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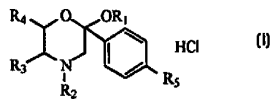
(54) Title: HYPOLIPIDEMIC AND ANTIOXIDANT MORPHOLINE DERIVATIVES



(I)

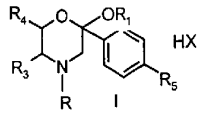
(57) Abstract

The present invention relates to the synthesis and the evaluation of the antioxidant, hypocholesterolemic and hypolipidemic activity of substituted morpholine derivatives of formula (I) in which R_1=CH_2CH_3, R_2=CH_3, R_3, R_4=H, R_5=C_6H_5 (compound 1) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3, R_4=H, R_5=C_6H_5 (compound 2) or R_1=H, R_2–R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 3) or R_1=$CH_2CH_2CH_3$, R_2–R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 4) or R_1=$CH_2CH_2CH_2ONO_2$, R_2–R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 5) or R_1=H, R_2=CH_3, R_3–R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 6) or R_1=$CH_2CH_2CH_3$, R_2=CH_3, R_3–R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 7) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3–R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 8) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3, R_4=H, R_5=H (compound 9) or R_1=H, R_2=p–NO_2–C_6H_4–CH_2CH_2, R_3, R_4=H, R_5=C_6H_5 (compound 10). The 2–hydroxy– morpholine derivatives 3, 6 and 10 are synthesised by the reaction of the appropriate aminoalcohol (22 mmol) and the 2–bromo–4–phenylacetophenone or the 2–bromoacetophenone (10 mmol) in ether and acetone for 15 hours at room temperature. The 2–alkoxy derivatives 1, 4 and 7 are synthesised by the reaction of the respective 2–hydroxy derivative with the appropriate alcohol, in acid medium and reflux. Compounds 2, 5, 8 and 9 are synthesised by the reaction of the respective 2–hydroxy derivative with the 3–bromopropanol in acidic medium and reflux. The 2–(3–bromopropoxy) derivatives then reacted with silver nitrate in acetonitrile and reflux. The compounds of formula (I) decrease significantly total cholesterol, triglyceride and LDL–cholesterol levels in plasma. The compounds of formula (I) possess potent antioxidant activity. The compounds of formula (I) with the above properties could be useful to the treatment of hypercholesterolemia, hyperlipidemia and atheromatosis.

Abstract

Hypolipidemic and antioxidant morpholine derivatives.

The present invention relates to the synthesis and the evaluation of the antioxidant, hypocholesterolemic and hypolipidemic activity of substituted morpholine derivatives and their pharmaceutically accepted salts, of the formula I



in which R_1=CH_2CH_3, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 1) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 2) or R_1=H, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 3) or R_1=$CH_2CH_2CH_3$, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 4) or R_1=$CH_2CH_2CH_2ONO_2$, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 5) or R_1=H, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 6) or R_1=$CH_2CH_2CH_3$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 7) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 8) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=H (compound 9) or R_1=p-NO_2-C_6H_4-CH_2CH_2, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 10), or R_1=$CH_2CH_2CH_2OH$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 11), R_1=$C_6H_4C_6H_5$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 12), R_1=$CH(CH_2OH)CH_3$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 13), R_1=H, R_2-R_3=$CH_2CH_2CH_2CH$, R_3-R_4=$CHCH_2CH_2CH_2$, R_5=C_6H_5 (compound 14), R_1=Et, R_2-R_3=$CH_2CH_2CH_2CH$, R_3-R_4=$CHCH_2CH_2CH_2$, R_5=C_6H_5 (compound 15), R_1=OH, R_2=CH_3, R_3,R_4=H, R_5=2-thienyl (compound 16), R_1=Et, R_2=CH_3, R_3,R_4=H, R_5=2-thienyl (compound 17), R_1=$CH(CH_2ONO_2)$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 18), R_1=$CH(CH_2ONO_2)$, R_2-R_3=$(CH_2)_4$,R4=H, R_5=C_6H_5 (compound 19), R_1=$CH(CH_2ONO_2)$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 20), R_1=H, R_2=$CH_2CH_2ONO_2$, R_3,R_4=H, R_5=C_6H_5 (compound 21), or R_1=H, R_2=$CH_2CH_2ONO_2$, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 22).

