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Full Paper

Thiomorpholine Derivatives with Hypolipidemic and Antioxidant Activity

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A number of thiomorpholine derivatives that are structurally similar to some substituted morpholines possessing antioxidant and hypocholesterolemic activity were synthesized. The new compounds incorporate an antioxidant moiety as the thiomorpholine N-substituent. The derivatives were found to inhibit the ferrous/ascorbate-induced lipid peroxidation of microsomal membrane lipids, with IC_{50} values as low as 7.5 μM. In addition, these compounds demonstrate hypocholesterolemic and hypolipidemic action. The most active compound (**5**) decreases the triglyceride, total cholesterol, and low-density lipoprotein levels in the plasma of Triton WR-1339-induced hyperlipidemic rats, by 80, 78, and 76%, respectively, at 56 mmol/kg (i.p.). They may also act as squalene synthase inhibitors. The above results indicate that the new molecules may be useful as leads for the design of novel compounds as potentially antiatherogenic factors.

Keywords: Antioxidants / Cholesterol / Thiomorpholines / Triglycerides

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Introduction

Atherosclerosis, a condition affecting arterial blood vessels, is the main risk factor for cardiovascular disease, one of the most common diseases in the modern western world. Hyperlipidemia, especially elevated levels of low-density lipoprotein cholesterol (LDL), can lead to the formation of multiple plaques within the artery. Furthermore, dyslipidemia is one of the main alterations characterizing the metabolic syndrome [1]. Oxidation of LDL promotes inflammatory response, which includes impaired vasomotor function, platelet, and leukocyte adhesion to endothelial cells and increased free radical production, leading to plaque vulnerability [2]. Dyslipidemias are not adequately diagnosed and treated, thus, they are still poorly controlled, mainly because the origin of atherosclerosis is still not completely understood [3].

We have reported [4] that a number of properly substituted morpholines acquired antioxidant activity and were potent anti-dyslipidemic agents. Some of them possessed, in addition, nitric oxide-donating activity. Selected structures strongly inhibited squalene synthase activity and LDL oxidation. They also inhibit atherosclerotic lesions in the cholesterol-fed rabbit.

In this investigation, we synthesized and studied a number of substituted thiomorpholines, replacing the morpholine oxygen by a sulfur atom. Further changes involve the introduction of an antioxidant moiety as the thiomorpholine N-substituent, in order to augment the antioxidant potential of these molecules, as well as of a nicotinic acid residue, considering that nicotinic acid is a potent treatment clinically available, since it possesses both anti-dyslipidemic activity and lipid-independent actions on vascular endothelial oxidative and inflammatory events [5].

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Results and discussion

Chemistry

The preparation of the compounds is demonstrated in Schemes 1–4.

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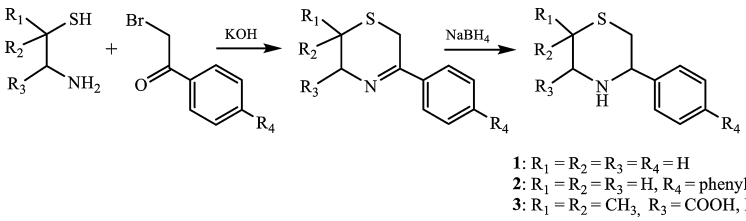


1: $R_1 = R_2 = R_3 = R_4 = H$
2: $R_1 = R_2 = R_3 = H$, R_4 = phenyl
3: $R_1 = R_2 = CH_3$, R_3 = COOH, R_4 = phenyl

Scheme 1. Synthesis of compounds **1–3**.

3-Arylthiomorpholines were prepared by the hydrogenation of the intermediate imine, obtained from the reaction of 2-aminoethanethiol (**1**, **2**) or D-penicillamine (**3**) with 2-bromo-1-phenyl-ethanone or 2-bromo-1-(4-phenyl)phenyl-ethanone in alkaline environment (Scheme 1). 2-Phenyl-thiomorpholine (**4**), prepared as described in the literature, gave compounds **8** and **9**, with reaction of the corresponding acid chlorides in the presence of triethylamine (Scheme 2). Similarly, 3-aryl-thiomorpholines or unsubstituted thiomorpholine reacted with the related acyl or alkyl chlorides in the presence of triethylamine, to give compounds **5**–**7** and **10**–**13** (Scheme 3). Compounds **14**–**16** were prepared from 2-hydroxy-substituted morpholine and the corresponding alcohol with reflux in acidic environment (Scheme 4).

