcd for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.79; N, 11.10. Found: C, 70.67; H, 4.90; N, 10.63. (Very sensitive to air oxidatation.)

***N*-Methyl-*N*-phenyl-5-hydroxyindole-2-carboxamide (7b)** was obtained after a reaction time of 3 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3275 (OH + NH), 3060−2925 (C−H), 1618 (CO). ^{1}H NMR ($CDCl_3$): δ 10.30−9.90 (1H, s, NH), 7.50−6.60 (9H, m, arom H), 5.20 (1H, s, arom H2), 3.50 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): δ 162.1 (CO), 144.0 (2 × arom C), 135.4 (arom C), 129.8 (2 × arom CH), 128.3 (arom CH), 127.9 (2 × arom CH), 127.5 (arom C), 124.2 (arom CH), 122.0 (arom CH), 120.0 (arom CH), 111.6 (arom CH), 107.0 (arom CH), 38.9 (NMe). Mp: 172−174 °C. Anal. Calcd for $C_{16}H_{14}ON_2$: C, 76.77; H, 5.63; N, 11.19. Found: C, 76.43; H, 5.68; N, 11.03.

***N*-Hexyl-*N*-phenyl-5-hydroxyindole-2-carboxamide (7c)** was obtained after a reaction time of 2.5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl/Nujol): 3420 (OH), 3269 (NH), 1613 (CO). ^{1}H NMR ($CDCl_3$/DMSO): δ 9.26 (1H, s, NH), 7.56−6.65 (8H, m, arom H), 5.00 (1H, s, arom H2), 4.84 (1H, s, OH), 4.00−3.78 (2H, m, NCH_2), 1.75−0.75 (11H, m, 4 × CH_2 + CH_3). ^{13}C NMR ($CDCl_3$/DMSO): δ 160.3 (CO), 149.8 (arom COH), 141.7 (arom C), 129.4 (arom C), 129.2 (arom C), 128.4 (2 × arom CH), 127.5 (2 × arom CH), 126.9 (arom CH), 126.7 (arom C), 113.9 (arom CH), 111.3 (arom CH), 104.2 (arom CH), 103.4 (arom CH), 49.3 (NCH_2), 30.2 (CH_2), 26.2 (CH_2), 25.2 (CH_2), 21.2 (CH_2), 12.8 (CH_3). Mp: 163−165 °C. Anal. Calcd for $C_{21}H_{24}O_2N_2$: C, 74.96; H, 7.19; N, 8.32. Found: C, 74.70; H, 7.27; N, 8.27.

***N*-Octyl-*N*-phenyl-5-hydroxyindole-2-carboxamide (7d)** was obtained after a reaction time of 3 hours and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3402 (OH), 3275 (NH), 2929−2850 (C−H), 1615 (CO). ^{1}H NMR ($CDCl_3$): δ 10.30 (1H, s, NH), 7.60−6.50 (9H, m, arom H + OH), 5.10 (1H, s, arom H2), 4.00−3.60 (2H, m, NCH_2), 1.90−0.60 (15H, m, 6 × CH_2 + CH_3). ^{13}C NMR ($CDCl_3$): δ 161.5 (CO), 147.7 (arom COH), 142.6 (arom C), 130.7 (arom C), 130.6 (arom C), 129.7 (2 × arom CH), 128.9 (arom CH), 128.4 (2 × arom CH), 128.2 (arom C), 115.1 (arom CH), 112.2 (arom CH), 106.1 (arom CH), 105.6 (arom CH), 51.0 (NCH_2), 31.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3). Mp: 159−161 °C. Anal. Calcd for $C_{23}H_{28}O_2N_2$: C, 75.78; H, 7.74; N, 7.68. Found: C, 76.06; H, 7.76; N, 7.70.

***N*-Phenyl-5-(hydroxymethyl)indole-2-carboxamide (7e)** was obtained after a reaction time of 2 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3284 (OH + NH), 1645 (CO). ^{1}H NMR ($CDCl_3$/DMSO); δ 10.00 (1H, s, NH), 8.60 (1H, s, OH), 7.90−6.70 (9H, m, arom H), 4.00 (3H, s, NMe). ^{13}C NMR ($CDCl_3$/DMSO): δ 159.9 (CO), 150.4 (arom COH), 137.8 (arom C), 133.0 (arom C), 131.3 (arom C), 127.5 (2 × arom CH), 122.6 (arom CH), 119.4 (2 × arom CH), 125.4 (arom C), 114.1 (arom CH), 109.5 (arom CH), 104.0 (arom CH), 103.5 (arom CH), 30.5 (NMe). Mp: 194−196 °C. Anal. Calcd for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.29; N, 10.52. Found: C, 71.67; H, 5.31; N, 10.13.

