74011-58-8; **2c**, 54132-31-9; **2d**, 87939-22-8; **2e**, 87939-21-7; **2f**, 63053-03-2; **2g**, 68998-57-2; **2h**, 74274-63-8; **2i**, 92741-52-1; **2j**, 93675-10-6; **2k**, 99726-87-1; **2l**, 99726-88-2; **2m**, 24677-82-5; **2m** (ethyl ester), 99727-01-2; **2n**, 99726-89-3; **2o**, 99726-90-6; **2p**, 99726-91-7; **2q**, 99726-92-8; **2r**, 99726-93-9; **3a**, 19562-30-2; **3b**, 51940-44-4; **4**, 82419-36-1; **5**, 28657-80-9; **6a**, 99726-94-0; **6b**, 99726-95-1; **6c**, 99726-96-2; **7a**, 70934-34-8; **7b**, 99726-97-3; **8**, 91188-89-5; **9**, 99727-00-1; **11**, 57018-74-3; **12**, 99727-03-4; **13**, 36707-44-5; **14**, 99727-04-5; **15**, 33821-58-8; thiazolidine, 504-78-9; 4-(trifluoromethyl)piperidine, 657-36-3; 4-piperidinecarboxamide, 39546-32-2; 4-[3-(dimethylamino)propyl]piperazine, 877-96-3; 1-methyl-4-(4-piperidinyl)piperazine monoacetate, 99726-99-5; 4-(1-pyrrolidinyl)piperidine, 5004-07-9; thiomorpholine, 123-90-0; 1-(aminoethyl)piperazine, 140-31-8; 2,5-dimethoxytetrahydrofuran, 696-59-3; chloroacetonitrile, 107-14-2; ethyl acetamidate hydrochloride, 2208-07-3; 4-methyl-1-piperazinamine, 6928-85-4; 7-[2-(dimethylamino)ethenyl]-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 63475-31-0; *N*-methylpiperazine, 109-01-3; pyrrolidine, 123-75-1; piperazine, 110-85-0; 1,4-dihydro-4-oxo-6-[2-(3-thienyl)]-3-pyridinecarboxylic acid, 96593-69-0.

N-Imidazolylchroman-4-ones, *N*-Imidazolyl-1-tetralones, and Their Alcohols as Hypolipemic Agents Raising High-Density Lipoproteins

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A series of 3-(1-imidazolyl)chroman-4-ones and 2-(1-imidazolyl)-1-tetralones II, some of their alcohols, and some related compounds were synthesized and tested for hypolipidemic activity. Compounds II, bearing appropriate lipophilic substituents on the phenyl ring, strongly reduced total serum cholesterol while raising high-density lipoprotein cholesterol in diet-induced hypercholesterolemic rats. 3-(1-Imidazolyl)chroman-4-ols and 2-(1-imidazolyl)-1-tetralols corresponding to II retained the hypolipidemic activity while removal of the carbonyl or hydroxy group adjacent to imidazole gave inactive compounds. Although many of the active compounds significantly increased liver weight, the one studied as a model, 6-chloro-3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**5**), caused no peroxisome proliferation. Compound **5** and the corresponding alcohol **40**, as representatives of the ketone and alcohol series, showed significant hypolipidemic activity in normolipemic rats. Some of the compounds assayed in cholesterol biosynthesis inhibited acetate incorporation but none inhibited HMG-CoA reductase. 5-Bromo-6-hydroxy-2-(1-imidazolyl)-3,4-dihydro-1(2*H*)-naphthalenone (**38**), which showed strong activity but caused little hepatomegaly in the rat, was chosen for further pharmacological evaluation.