The 2-hydroxy- morpholine derivatives 3, 6, 14, 21 and 22 are synthesised by the reaction of the appropriate aminoalcohol (22 mmol) and the 2-bromo-4-arylacetophenone or the 2-bromoacetophenone (10mmol) in ether and acetone for 15 hours at room temperature.

The 2-alkoxy derivatives 1, 4, 7, 10, 11, 12, 13, 15 and 17 are synthesised by the reaction of the respective 2-hydroxy derivative with the appropriate alcohol, in acid medium and reflux.

Compounds 2, 5, 8, 9, 18, 19 and 20 are synthesised by the reaction of the respective 2-hydroxy derivative with the 3-bromopropanol in acidic medium and reflux. The 2-(3-bromopropoxy) derivatives then reacted with silver nitrate in acetonitrile and reflux.

The compounds of formula I decrease significantly total cholesterol, triglyceride and LDL-cholesterol levels in plasma.

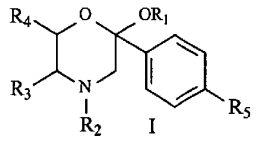
The compounds of formula I posses potent antioxidant activity.

The nitric ester derivatives are nitric oxide donors.

The compounds of formula I with the above properties could be useful to the treatment of hypercholesterolemia, hyperlipidemia and atheromatosis.

Hypolipidemic and antioxidant morpholine derivatives.

The present invention relates to the synthesis of novel morpholine derivatives and the evaluation of their hypocholesterolemic, hypolipidemic and antioxidant activity. Especially, the present invention relates to the synthesis and pharmacochemical evaluation of morpholine derivatives and their pharmaceutically accepted salts, of the formula I



I

in which R_1=CH_2CH_3, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 1) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 2) or R_1=H, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 3) or R_1=$CH_2CH_2CH_3$, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 4) or R_1=$CH_2CH_2CH_2ONO_2$, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 5) or R_1=H, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 6) or R_1=$CH_2CH_2CH_3$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 7) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 8) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=H (compound 9) or R_1=p-NO_2-C_6H_4-CH_2CH_2, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 10), or R_1=$CH_2CH_2CH_2OH$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 11), R_1=$CH(CH_2OH)CH_3$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 13), R_1=H, R_2-R_3=$CH_2CH_2CH_2CH$, R_3-R_4=$CHCH_2CH_2CH_2$, R_5=C_6H_5 (compound 14), R_1=CH_2CH_3, R_2-R_3=$CH_2CH_2CH_2CH$, R_3-R_4=$CHCH_2CH_2CH_2$, R_5=C_6H_5 (compound 15), R_1=H, R_2=CH_3, R_3,R_4=H, R_5=2-thienyl (compound 16), R_1= CH_2CH_3, R_2=CH_3, R_3,R_4=H, R_5=2-thienyl (compound 17), R_1=$CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 18), R_1=$CH_2CH_2ONO_2$, R_2-R_3=$(CH_2)_4$,R_4=H, R_5=C_6H_5 (compound 19), R_1=$CH_2CH_2ONO_2$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 20), R_1=H, R_2=$CH_2CH_2ONO_2$, R_3,R_4=H, R_5=C_6H_5 (compound 21), R_1=H, R_2=$CH_2CH_2ONO_2$, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 22)

It is well known that the pathogenesis of atheromatosis is related with a lot of factors, the most important of them are:

- oxidative modification of the low density lipoproteins (LDL)
- increased levels of cholesterol and LDL-cholesterol in blood
- increased levels of triglycerides in blood
- decreased levels of HDL-cholesterol in blood
- thrombogenesis, endothelial injury and haemodynamic factors.

Especially, the oxidative modification of LDL appears to be the most risky atherogenic process, which induces inflammatory and apoptotic mechanisms and finally the formation of foam cells and fatty streaks.

In addition, nitric oxide possesses hypocholesterolemic properties by influencing the metabolism of apoB-containing lipoproteins.
At this field of research, most of the synthetic compounds possess hypocholesterolemic or hypolipidemic or antioxidant activity. There are no reports about compounds able to decrease total cholesterol, triglycerides and LDL-cholesterol in blood in combination with antioxidant activity.

Considering the above we think that it would be interesting to design, synthesise and evaluate compounds with hypocholesterolemic, hypolipidemic and antioxidant activity.