***N*-Methyl-*N*-phenyl-5-(hydroxymethyl)indole-2-carboxamide (7f)** was obtained after a reaction time of 5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3850 (OH), 2926 (C−H), 1619 (CO). ^{1}H NMR ($CDCl_3$): δ 6.60−7.50 (8H, m, arom H), 5.85 (1H, s, OH), 5.00 (1H, s, arom H2), 3.90 (3H, s, NMe), 3.50 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): δ 164.0 (CO), 150.1 (arom COH), 144.5 (arom C), 133.1 (arom C), 132.0 (2 × arom C), 129.2 (2 × arom CH), 126.9 (arom CH), 126.4 (arom CH), 125.3 (arom CH), 114.2 (arom CH), 110.2 (arom CH), 106.5 (arom CH), 105.3 (arom H), 38.2 (NMe), 31.4 (NMe). Mp: 138−140 °C. Anal. Calcd for $C_{17}H_{16}O_2N_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.99; H, 5.79; N, 9.96.

***N*-Butyl-*N*-phenyl-5-(Hydroxymethyl)indole-2-carboxamide (7g)** was obtained after a reaction time of 2.5 h and isolated with AcOEt/PE (30/70 as eluent. IR (NaCl): 3373 (OH), 2959−2871 (C−H), 1614 (CO). ^{1}H NMR ($CDCl_3$): δ 7.40−6.50 (9H, m, arom H + OH), 5.70 (1H, s, arom H2), 4.00−3.70 (2H, m, NCH_2), 3.70 (3H, s, NMe), 1.90−1.10 (4H, m, 2 × CH_2), 1.10−0.70 (3H, m, CH_3). ^{13}C NMR ($CDCl_3$): δ 163.7 (CO), 149.9 (arom COH), 143.1 (arom C), 133.0 (arom C), 132.6 (arom C), 129.1 (2 × arom CH), 127.3 (arom CH), 127.0 (2 × arom CH), 126.5 (arom C), 114.0 (arom CH), 110.1 (arom CH), 106.0 (arom CH), 105.4 (arom CH), 50.2 (NCH_2), 31.4 (NMe), 29.7 (CH_2), 20.0 (CH_2), 13.7 (CH_3). Mp: 149−151 °C. Anal. Calcd for $C_{20}H_{22}O_2N_2$: C, 74.50; H, 6.87; N, 8.69. Found: C, 74.45; H, 7.18; N, 8.49.

***N*-Hexyl-*N*-phenyl-5-(hydroxymethyl)indole-2-carboxamide (7h)** was obtained after a reaction time of 2.5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3344 (OH), 2931−2857 (C−H), 1619 (CO). ^{1}H NMR ($CDCl_3$): δ 7.30−6.61 (9H, m, arom H + OH), 5.75 (1H, s, arom H2), 4.00−3.64 (2H, m, NCH_2), 3.78 (3H, s, NMe), 1.71−0.75 (11H, m, 4 × CH_2 + CH_3). ^{13}C NMR ($CDCl_3$): δ 163.7 (CO), 150.1 (arom COH), 143.0 (arom C), 133.0 (arom C), 132.4 (arom C), 129.1 (arom CH), 127.2 (arom CH), 126.9 (arom CH), 126.4 (arom C), 114.0 (arom CH), 110.0 (arom CH), 106.0 (arom CH), 105.3 (arom CH), 50.3 (NCH_2), 31.3 (NMe), 31.3 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 22.4 (CH_2), 13.8 (CH_3). Mp: 89−91 °C. Anal. Calcd for $C_{22}H_{26}O_2N_2$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.27; H, 7.39; N, 7.89.