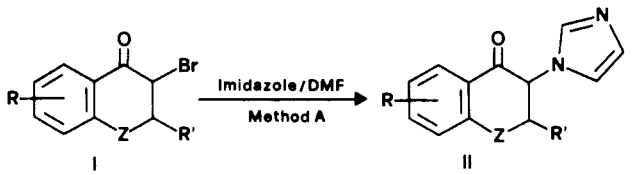
Lipid-lowering drugs have been sought for many years for the treatment of hyperlipidemia.[1] Recently new agents reducing atherogenic low-density lipoproteins (LDL) and raising high-density lipoproteins (HDL) have been sought[2] on the basis that high HDL levels are associated with a reduced risk of coronary heart disease.[3]

This paper reports a series of *N*-imidazolyl derivatives of the chroman and of the tetraline ring (Table I) and some related compounds (Table II). The compounds were tested in diet-induced hypercholesterolemic rats and some of them significantly lowered total serum cholesterol while raising HDL cholesterol. The compounds are structurally unrelated to known hypolipemic drugs although some *N*-alkylimidazole[4] and *N*-benzylimidazole[5] derivatives and more recently khellin and some related chromones and chromanones[2e] were reported to possess hypolipemic activity. The many hypolipemic chroman derivatives described by Witiak et al.[6] are more closely related to clofibrate than to the chroman derivatives described here.

Chemistry. *N*-Imidazolylchromanones and *N*-imidazolyltetralones synthesized following Schemes I and II are reported in Table I, which summarizes their physicochemical properties and biological activity in the rat made hypercholesterolemic by diet.

Compounds II where Z is CH_2, namely 2-(1-imidazolyl)-3,4-dihydro-1(2*H*)-naphthalenones, were prepared following Scheme I analogously to the procedure described by Schröder[7] et al. (method A). Compounds II where Z is oxygen, namely 3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-ones, were prepared in a few cases with the same method A, reported in Scheme I or, more often,

Scheme I



I II

Z = O, CH_2

R = H, Alkyl, Phenyl, NO_2, NH_2, Cl, Br, OH, OCH_3, COOH

R' = H, CH_3

following Scheme II. In this case 2-bromo-2'-hydroxyacetophenones III were reacted with imidazole (method

† Department of Chemistry.
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(1) See for example: (a) Holland, G. F. "Burger's Medicinal Chemistry", Wolff, M. E., Ed.; Wiley: New York, 1979; Part 2, Chapter 35. (b) Cayen, M. N.; Kallai-Sanfacon, M. A. "Annual Reports in Medicinal Chemistry"; Hess, H. J., Ed.; Academic Press: New York, 1980; Vol. 15, p 162.
(2) See for example: (a) Day, C. E.; Schurr, P. E.; Heyd, W. E.; Lednicer, D. *Adv. Exp. Med. Biol.* **1976**, *67*, 231. (b) Sirtori, C. R.; Gomarasca, P.; d'Atri, G.; Cerutti, S.; Tronconi, G.; Scolastico, G. *Atherosclerosis* **1978**, *30*, 45. (c) Schwandt, P.; Weisweiler, P.; Neureuther, G. *Artery* **1979**, *5*, 117. (d) Sircar, I.; Hoefle, M.; Maxwell, R. E. *J. Med. Chem.* **1983**, *26*, 1020. (e) Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1674 and references therein.
(3) (a) Miller, N. E.; Forde, O. H.; Thelle, D. S.; Mjes, O. D. *Lancet* **1977**, *1*, 965. (b) Rossner, S.; Kjellin, K. G.; Mettinger, R. L.; Linden, A.; Soderstrom, C. E. *Lancet* **1978**, *1*, 577. (c) Goldbourt, U.; Medalie, J. H. *Am. J. Epidemiol.* **1979**, *109*, 296.
(4) Atkin, S. D.; Morgan, B.; Baggaley, K. H.; Green, J. *Biochem. J.* **1972**, *130*, 153.
(5) Baggaley, K. H.; Heald, M.; Hindley, R. M.; Morgan, B.; Tee, J. L.; Green, J. *J. Med. Chem.* **1975**, *18*, 833.