A desirable outcome of the novel derivatives we are reporting is to decrease total cholesterol levels in plasma significantly.
Also, a further desirable outcome of the novel derivatives is to decrease triglycerides and LDL-cholesterol levels in plasma and some of them are nitric oxide donors.

The novel derivatives, except their hypolipidemic activity possess also potent antioxidant activity. We think that the combination of the hypolipidemic and the antioxidant activity is necessary for the prevention and treatment of atheromatosis more effectively.

The present invention relates to the synthesis and the evaluation of antioxidant, hypocholesterolemic, hypolipidemic and nitric oxide donating activity of novel morpholine derivatives of the general structure (I).

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

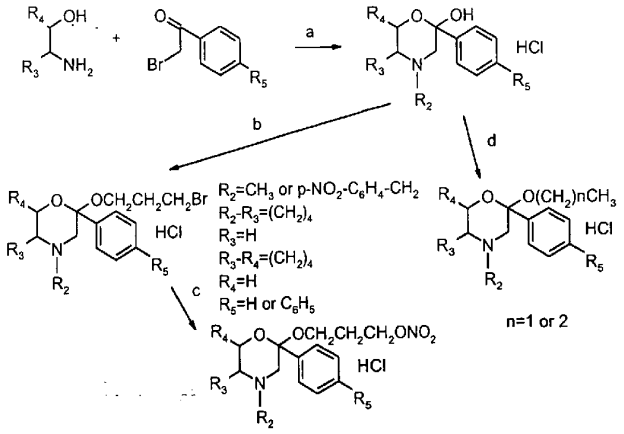
Methods

Synthesis

The 2-hydroxy- morpholine derivatives 3, 6, 14, 21 and 22 are synthesised by the reaction of the appropriate aminoalcohol (22 mmol) and the 2-bromo-4-arylacetophenone or the 2-bromoacetophenone (10mmol) in ether and acetone for 15 hours at room temperature. After washing with saturated solution of sodium chloride, drying with potassium carbonate, evaporation in vacuo and neutralisation with hydrochloric acid 10% in ether, the 2-hydroxy derivatives are obtained and recrystallised from acetone and ether.

The 2-alkoxy derivatives 1, 4, 7, 10, 11, 12, 13, 15 and 17 are synthesised by the reaction of the respective 2-hydroxy derivative with the appropriate alcohol, in acid medium and reflux.

Compounds 2, 5, 8, 9, 18, 19 and 20 are synthesised by the reaction of the respective 2-hydroxy derivative with the 3-bromopropanol in acidic medium and reflux. The 2-(3-bromopropoxy) derivatives then react with silver nitrate in acetonitrile and reflux.



a) room temperature, HCl in ether; b) 3-bromopropanol, reflux for 3h; c) $AgNO_3$, acetonitrile, reflux for 2h; d) ethanol, propanol, 1,3-propanodiol or p-nitrophenylethyl alcohol, reflux for 15h

Scheme 1 : Synthetic pathway for the morpholine derivatives

Evaluation of the antioxidant activity

[Method]

The evaluation of the antioxidant activity of the novel compounds was performed in vitro by peroxidation of rat hepatic microsomal membrane lipids. Lipid peroxidation was induced by the Fe^{2+} / ascorbic acid system. Rat hepatic microsomes were heat-inactivated (90°C for 90 s). A fresh solution of ascorbic acid (0.2 mM) in Tris-HCl buffer (pH 7.4) and the tested compounds, dissolved in DMSO to give final concentrations of 1 mM to 0.1 mM, were added to microsomes. Equal amount of buffer was added to the control samples. The reaction was initiated by addition of $FeSO_4$ (10 µM). The mixture was incubated at 37°C for 45 min. Aliquots were taken at various time intervals and lipid peroxidation was assessed by spectrophotometric determination of the 2-thiobarbituric acid reactive material at 535 nm.

[Results]

All tested compounds inhibited lipid peroxidation 100% at 1mM and this action is maintained even at 0.1mM.

Evaluation of the hypolipidemic activity

[Method]

The hypocholesterolemic and hypolipidemic activity of the synthesised compounds was performed by the inhibition of the hyperlipidemia induced by the Triton WR 1339 in rats. Triton WR 1339 as an intraperitoneal (i.p.) injection acts due to induction of HMG-CoA reductase. Using male Fischer rats (230-280g) in group of five (test group), we injected a solution of 200mg/Kg Triton WR 1339 i.p. and the same time 28 to 56µmol/Kg of the tested compounds and probucol (as reference), suspended in aqueous solution was injected i.p.