***N*-(3-Chlorophenyl)-5-(hydroxymethyl)indole-2-carboxamide (7i)** was obtained after a reaction time of 5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3430 (OH), 3272 (NH), 1644 (C═O). ^{1}H NMR ($CDCl_3$): δ 9.1 (s, 1H, NH), 7.9−6.7 (9H, m, arom H + OH), 4.0 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 159.24 (CO), 150.08 (arom COH), 138.93 (arom C), 132.43 (arom C), 131.79 (arom C), 130.15 (arom CCl), 128.13 (arom CH), 124.65 (arom C), 121.46 (arom CH), 118.22 (arom CH), 116.75 (arom CH), 113.79 (arom CH), 109.09 (arom CH), 103.41 (arom CH), 103.20 (arom CH), 29.85 (NCH_3). Mp: 186−188 °C. Anal. Calcd for $C_{16}H_{13}O_2N_2Cl$: C, 63.89; H, 4.35; N, 9.31; Cl, 11.78. Found: C, 63.88; H, 4.25; N, 9.00; Cl, 11.36.

***N*-Methyl-*N*-(3-chlorophenyl)-5-(hydroxymethyl)indole-2-carboxamide (7j)** was obtained after a reaction time of 5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3340 (OH), 2930 (C−H), 1619 (CO). ^{1}H NMR ($CDCl_3$): δ 7.40−6.60 (7H, m, arom H), 5.80 (1H, s, arom H2), 5.10 (1H, s, OH), 3.80 (3H, s, NMe), 3.40 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): δ 163.9 (CO), 150.1 (arom COH), 145.7 (arom C), 134.5 (arom C), 133.3 (arom C), 131.5 (arom C), 130.1 (arom CH), 127.0 (arom CH), 126.4 (arom CH), 125.0 (arom CH), 126.3 (arom C), 114.4 (arom CH), 110.3 (arom CH), 106.7 (arom CH), 105.4 (arom CH), 38.2 (NMe), 31.4 (NMe). Mp: 141−143 °C. Anal. Calcd for $C_{17}H_{15}O_2N_2Cl$: C, 64.86; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.90; H, 4.84; N, 8.87; Cl, 11.55.

***N*-Methyl-*N*-[3-(trifluoromethyl)phenyl]-5-(hydroxymethyl)indole-2-carboxamide (7k)** was obtained after a reaction time of 3 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3349 (OH), 2930 (C−H), 1629 (CO). ^{1}H NMR ($CDCl_3$): δ 7.70−6.50 (7H, m, arom H), 5.80 (1H, s, arom H), 5.50 (1H, s, OH), 3.80 (3H, s, CH_3), 3.50 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 163.9 (CO), 150.0 (arom COH), 145.2 (arom C), 131.6 (2 × arom C), 130.1 (arom CH), 129.8 (arom CH), 123.5 (arom CH), 122.8 (arom CH), 126.4 (arom C), 121.6 (CF_3), 114.4 (arom CH), 110.4 (arom CH), 106.6 (arom CH), 105.4 (arom CH), 38.2 (NMe), 31.5 (NMe). Mp: 157−159 °C. Anal. Calcd for $C_{18}H_{15}O_2N_2F_3$: C, 62.06; H, 4.34; N, 8.04; F, 16.36. Found: C, 62.32; H, 4.52; N, 7.78; F, 15.99.

***N*-Methyl-*N*-(3-bromophenyl)-5-(hydroxymethyl)indole-2-carboxamide (7l)** was obtained after a reaction time of 5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3348 (OH), 2937 (C−H), 1627 (CO). ^{1}H NMR ($CDCl_3$): δ 7.50−6.60 (7H, m, arom H), 5.90 (1H, s, arom H2), 5.00 (1H, s, OH), 3.80 (3H, s, NMe), 3.40 (3H, s, NMe). ^{13}C NMR ($CDCl_3$): δ 163.9 (CO), 150.1 (arom COH), 145.7 (arom C), 134.5 (arom C), 133.3 (arom C), 131.5 (arom C), 130.1 (arom CH), 127.0 (arom CH), 126.4 (arom CH), 125.0 (arom CH), 126.3 (arom C), 114.4 (arom CH), 110.3 (arom CH), 106.7 (arom CH), 105.3 (arom CH), 38.2 (NMe), 31.4 (NMe). Mp: 143−145 °C. Anal. Calcd for $C_{17}H_{15}O_2N_2Br$: C, 56.83; H, 4.20; N, 7.80; Br, 22.24. Found: C, 57.17; H, 4.26; N, 7.81; Br, 21.60.