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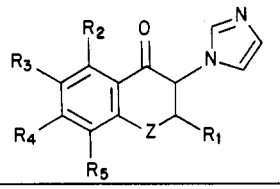
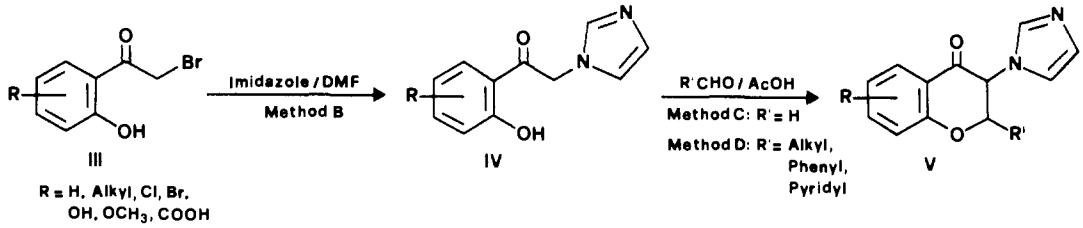
Table I. (1-Imidazolyl)chromanones and (1-Imidazolyl)tetralones: Physical Properties and Biological Activities in Diet-Induced Hypercholesterolemic Rats



												activity: change % vs. the control[d]		
no.	Z	R_1	R_2	R_3	R_4	R_5	formula[a]	mp,[b] °C	method	yield[c]	dose, mg/kg po	serum total cholesterol	serum HDL cholesterol	liver wt
1	O	H	H	H	H	H	$C_{12}H_{10}N_2O_2$	156–158	C	55	50	+34[e]	+4	+16[f]
2	O	H	H	CH_3O	H	H	$C_{13}H_{12}N_2O_3$	150–152	A	40	50	−21	+88[f]	+20[f]
3	O	H	H	OH	H	H	$C_{12}H_{10}N_2O_3$	153–155	E	75	50	+9	−4	+3
4	O	H	H	H	CH_3O	H	$C_{13}H_{12}N_2O_3$	153–155	A	40	50	+11	−1	+3
5	O	H	H	Cl	H	H	$C_{12}H_9ClN_2O_2$	123–125	C	45	50	−65[f]	+146[f]	+28[f]
6	O	H	H	Br	H	H	$C_{12}H_9BrN_2O_2 \cdot HCl$	260–265	F	90	50	−50[f]	+144[f]	+23[f]
7	O	H	H	CH_3	H	H	$C_{13}H_{12}N_2O_2$	105–107	C	50	50	+7	+32[e]	
8	O	H	H	H	Ph	H	$C_{18}H_{14}N_2O_2$	198–200	A	25	50	−48[f]	+118[f]	+22[f]
9	O	H	H	Br	H	Br	$C_{12}H_8Br_2N_2O_2 \cdot HCl$	280 dec	F	60	50	−68[f]	+171[f]	+29[f]
10	O	H	H	CH_3	H	Br	$C_{13}H_{11}BrN_2O_2 \cdot HCl$	270–272 dec	F	60	45	−15	+21	+7[e]
11	O	H	H	CH_3O	H	Br	$C_{13}H_{11}BrN_2O_3$	82–85	A	40	50	+14	+64[f]	+6[e]
12	O	H	H	OH	H	Br	$C_{12}H_9BrN_2O_3 \cdot HBr$	290–295	E	90	50	+2	+1	−1
13	O	H	H	*t*-Bu	OH	H	$C_{16}H_{18}N_2O_3$	243–245	A	40	50	−55[f]	+97[f]	+11[f]
14	O	H	H	*t*-Bu	H	Br	$C_{16}H_{17}BrN_2O_2 \cdot HCl$	230 dec	A	40	50	−12	+57[f]	+15[f]
15	O	CH_3[g]	H	H	H	H	$C_{13}H_{12}N_2O_2$	144–146	D	85	50	−67[f]	+115[f]	+15[f]
16	O	CH_3[g]	H	H	CH_3O	H	$C_{14}H_{14}N_2O_3$	130–132	D	80	50	+11	+5	+2
17	O	CH_3[g]	H	H	OH	H	$C_{13}H_{12}N_2O_3$	255–257	E	85	50	−22[e]	+2	+3