Control group was treated i.p. with Triton WR 1339 and 10ml/Kg of the vehicle of the tested compounds i.p. After 24 hours, blood was taken from the celiac aorta and collected to heparinised tubes. Blood was centrifuged for 15 minutes at 3000 rpm and plasma was selected for the determination of total cholesterol (TC), LDL cholesterol (LDL-C) and triglycerides (TG) using commercial kits.

[Results]

Our results indicate that the tested compounds decrease total cholesterol levels in plasma even by 61%, triglyceride levels even by 74% and LDL-cholesterol level even by 51% and all compounds were more potent than probucol (table 1).

The above results indicate that the novel compounds possess antioxidant and potent hypolipidemic and hypocholesterolemic action. This combination of antioxidant and hypolipidemic properties may be useful against atheromatosis.

[Results]

The synthesised nitrate esters were found to release nitric oxide by 25% at 0.1mM.

Evaluation of the nitric oxide donating activity

[Method]

The release of nitric oxide was measured spectrophotometrically by the product of Griess reaction at 540nm and expressed as percent NO_2^- (mol/mol).

Table 1. Effect of selected compounds and probucol on plasma Total Cholesterol (TC), Triglyceride (TG) and Low Density Lipoprotein (LDL) levels.

	Dose	Percent decrease compared to controls $^{\alpha}$		
compd	**(µmol/kg, ip)**	**TC**	**TG**	**LDL**
1	56	30*	39*	22*
2	56	61**	74**	43**
3	56	22*	20*	51*
4	56	36*	34*	17^{NS}
6	28	54**	49*	51*
7	56	50*	41*	28*
9	56	ND	ND	38**
Probucol	56	18*	11^{NS}	18^{NS}

$^{\alpha}$ All determinations are performed at least in duplicate and SD is always within ±10% of the absorbance values. Asterisks indicate statistical significance (Student's t-test) as follows: ** P<0.005, * P<0.05, ^{NS} not significant (P>0.1), ND: not determined.

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Examples

Synthesis of compound 1

10 mmol of the 2-hydroxy derivative was refluxed in 100ml of absolute ethanol in acidified medium by HCl in ether. After 15h of reflux, most of the solvent was removed in vacuo and the product was crystallised with ether.

Synthesis of compound 2

10 mmol of the 2-hydroxy derivative and 22mmol of 3-bromopropanol in acetone (30ml) and acidic medium, were refluxed for 3h. After 3h the product, the 2-(3-bromopropoxy) derivative, was crystallised by ether. 10mmol of the 2-(3-bromopropoxy) derivative reacted with15 mmol of silver nitrate and refluxed for 2h. After removing of the solvent in vacuo, dissolving of the residue in chloroform, filtration, washing of the filtrate with water, drying of the chloroformic layer with calcium chloride, removing of the chloroform in vacuo, neutralisation with hydrobromic acid in ether and crystallisation by ether, the final product was obtained.

Synthesis of compound 3

22 mmol of 2-hydroxymethylpiperidine reacted with 10mmol of 2-bromo-4-phenylacetophenone in ether and acetone for 15h at room temperature. After washing with saturated solution of sodium chloride, drying with potassium carbonate, evaporation in vacuo and neutralisation with hydrochloric acid 10% in ether, compound 3 was obtained and was recrystallised from acetone and ether.

Synthesis of compound 4

10 mmol of compound 3 was refluxed in 100ml of n-propanol in acidic medium by HCl in ether. After 15h of reflux the solvent was removed in vacuo and the product was crystallised with ether.

Synthesis of compound 5

10 mmol of compound 3 and 22mmol of 3-bromopropanol in acetone (30ml) in acidic medium, were refluxed for 3h. After 3h the product, the 2-(3-bromopropoxy) derivative, was crystallised with ether. 10mmol of the 2-(3-bromopropoxy) derivative reacted with15 mmol of silver nitrate and refluxed for 2h. After removing of the solvent in vacuo, dissolving of the residue in chloroform, filtration, washing of the filtrate with water, drying of the chloroformic layer with calcium chloride, removing of the chloroform in vacuo, neutralisation with hydrobromic acid in ether and crystallisation by ether, the final product was obtained.