2-[[[Bis(*p*-fluorophenyl)methyl]piperazino]carbonyl]-5-(hydroxymethyl)indole (7o) was obtained after a reaction time of 2.5 h and isolated with AcOEt/PE (30/70) as eluent. IR (NaCl): 3330 (OH), 2922−2812 (C−H), 1605 (CO). ^{1}H NMR (DMSO): δ 8.80 (1H, s, OH), 7.60−6.60 (11H, m, arom H), 6.40 (1H, s, arom H2), 4.40 (1H, s, NCH), 3.80−3.50 (5H, m, NMe + NCH_2), 3.30 (2H, s, NCH_2), 2.60−2.10 (4H, m, 2 × CH_2). ^{13}C NMR ($CDCl_3$): δ 190.9−157.7 (arom CF), 160.15 (CO), 149.5 (arom COH), 136.2 (arom C), 130.3 (arom C), 130.0 (arom C), 127.5 (2 × arom CH), 127.4 (2 × arom CH), 124.7 (2 × arom C), 113.5 (2 × arom CH), 113.2 (2 × arom CH), 111.8 (arom CH), 108.5 (arom CH), 102.6 (arom CH), 100.0 (arom CH), 71.0 (CH), 49.5 (4 × CH_2), 28.9 (NMe). Mp: 219−221 °C. Anal. Calcd for $C_{27}H_{24}O_2N_3F_2$: C, 70.26; H, 5.46; N, 9.10; F, 8.23. Found: C, 70.13; H, 5.65; N, 9.40; F, 8.01.

Synthesis of Hydroxyindoles 6 (Scheme 3): Typical Procedure for the Preparation of *N*-(3,4,5-Trimethoxyphenyl)-5-hydroxyindole-2-carboxamide (7m). To a stirred solution of commercially available 5-hydroxy 2-indolecarboxylic acid (1 g) in benzene (85 mL) was dropwise added 15 equiv of $SOCl_2$ (6.25 mL). The reaction mixture was refluxed during 24 h and then filtered. The filtrate was evaporated *in vacuo* to yield the crude carbonyl chloride that was dissolved in anhydrous ether (100 mL) at 0 °C, and 2 equiv of 3,4,5-trimethoxyaniline (2 g) in dioxane (30 mL) was added. Thus the reaction was performed at room temperature for 12 h. After classical workup, *N*-(3,4,5-trimethoxyphenyl)-5-hydroxyindole-2-carboxamide (**7m**) was isolated by flash chromatography with AcOEt/PE (40/60) as eluent. Yield: 30%. IR (NaCl/Nujol): 3427 (OH), 3278 (NH), 1594 (CO). ^{1}H NMR ($CDCl_3$/DMSO): δ 10.20 (1H, s, OH), 8.35 (1H, s, NH), 7.55−6.55 (6H, m, arom H), 4.10−3.70 (13H, m, 2 × CH_2 + 3 × CH_3), 3.50 (2H, s, CH_2), 2.75−2.45 (4H, m, 2 × CH_2). ^{13}C NMR ($CDCl_3$/DMSO): δ 160.3 (CO), 150.8 (arom *C*OMe), 150.3 (arom *C*OMe), 149.3 (arom COH), 140.1 (arom *C*OMe), 128.9 (arom C), 128.2 (arom C), 125.7 (arom C), 123.0 (arom CH), 121.5 (arom C), 112.6 (arom CH), 110.6 (arom CH), 105.5 (arom CH), 102.4 (arom CH), 101.3 (arom CH), 59.1 (OMe), 58.4 (OMe), 54.2 (CH_2), 53.9 (OMe), 50.9 (4 × CH_2). Mp: 180−182 °C. Anal. Calcd for $C_{23}H_{27}O_5N_3$: C, 64.92; H, 6.39; N, 9.87. Found: C, 65.33; H, 6.49; N, 10.02.

2-[[[(2,3,4-Trimethoxyphenyl)methyl]piperazino]-carbonyl]-5-hydroxyindole (7n). IR (NaCl): 3312 (OH + NH), 2938 (C−H), 1696 (CO). ^{1}H NMR ($CDCl_3$): δ 10.70 (1H, s, NH), 9.40 (1H, s, NH), 7.20−6.50 (7H, m, arom H), 3.80 (6H, s, 2 × OCH_3), 3.70 (3H, s, OCH_3). ^{13}C NMR ($CDCl_3$): δ 159.4 (CO), 152.2 (arom COH), 150.6 (arom C), 134.3 (2 × arom C), 133.4 (arom C), 131.2 (arom C), 131.1 (arom C), 127.5 (arom

C), 114.8 (arom CH), 112.0 (arom CH), 104.3 (arom CH), 103.1 (arom CH), 97.4 (2 × arom CH), 60.11 (OMe), 55.3 (2 × OMe). Mp: 219−221 °C. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.14; H, 5.29; N, 8.18. Found: C, 63.40; H, 5.38; N, 8.30.