18	O	CH_3[g]	H	COOH	H	H	$C_{14}H_{12}N_2O_4$	>250	D	95	42.5	−12	−18	+3
19	O	CH_3[g]	H	Br	OH	H	$C_{13}H_{11}BrN_2O_3 \cdot HCl$	305–308	D	60	21	−10	+2	+1
20	O	CH_3[g]	H	COOH	H	Br	$C_{14}H_{11}BrN_2O_4$	278–281	D	70	50	−23[e]	−11	+4
21	O	CH_3[g]	H	*n*-Pr	CH_3O	H	$C_{17}H_{20}N_2O_3$	oil	D	50	30	−57[f]	+152[f]	+24[f]
22	O	CH_3[g]	H	*n*-Pr	OH	H	$C_{16}H_{18}N_2O_3$	130 dec	D	70	25	−15	+28	+8[e]
23	O	CH_3[g]	H	*t*-Bu	OH	H	$C_{17}H_{20}N_2O_3$	266–268 dec	H	60	50	−7	+32[e]	+9[f]
24	O	*n*-Pr[g]	H	H	H	H	$C_{15}H_{16}N_2O_2$	wax	D	80	45	−4	+53[f]	+20[f]
25	O	Ph[g]	H	H	H	H	$C_{18}H_{14}N_2O_2$	201–203	D	75	50	+27	−3	+5
26	O	3-Py[h]	H	H	H	H	$C_{17}H_{13}N_3O_2$	70 dec	D	55	50	−4	+12	+4
27	CH_2	H	H	H	H	H	$C_{13}H_{12}N_2O \cdot HNO_3$	165–170 dec	A	70	50	−34[f]	+94[f]	+13[f]
28	CH_2	H	H	OCH_3	H	H	$C_{14}H_{14}N_2O_2$	113–115	A	40	50	−40[f]	+52[f]	+10[f]
29	CH_2	H	H	H	OCH_3	H	$C_{14}H_{14}N_2O_2$	174–176	A	45	10	−37[f]	+34[e]	±0
30	CH_2	H	H	H	OH	H	$C_{13}H_{12}N_2O_2 \cdot HBr$	298–300	E	42	50	+30	+12	−3
31	CH_2	H	H	NO_2	H	H	$C_{13}H_{11}N_3O_3$	155 dec	A	13	50	−16	+23[e]	+5
32	CH_2	H	H	NH_2	H	H	$C_{13}H_{13}N_3O$	212	A	84	35	−24[e]	+31[e]	+3
33	CH_2	H	H	$N(CH_3)_2$	H	H	$C_{15}H_{17}N_3O$	160–162	G	25	37	−37[f]	+69[f]	+11[f]
34	CH_2	H	H	COOH	H	H	$C_{14}H_{12}N_2O_3$	>290	A	84	45	−5	−9	−3
35	CH_2	H	COOH	H	H	H	$C_{14}H_{12}N_2O_3$	280–283	A	52	40	−19	−9	−4
36	CH_2	H	H	H	Br	H	$C_{13}H_{11}BrN_2O$	183–185	A	68	30	−84[f]	+228[f]	+31[f]
37	CH_2	H	H	Ph	H	H	$C_{19}H_{16}N_2O$	128–130	A	28	23	+4	+8	+2
38	CH_2	H	H	H	OH	Br	$C_{13}H_{11}BrN_2O_2 \cdot HCl$	>300	F	33	50	−44[f]	+109[f]	+13[f]
39 pirinixil	CH_2	CH_3[g]	H	H	H	H	$C_{14}H_{14}N_2O$	153–155	A	10	50	−54[f] −43[f]	+102[f] +105[f]	+26[f] +54[f]