Synthesis of compound 6

22 mmol of N-methylamino-cyclohexanol-2 reacted with 10mmol of 2-bromo-4-phenylacetophenone in ether and acetone for 15h at room temperature. After washing with saturated solution of sodium chloride, drying with potassium carbonate, evaporation in vacuo and neutralisation with hydrochloric acid 10% in ether, compound 3 was obtained and was recrystallised from acetone-ether.

Synthesis of compound 7

10 mmol of compound 6 was refluxed in 100ml of n-propanol in acidic medium by HCl in ether. After 15h of reflux the solvent was removed in vacuo and the product was crystallised with ether.

Synthesis of compound 8

10 mmol of compound 6 and 22mmol of 3-bromopropanol in acetone (30ml) and acidic medium, were refluxed for 3h. After 3h the product, the 2-(3-bromopropoxy) derivative, was crystallised in ether. 10mmol of the 2-(3-bromopropoxy) derivative reacted with15 mmol of silver nitrate and reflux for 2h. After removing of the solvent in vacuo, dissolving of the residue in chloroform, filtration, washing of the filtrate with water, drying of the chloroformic layer with calcium chloride, removing of the chloroform in vacuo, neutralisation with hydrobromic acid in ether and crystallisation by ether, the final product was obtained.

Synthesis of compound 9

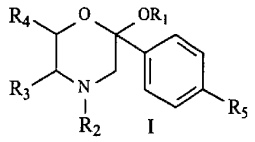
10 mmol of the 2-hydroxy derivative and 22mmol of 3-chloropropanol in acetone (30ml) and acidic medium, were refluxed for 3h. After 3h the product, the 2-(3-bromopropoxy) derivative, was crystallised in ether. 10mmol of the 2-(3-bromopropoxy) derivative reacted with15 mmol of silver nitrate and refluxed for 2h. After removing of the solvent in vacuo, dissolving of the residue in chloroform, filtration, washing of the filtrate with water, drying of the chloroformic layer with calcium chloride, removing of the chloroform in vacuo, neutralisation with hydrobromic acid in ether and crystallisation by ether, the final product was obtained.

Synthesis of compound 10

22 mmol of p-nitro-phenethylaminoethanol reacted with 10 mmol of 2-bromo-4phenylacetophenone in ether and acetone for 15h at room temperature. After washing with saturated solution of sodium chloride, drying with potassium carbonate, evaporation in vacuo and neutralisation with hydrochloric acid 10% in ether, compound 3 was obtained and was recrystallised from acetone-ether.

The claims defining the invention are as follows:

1. Substituted morpholine derivatives and their pharmaceutically accepted salts, of the formula I



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in which R_1=CH_2CH_3, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 1) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 2) or R_1=H, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 3) or R_1=$CH_2CH_2CH_3$, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 4) or R_1=$CH_2CH_2CH_2ONO_2$, R_2-R_3=$(CH_2)_4$, R4=H, R_5=C_6H_5 (compound 5) or R_1=H, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 6) or R_1=$CH_2CH_2CH_3$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 7) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 8) or R_1=$CH_2CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=H (compound 9) or R_1=p-NO_2-C_6H_4-CH_2CH_2, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 10), or R_1=$CH_2CH_2CH_2OH$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 11), R_1=$CH(CH_2OH)CH_3$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 13), R_1=H, R_2-R_3=$CH_2CH_2CH_2CH$, R_3-R_4=$CHCH_2CH_2CH_2$, R_5=C_6H_5 (compound 14), R_1= CH_2CH_3, R_2-R_3=$CH_2CH_2CH_2CH$, R_3-R_4=$CHCH_2CH_2CH_2$, R_5=C_6H_5 (compound 15), R_1=H, R_2=CH_3, R_3,R_4=H, R_5=2-thienyl (compound 16), R_1= CH_2CH_3, R_2=CH_3, R_3,R_4=H, R_5=2-thienyl (compound 17), R_1=$CH_2CH_2ONO_2$, R_2=CH_3, R_3,R_4=H, R_5=C_6H_5 (compound 18), R_1=$CH_2CH_2ONO_2$, R_2-R_3=$(CH_2)_4$,R_4=H, R_5=C_6H_5 (compound 19), R_1=$CH_2CH_2ONO_2$, R_2=CH_3, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 20), R_1=H, R_2=$CH_2CH_2ONO_2$, R_3,R_4=H, R_5=C_6H_5 (compound 21), R_1=H, R_2=$CH_2CH_2ONO_2$, R_3-R_4=$(CH_2)_4$, R_5=C_6H_5 (compound 22).