Biological activity

The effect of the synthesized compounds on plasma lipids of hyperlipidemic rats and on the *in vitro* peroxidation of rat hepatic microsomal membrane lipids is shown in Table 1. Most compounds reduced triglyceride, total cholesterol, and LDL-cholesterol levels more than 50%. Furthermore, most of them could effectively inhibit lipid peroxidation.

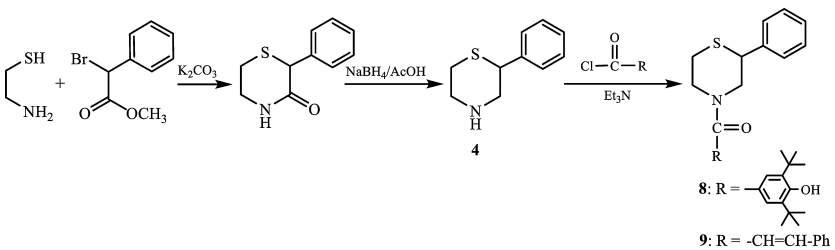
Atherosclerosis is a complex disorder of lipid metabolism and a chronic inflammatory disease. Changes in lipoprotein metabolism and hyperlipidemia play an important role in the progression of atherosclerosis and are significant in predicting the development of cardiovascular events as risk factors [6].

The Triton-1339-induced hyperlipidemia is characterized by a dramatic increase of serum concentration of cholesterol and especially triglycerides, the latter due to surfactant-mediated inhibition of lipoprotein lipase activity. Triton-induced hyperlipidemia occurs 24 h after the administration. It has been shown that Triton produces significant increase in the concentrations of atherogenic C-LDL, C-VLDL, and IDL in mice and rats [7].

The highest hypolipidemic activity was offered by compound **5**. Lower than 50% reduction of the lipidemic indices was caused by **3**, **12**, and **16**. The low activity of **3** and **16** could be attributed to their low lipophilicity (Table 1). Compound **12**, however, is quite lipophilic, with a clogP value close to that of the most active **5**. We have reported that a biphenyl moiety at position 2 of morpholines is needed for hypolipidemic activity, since they are considered to inhibit squalene synthase (SQS) activity [4]. This is further verified in this work, compound **15** is a potent SQS inhibitor (IC_{50} 0.05 μM), the IC_{50} value of **14** is 19.0 μM, while **16** is lacking this activity. The case may not be completely the same for the thiomorpholine derivatives, although 3-[(4-phenyl)phenyl]thiomorpholine (**2**) is found to inhibit SQS activity with IC_{50} 0.40 μM, since the monophenyl-substituted **8** and **9** are quite active hypolipidemics. Still, both are very potent inhibitors of lipid peroxidation (IC_{50} 15 μM). The implication of antioxidant activity in hypolipidemic potential is further supported by the high hypolipidemic action of **13**, comparable to that of **7**, with no phenyl substitution on the thiomorpholine ring. Compound **13** is the most potent antioxidant in this series, and this property may add to the hypolipidemic activity, since oxidative stress plays an important role in LDL oxidation and the pathogenesis of atherosclerosis [8–10].

Compound **10**, with hypolipidemic activity similar to that of **9**, is a weaker antioxidant than **9**, while **7**, a very potent hypolipidemic agent, has no antioxidant effect. Part of their activity may be due to their N-substituent, a cinnamic acid residue, since cinnamaldehyde [11], cinnamic acid [12], and some cinnamic acid derivatives [13] have been reported to possess antidyslipidemic activity.

In conclusion, properly substituted thiomorpholine derivatives possess antidyslipidemic activity, which in most cases seems to be connected with a biphenyl substituent. We suggest that part of the mechanism of action of