[a] All compounds are analyzed for C, H, N, and Cl or Br, when present; analytical results were within ±0.4% of the theoretical values. [b] All compounds were purified by chromatographic column separation except for compounds **2**, **3**, **5**, **6**, and **23**, crystallized from alcohols or water–alcohol mixtures. [c] No effort was made to optimize yields. [d] Groups of 10 rats were used to test all products. The animals were killed in a fasting state. [e] Statistically significant ($p < 0.05$) according to Dunnett's test. [f] Statistically highly significant ($p < 0.01$) according to Dunnett's test. [g] Pure trans. [h] Mixture of cis and trans: J = 2.2 Hz (cis), J = 12.2 Hz (trans).

Scheme II



B) giving 2-(1-imidazolyl)-2′-hydroxyaceetophenones IV, which in turn by reaction with paraformaldehyde (method C) or other aldehydes (method D) gave imidazolylchromanones V, in the latter case predominantly in the trans configuration, according to the large ^1H NMR coupling constant (J = 12 Hz). The chemistry referring to Scheme II was discussed in a previous paper.[8]

Some of the bromochromanones[9] and bromotetralones[7] of formula I and some of the 2-bromo-2′-hydroxyacetophenones[10] III used as starting materials are known compounds; others were prepared following the procedures reported in the cited references.[7,9,10]

Some compounds in the chromanone and tetralone series were prepared by modifying a substituent or by introducing a new substituent on the phenyl ring of parent compounds prepared in turn following Schemes I and II. For example, some phenolic derivatives (**3**, **12**, **17**, **22**, **30**) were obtained from the corresponding methoxy analogues (**2**, **11**, **16**, **21**, **29**) by reaction with concentrated HBr (method E). The bromo derivatives **6**, **9**, **10**, and **38** were obtained by bromination of **1**, **7**, and **29** with Br_2 in the presence of an excess of $AlCl_3$ in order to avoid bromination α to the keto group.[11] In the case of **29**, concomitant demethylation took place (method F).

The dimethylanilino derivative **33** was obtained from the anilino **32** by methylation with CH_3I (method G). Compound **23** was obtained from **17** by alkylation with t-BuOH in H_3PO_4 85% (method H).

In order to assess the minimal structural requirements for activity, some derivatives of the above N-imidazolylchromanones and tetralones and some analogues were prepared and tested. Table II reports the physicochemical properties and biological activities in rats of some of them having the same substituents on the phenyl ring that confer the best activity to compounds listed in Table I.

7-Methoxy-tetralol **44** (pure trans) was obtained from tetralone **28** by reduction with $NaBH_4$ (method I).

In the case of chromanone **5**, the same reduction method gave a mixture of *cis*- and *trans*-3-(1-imidazolyl)-6-chlorochroman-4-ol (*cis*-**40** and *trans*-**41**), which were separated on a silica gel chromatographic column. The cis and trans configuration was attributed by evaluating the ^1H NMR coupling constants, reported in the Experimental Section, as discussed in the literature[7] for similar 1-tetralols.

The above mixture of chromanol **40** and **41**, by alkylation with the desired alkyl halide (method J), gave the ethers **42** and **43** (cis–trans mixture) and, by dehydration in acidic medium (method K), 3-(1-imidazolyl)-6-chloro-2H-chromene (**45**). 3-(2-Methyl-1-imidazolyl)-6-chlorochromanone (**46**) and 3-(1-pyrazolyl)-6-chlorochromanone (**47**) were prepared by the same ring closure described in Scheme II (method C).

2-(1-Pyrazolyl)-1-tetralone (**48**) and the isosteric benzothiophene derivative **49** were prepared according to the procedure described in Scheme I (method A).

Biological Results and Discussion

The compounds were evaluated as regards total serum cholesterol, HDL cholesterol, and increase in liver weight in rats made hypercholesterolemic by diet, as described in the Experimental Section. Though in a few cases the dosage used was lower than the usual 50 mg/kg po, the data reported in Tables I and II permit some observations about the structure–activity relationship (SAR). First of all, it can be seen from Table I that hypocholesterolemic activity, HDL raising activity, and, to some degree, hepatomegaly go together.

Differences in activity between compounds of the chroman and the tetralone series are not too clearly defined and the two series can be analyzed as a whole. However, in comparison of some pairs of derivatives with similar or identical substitution pattern on the phenyl ring in the two series, the more lipophilic tetralones are often active while the similarly substituted chromanones are inactive (**27** and **1**, **29** and **4**, **38** and **12**) or less active (**36** and **6**).

A positive correlation between activity and lipophilicity seems more clearly suggested by the substitution pattern on the phenyl ring. Hydrophilic substitution gives inactive compounds (**3**, **17**, **18**, **30**, **31**, **34**, **35**) while lipophilic substituents are present in more active compounds (**5**, **6**, **8**, **9**, **21**, **36**) with the notable exception of compounds bearing a methyl group (**7**, **10**). This feature seems confirmed by comparing the activity of some pairs of close analogues such as **2** and **3**, **11** and **12**, **21** and **22**, **32** and **33**, in which the more lipophilic derivative is the more active.