2. A process for preparing a 2-alkoxy derivative selected from the group consisting of compounds 1,4,7,10,11,13,15 and 17 of claim 1 which comprises reacting the appropriate 2-hydroxy derivative with the appropriate alcohol in an acidic medium under reflux.

3. A process for preparing a 2-alkoxy derivative selected from the group consisting of compounds 2,5,8,9,18,19 and 20 of claim 1 which comprises reacting the respective 2-hydroxy derivative with the 3-bromopropanol in acidic medium under reflux, then reacting the 2-(3-bromopropoxy) derivatives produced with silver nitrite in acetonitrile under reflux.

4. A process for preparing a 2-hydroxy-morpholine derivative selected from the group consisting of compound 3, 6, 14, 16, 21 and 22 of claim 1, which comprises the reaction of the appropriate amino alcohol with the appropriate 2-bromoarylacetophenone of the 2-bromoacetophenone in ether and acetone at room temperature, followed by washing a saturated aqueous solution of sodium chloride, drying with potassium carbonate, evaporation in vacuole and neutralization with 10% hydrochloric acid in ether to produce said 2-hydroxy derivatives.

5. A process according to claim 4, wherein the 2-hydroxy derivatives produced by the reactions is recrystallized from acetone and ether.

6. Use of a substituted morpholine derivative of the formula I of claim 1 for the inhibition of lipid peroxidation and antioxidant activity.

7. Use of a substituted morpholine derivative of the formula I of claim 1 for the reduction of cholesterol levels in plasma.

8. Use of a substituted morpholine derivative of the formula I of claim 1 for the reduction of triglyceride levels in plasma.

9. Use of a substituted morpholine derivative of the formula I of claim 1 for the reduction of LDL-cholesterol levels in plasma.

10. Use of a substituted morpholine derivative of the formula I of claim 1 for the manufacture of a medicament for the prevention and treatment of hypercholesterolemia.

11. Use of a substituted morpholine derivative of the formula I of claim 1 for the manufacture of a medicament for the prevention and treatment of hyperlipidemia.

12. Use of a substituted morpholine derivative of the formula I of claim 1 for the manufacture of a medicament for the prevention and treatment of atheromatosis.

13. A compound according to claim 1 substantially as hereinbefore described, with reference to any of Table 1, Formula 1 and/or the Examples.

14. A process according to any one of claims 2 to 5 substantially as hereinbefore described, with reference to any of Table 1, Formula 1 and/or the Examples.

15. A use according to any one of claims 6 to 12 substantially as hereinbefore described, with reference to any of Table 1, Formula 1 and/or the Examples.

16. A method of treatment of hypercholesterolemia which comprises administering a patient in need thereof an effective amount of the substituted morpholine derivatives of the formula I of claim 1.

17. A method of treatment of hyperlipidemia which comprises administering a patient in need thereof an effective amount of the substituted morpholine derivatives of the formula I of claim 1.

18. A method of treatment of atheromatosis which comprises administering a patient in need thereof an effective amount of the substituted morpholine derivatives of the formula I of claim 1.

19. A method of inhibiting lipid peroxidation and antioxidant activity which comprises administering to a patient in need thereof an effective amount of the substituted morpholine derivatives of the formula I of claim 1.

20. A method of reducing cholesterol levels in plasma which comprises administering to a patient in need thereof an effective amount of the substituted morpholine derivative of the formula I of claim 1.

21. A method of reducing triglyceride levels in plasma which comprises administering to a patient in need thereof an effective amount of the substituted morpholine derivative of the formula I of claim 1.

22. A method of reducing LDL-cholesterol levels in plasma which comprises administering to a patient in need thereof an effective amount of the substituted morpholine derivative of the formula I of claim 1.

23. A method according to any one of claims 16 to 22 substantially as hereinbefore described, with reference to any of Table 1, Formula 1 and/or the Examples.

DATED: 7 May, 2002
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