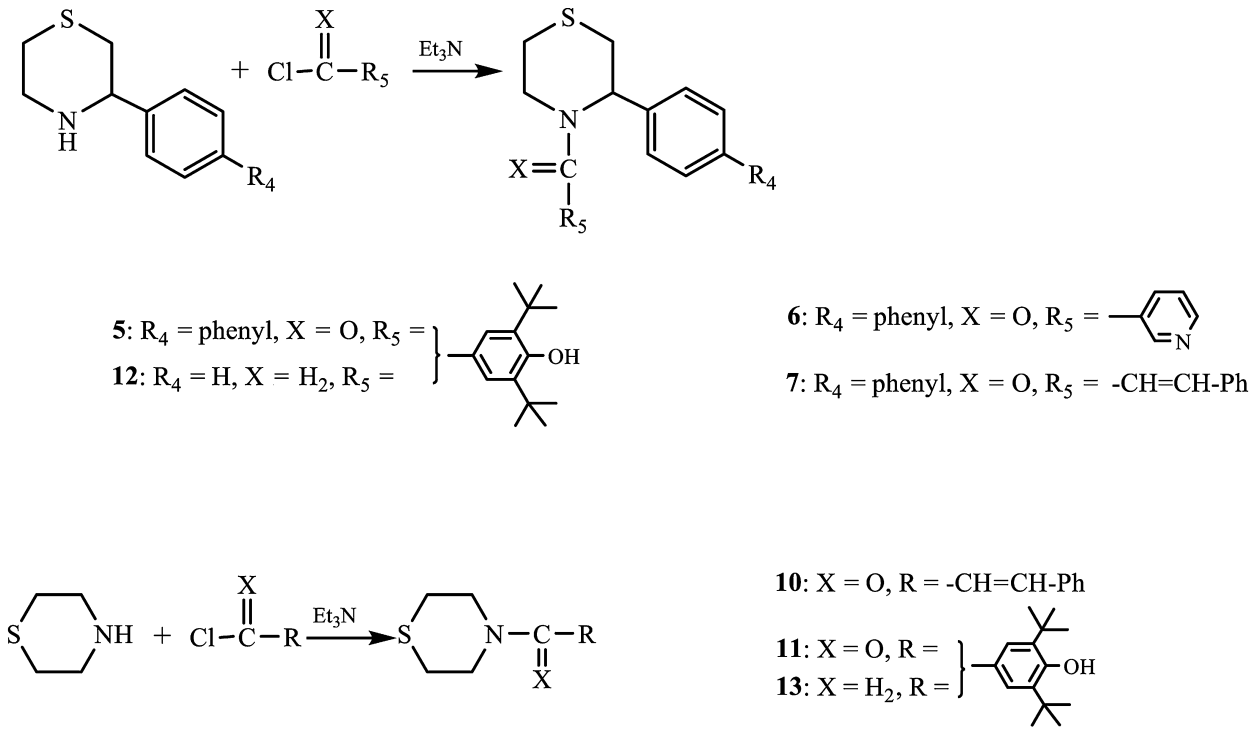


4

8: R =

9: R = -CH=CH-Ph

Scheme 2. Synthesis of compounds **4**, **8**, and **9**.



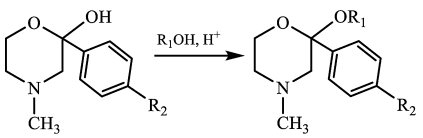
Scheme 3. Synthesis of compounds **5–7** and **10–13**.

biphenyl-morpholine or biphenyl-thiomorpholine derivatives may be due to their squalene synthase inhibitory activity [4]. One of the limiting stages of cholesterol synthesis occurs in the endoplasmic reticulum and is catalyzed by squalene synthase. Inhibition of squalene synthase leads to a reduction of cholesterol synthesis without affecting the synthesis of other nonsterol products of the mevalonate metabolism. The biphenyl moiety may mimic the lipophilic end of farnesyl pyrophosphate, as is the case of 3-(biphenyl-4-yl)-3-hydroxyquinuclidine [14]. The hypolipidemic activity may be further enhanced by the antioxidant properties of these compounds, expected to inhibit LDL oxidation. Furthermore, compounds causing a more than 50% reduction of total cholesterol have an analogous effect on plasma triglyceride levels. This is considered significant, because, currently, there is still a need for a safe and effective treatment for the reduction of both cholesterol and triglycerides, without the risk of undesired effects, such as rhabdomyolysis. The synthesized type of compounds may add to this direction.

Experimental

General

All commercially available reagents were purchased from Merck or Sigma and used without further purification. The IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. The ^{1}H NMR spectra were recorded using a Bruker AC-400 MHz spectrometer. All chemical shifts are reported in δ (ppm) and signals are given as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Melting points (mp) were determined with a MEL-TEMPII (Laboratory Devices, USA) apparatus and are uncorrected. The microanalyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer and were found within ±0.4% of the theoretical values. Male Fischer-344 rats (220–240 g body weight), about 3 months old, were kept in a controlled temperature room (22 ± 2°C), with free access to laboratory chow and tap water, under a 12 h light/dark cycle, and treated according to the European Communities Council Directive of 24 November 1986 (86/609/EEC).