Pharmacology. Pharmacological Methods: Antioxidant Property. LDL were isolated by ultracentrifugation from the pooled plasma of healthy normolipidemic human subjects. The LDL oxidation was promoted by copper (5 μmol^{-1}, 3 h, t = 24 °C). The compounds in DMSO are incubated at 10 concentrations just before the beginning of the oxidation. For each compound, protection against lipid peroxidation formation was estimated by dosing the inhibition of thiobarbituric acid reactive substance at each concentration according to the method of Yagi.[42] For each compound 10 concentrations between 10^{-7} and 10^{-3} M were evaluated in duplicate. The variability between the duplicate was less than 5% in all cases. IC_{50} values were calculated using linear regression analysis.

Cyclooxygenase and 5-Lipoxygenase Activities. Isolated rabbit granulocytes were preincubated during 15 min at 37 °C with seven different concentrations of compounds (between 10^{-5} and 10^{-8} M in DMSO). Each concentration was performed in triplicate. Calcic ionophore A 23187 (5×10^{-6} M in DMSO) was added during 15 min. For each compound, at each concentration, cyclooxygenase and 5-lipoxygenase inhibition were evaluated by dosing respectively PGE_2 and LTB_4 formation using the enzymoimmunoassay (EIA) method.[37] Then the IC_{50} value was calculated using linear regression analysis. The reference compounds used were indomethacine ($IC_{50} = 2.7 \times 10^{-9}$ M) and NDGA ($IC_{50} = 4 \times 10^{-7}$ M) respectively for inhibition of PGE_2 and LTB_4 formation.

15-Lypoxygenase Activity. Isolated HUVEC were preincubated during 15 min at 37 °C with each compound (10^{-5} M in triplicate in DMSO). Stimulation was performed using A 23187 (5×10^{-6} M) in DMSO. To evaluate 15-lipoxygenase activity, 15-hydroxyeicosatetraenoique (15-HETE) was measured by radioimmunoassay (RIA).[38] Results are expressed as a percentage of inhibition of control values. The reference compound used was eicosatetraynoic acid (ETYA) which inhibited 45 ± 3% of 15-HETE formation at 10^{-5} M.

Calcium Channel Blocking Activity. Isolated rat aorta contracted by hyperpotassic solution (KCl, 60 mM).[39] The inhibition of the contraction was evaluated in the presence of increasing concentrations of compound (eight concentration between 10^{-8} and 3×10^{-5} M). Each concentration was performed in duplicate. Two different preparations were used. The concentration-related curve allowed us to calculate the IC_{50} values using linear regression analysis. The flunarizine is used as a reference compound and inhibits with an IC_{50} of 2.7×10^{-7} M.

Cytoprotective Effect of Antioxidants against LDL Toxicity. In continuous pulse experiments, cells were grown in the presence of oxidized LDL until the cell viability was determined at the indicated time (48-h pulse period, under standard conditions).[43] Cells were washed twice with phosphate-buffered saline, and the cell viability was determined by the MTT test.[44] Briefly, cells were incubated with MTT dissolved in phenol red-free RPMI (250 $\mu g\ mL^{-1}$), for 2 h at 37 °C. Then this incubation medium was discarded, and after addition of 500 μL of dimethyl sulfoxide (DMSO) the optical density was immediately measured (at 540 nm, with a Titertek spectrophotometer). The results were expressed as percentage of control (cells grown in the absence of oxidized LDL). Six concentrations were used (five assays for each concentration), allowing us to calculate the IC_{50} values using linear regression analysis.

In order to evaluate the remaining protective effect, cells were incubated with a fixed concentration of these compounds for 48 h, washed twice, and grown in fresh culture medium (free of any additional antioxidant) for variable intervals of time (up to 5 days). Then oxidized LDL (UV radiation in the presence of 2 $\mu mol\ L^{-1}$ CUS 04) was added to the culture medium, and the cytotoxicity was evaluated 2 days later by the MTT test. The results were expressed as a percentage of control values. The IC_{50} values were calculated using linear regression analysis.

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