14: $R_1 = CH_2CH_2SCH_3$, R_2 = phenyl
15: $R_1 = CH_2CH_2CH_2ONO_2$, R_2 = phenyl
16: $R_1 = CH_2CH_2CH_2ONO_2$, R_2 = H

Scheme 4. Synthesis of compounds **14–16**.

Table 1. Effect of the synthesised compounds on lipid peroxidation, on lipidemic indices in hyperlipidemic rats and their calculated lipophilicity (clogP).

Compound	Lipid peroxidation inhibition: IC_{50} (μM)	Percent reduction of lipidemic indices[a)]			clogP
		TG	TC	LDL	
2	450	62**	35**	76**	3.83
3	30	–	14*	30*	3.04
5	200	80**	78**	76**	8.71
6	100	53**	65**	66**	4.24
7	–	70**	70**	82**	6.09
8	15	52**	80**	76**	6.39
9	15	62**	50**	72**	4.06
10	350	77**	85**	65**	2.50
11	>750	70**	66**	44*	4.84
12	23	20*	20*	25*	9.05
13	7.5	62**	82**	70**	5.41
14	500	35**	36**	52**	4.26
15	120	85**	63**	47**	1.87
16	300	45**	20*	43**	−0.02

Asterisks indicate statistical significance (Student's *t*-test) of the absorbance values as follows: $^{**}P < 0.005$; $^{*}P < 0.05$. Each group is composed of five to six rats. Results are from two to three independent experiments. TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein cholesterol.
[a)]All determinations are performed at least in duplicate and SD is always within ±10% of the absorbance values.

Synthesis

General method for the synthesis of 3-aryl-thiomorpholines

2-Amino-ethanethiol hydrochloride (0.02 mol) was added to a solution of potassium hydroxide (0.04 mol) in 50 mL of methanol cooled to 0–5°C under nitrogen. To this mixture, a solution of 2-bromo-1-aryl-ethanone (0.02 mol) in 10 mL of methanol was added. The reaction mixture was stirred below 5°C for 1 h and then acidified with 30% methanolic hydrochloric acid. After stirring for an additional 1 h at 0°C, sodium borohydride (0.04 mol) was slowly added and the mixture was stirred for 30 min. The hydrolysis was carried out with aqueous hydrochloric acid, the solvent was evaporated to dryness, and the residue was treated with water. The aqueous layer was made alkaline with a saturated solution of sodium bicarbonate and extracted with chloroform. The extracts were dried (K_2CO_3) and the solvent was removed at reduced pressure to give the final products.

*3-Phenyl-thiomorpholine (**1**)*

Prepared from 2-bromo-1-phenyl-ethanone. White solid, yield 52%, mp 62–64°C. IR (Nujol): 2705, 2641, 2598, 2449 cm^{-1} [15].

*3-[(4-Phenyl)phenyl]thiomorpholine (**2**)*

Obtained as the hydrochloride from acetone-diethyl ether, starting from 2-bromo-1-(4-phenyl)phenyl-ethanone. White solid, yield 78%, mp 191–193°C. IR (Nujol): 2452, 1577 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.1–2.7 (d, 2H, C-6), 2.9–3.5 (m, 4H, C-2, C-5), 4.0–4.3 (t, 1H, C-3), 7.2–7.3 (m, 5H, arom.), 7.4–7.6 (m, 4H, arom.). Anal. calcd. for $C_{16}H_{18}ClNS$: C 65.85, H 6.22, N 4.80; Found: C 65.80, H 6.25, N 4.60%.

*2,2-Dimethyl-5-[(4-phenyl)phenyl]thiomorpholine-3-carboxylic acid (**3**)*

Obtained as the hydrochloride from acetone-diethyl ether, starting from 2-bromo-1-(4-phenyl)phenyl-ethanone and D-penicillamine ((2*S*)-2-amino-3-methyl-3-sulfanyl-butanoic acid) hydrochloride. White solid, yield 88%, mp 234–236°C. IR (Nujol): 3389, 2450, 1744, 1606 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.5 (s, 6H, CH_3), 2.7 (d, 1H, C-6ax), 3.55 (t, 1H, C-5), 3.4–3.9 (bs, 1H, NH), 4.15 (s, 1H, C-3), 4.4 (d, 1H, C-6eq), 7.2–7.4 (m, 3H, arom), 7.5–7.6 (m, 4H, arom), 7.75–7.85 (d, 2H, arom). Anal. calcd. for $C_{19}H_{22}ClNO_2S \times 0.545H_2O$: C 61.06, H 6.23, N 3.75; Found: C 61.05, H 6.04, N 3.69%.

*2-Phenyl-thiomorpholine (**4**)*

Prepared as described in the literature [16], from 2-amino-ethanethiol hydrochloride and methyl α-bromophenyl acetate, followed by reduction of the intermediate lactam with sodium borohydride. Yield 90%, mp 59–60°C.

General method for the preparation of amide derivatives of thiomorpholines

To a solution or suspension of the appropriate thiomorpholine (4 μmol) in dry diethylether (20 mL) triethylamine (4.4 μmol) was added. Then, the corresponding acyl chloride (4 μmol), in dry ether (40 mL) was added, the mixture was stirred at room temperature (3–12 h), filtered and the filtrate

was concentrated, washed with water, dried (K_2CO_3), the solvent was distilled off and the final product was received with flash chromatography of recrystallization.

*3-[(4-Phenyl)phenyl]-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)-thiomorpholine (**5**)*
Prepared from **2** and 3,5-di-*t*-butyl-4-hydroxy-benzoyl chloride and isolated with flash chromatography, using petroleum ether/ethyl acetate 2:1. White solid, yield 60%, mp 131–134°C. IR (Nujol): 3615, 1680, 1598 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.5 (s. 18H, CH_3), 3.4–3.55 (m, 4H, C-2, C-6), 3.6–3.7 (m, 1H, C-5ax), 3.8–3.9 (m, 1H, C-5eq), 4.5–4.7 (m, 1H, C-3), 5.7 (s, 1H, OH), 7.2–7.4 (m, 3H, arom), 7.5–7,6 (m, 4H, arom), 7.8–7.9 (d, 2H, arom), 8.15 (s, 2H, arom). Anal. calcd. for $C_{31}H_{37}NO_2S$: C 76.35, H 7.65, N 2.87; Found: C 76.31, H 7.70, N 2.85%.

*3-[(4-Phenyl)phenyl]-4-nicotinoylthiomorpholine (**6**)*
Prepared from **2** and nicotinoyl chloride and isolated with flash chromatography, using petroleum ether/ethyl acetate 1:1. White solid, yield 70%, mp 139–142°C. IR (Nujol): 1680, 1598 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.4–2.6 (m, 2H, C-6), 2.8–3.0 (m, 2H, C-2), 3.1–3.2 (m, 1H, C-5ax), 3.4–3.5 (m, 1H, C-5eq), 3.9–4.1 (t, 1H, C-3), 7.3–7.8 (m, 13H, arom). Anal. calcd. for $C_{22}H_{20}N_2OS$: C 73.30, H 5.59, N 7.77; Found: C 73.40, H 5.69, N 7.40%.

*3-[(4-Phenyl)phenyl]-4-cinnamoylthiomorpholine (**7**)*
Prepared from **2** and cinnamoyl chloride ((*E*)-3-phenylprop-2-enoic acid chloride) and purified with recrystallization from dichloromethane and diethyl ether. White solid, yield 65%, mp 137–140°C. IR (KBr): 1643, 1597 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45–3.55 (m, 4H, C-2, C-6), 3.7–3.8 (m, 1H, C-5ax), 3.8–3.9 (m, 1H, C-5eq), 4.8–4.95 (m. 1H, C-3), 7.2–7.65 (m, 16H, 14arom, –C**H**=C**H**–). Anal. calcd. for $C_{25}H_{23}NOS$: C 77.89, H 6.01, N 3.63; Found: C 77.92, H 6.06, N 3.50%.

*2-Phenyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)-thiomorpholine (**8**)*
Prepared from **3** and 3,5-di-*t*-butyl-4-hydroxy-benzoyl chloride and recrystallized from acetone and diethyl ether. White solid, yield 80%, mp 147–149°C. IR (Nujol): 3615, 1651, 1598 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.4 (s, 18H, CH_3), 3.4–3.8 (m, 7H, C-2, C-3, C-5, C-6), 5.3 (s, 1H, OH), 7.2–7.5 (m, 7H, arom). Anal. calcd. for $C_{25}H_{33}NO_2S$: C 72.95, H 8.08, N 3.40; Found: C 72.92, H 8.50, N 3.13%.

*2-Phenyl-4-cinnamoylthiomorpholine (**9**)*
Prepared from **3** and cinnamoyl chloride, recrystallized from dichloromethane and diethyl ether. White solid, yield 70%, mp 145–148°C. IR (KBr): 1643, 1597 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.5–2.65 (m, 2H, C-6), 2.9–3.0 (m. 2H, C-5), 3.3-3.4 (m, H, C-3ax), 3.5–3.7 (m. H, C-3eq), 4.0–4.15 (t, 1H, C-2), 7.3–7.5 (m, 12H, 10arom, –C**H**=C**H**–). Anal. calcd. for $C_{19}H_{19}NOS$: C 73.75, H 6.19, N 4.35; Found: C 73.85, H 6.39, N 4.25%.

*4-Cinnamoyl-thiomorpholine (**10**)*
Prepared from thiomorpholine and cinnamoyl chloride, recrystallized from dichloromethane and diethyl ether. Yellow solid, yield 95%, mp. 144–148°C. IR (Nujol): 1642, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.60–2.75 (m, 4H, C-2, C-6), 3.86–4.05 (m, 4H, C-3, C-5), 6.80–6.90 (d, 1H, –CH=C**H**–phenyl), 7.25–7.74 (m, 6H, 5Harom, –C**H**=CH–phenyl). Anal. calcd. for $C_{13}H_{15}NOS$: C 66.92, H 6.48, N 6.00; Found: C 67.16, H 6.83, N 5.69%.

*2-[(4-Phenyl)phenyl]-2-(2-methylthio)ethoxy-4-methylmorpholine (**14**)*
Prepared by heating (12 h) 2-[(4-phenyl)phenyl-4-methylmorpholin-2-ol [17] (0.01 mol) and 2-(methylthio)ethanol (0.06 mol) in dry, acidified acetone (60 mL) and obtained as hydrochloride. White solid, yield 85%, mp 157–158°C. ^1H NMR (DMSO-d_6) δ: 1.7 (m, 1H), 2.1 (s, 3H, S-CH_3), 2.7 (d, 1H), 2.8–3.0 (m, 5H), 3.3 (m, 2H), 3.6 (m, 3H), 4.1 (d, 1H), 4.6 (t, 1H), 7.2–7.65 (m, 9Harom). Anal. calcd. for $C_{20}H_{26}ClNO_2S$: C 63.22, H 6.90, N 3.69; Found: 62.73, H 7.03 N 3.56.

The following compounds: 4-cinnamoyl-thiomorpholine (**10**) [18], (3,5-di-*t*-butyl-4-hydroxy-benzoyl)thiomorpholine (**11**), 2,6-di-*t*-butyl-4-(3-phenyl-thiomorpholin-4-ylmethyl)-phenol (**12**), 2,6-di-*t*-butyl-4-thiomorpholin-4-ylmethyl-phenol (**13**) [15], 2-(4-biphenyl)-2-(3-nitrooxypropoxy)-4-methylmorpholine (**15**), and 2-phenyl-2-(3-nitrooxypropoxy)-4-methylmorpholine (**16**) [19] were prepared as reported earlier.

Biological activity

In vivo evaluation of hypolipidemic activity
An aqueous solution of Triton WR 1339 was administered i.p. to rats (200 mg/kg), [19] and 1 h later the examined compounds (56 μmol/kg) dissolved in saline or saline only were given i.p. In all cases, 24 h after the administration of Triton, blood was taken from the aorta and used for the determination of plasma total cholesterol, LDL, and triglyceride concentrations.

In vitro lipid peroxidation
The incubation mixture contained heat-inactivated hepatic microsomal fraction from untreated rats (corresponding to 2.5 mg of hepatic protein per milliliter or 4 mM fatty acid residues) [20], ascorbic acid (0.2 mM) in Tris-HCl/KCl buffer (50 mM, 150 mM, pH 7.4), and the studied compounds in dimethyl sulfoxide (DMSO) at various concentrations. The peroxidation reaction was started with $FeSO_4$ solution (10 μM), and aliquots were taken from the incubation mixture (37°C) at various time intervals for 45 min. Lipid peroxidation was assessed by spectrophotometric (535 against 600 nm) determination of the 2-thiobarbituric acid reactive material consisting mainly of malondialdehyde, an end product of polyunsaturated lipid peroxidation [19]. All compounds and solvents were tested and not found to interfere with the assay.

In vitro squalene synthase activity evaluation
Squalene synthase (SQS) activity was evaluated by determining the amount of [^{3}H]farnesyl pyrophosphate converted to squalene as previously described [21]. IC_{50} values of the tested compounds **2**, **14**, **15**, **16** represent the mean concentration of compounds that inhibits the activity of the enzyme by 50%. All standard errors are within 10% of the respective reported values.

The authors have declared no conflicts of interest.

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