From the above examples it is evident that the electronic pattern of the substituents is irrelevant as concerns activity. The two most lipophilic compounds in Table I, **14** and **37**, are either scarcely active or else inactive. This could not be an argument against the above statement that lipophilicity favors activity but simply underlines a parabolic activity–lipophilicity relationship as often occurs in different pharmacological series.[12]

Compounds with double hydrophilic–lipophilic substitution were synthesized in a relatively large number in an attempt to achieve low hepatomegaly while maintaining good activity, but no clear conclusion about the SAR can be drawn.

As regards substituent R_1, groups bulkier than methyl have a definite negative effect on activity (**24**–**26**). As

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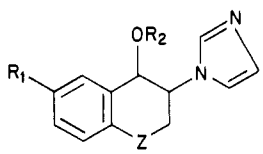
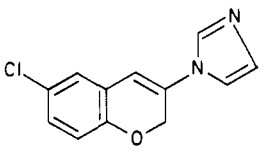
Table II. Analogues of *N*-Imidazolylchromanones and -tetralones: Physical Properties and Biological Activities in Diet-Induced Hypercholesterolemic Rats


40-44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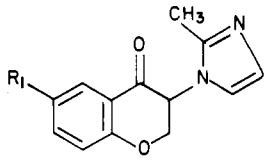
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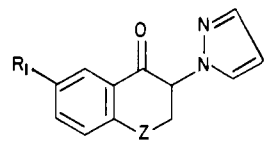
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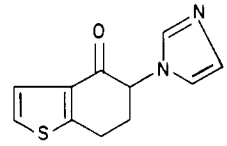
49

no.	Z	R_1	R_1	formula[a]	mp,[b] °C	method	yield[c]	dose, mg/kg po	activity: change % vs. the control[d] serum total cholesterol	serum HDL cholesterol	liver wt
40	O	Cl	H	$C_{12}H_{11}ClN_2O_2$ (cis)	60–65	I	55	50	−42[f]	+121[f]	+24[f]
41	O	Cl	H	$C_{12}H_{11}ClN_2O_2$ (trans)	153–160	I	29	50	−14	+83[f]	+20[f]
42	O	Cl	CH_3	$C_{13}H_{13}ClN_2O_2$ (cis,trans mixture)	oil	J	50	50	+8	−7	+15[f]
43	O	Cl	C_8H_{17}	$C_{20}H_{27}ClN_2O_2 \cdot HNO_3$ (cis,trans mixture)	110–117	J	50	50	+42	+18	
44	CH_2	OCH_3	H	$C_{14}H_{16}N_2O_2$ (trans)	168–171	I	79	50	−24[e]	+88	+21[f]
45				$C_{12}H_9ClN_2O$	118–120	K	78	50	−10	+25	+2
46				$C_{13}H_{11}ClN_2O_2$	196–198	C	55	50	+39	+23[e]	+14[f]
47	O	Cl		$C_{12}H_9ClN_2O_2$	148–150	C	63	50	+35	+13	+6
48	CH_2	H		$C_{13}H_{12}N_2O$	105–108	A	40	50	+52[e]	−3	+9[f]
49				$C_{11}H_{10}N_2OS$	162–164	A	69	50	+17	+2	
pirinixil								50	−43[f]	+105[f]	+54[f]

[a–e] See corresponding footnotes in Table I.

Table III. Hypolipidemic Activity in Normocholesterolemic Rats[a]

compd	dose, mg/kg po	serum[b] total cholesterol	LDL cholesterol	HDL cholesterol	HDL/LDL ratio	serum triglycerides	liver wt
5	50	−18[d]	−53[d]	+16	+153[d]	−46[d]	+34[d]
40	50	−19[d]	−50[d]	+11	+123[d]	−36[c]	+24[d]
pirinixil	50	−23[d]	−19[d]	−27[d]	−9	−48[d]	+42[d]
clofibrate	200	−35[d]	−40[d]	−32[d]	+13	−52[d]	+25[d]
procetofene	100	−28[d]	−31[d]	−27[d]	+7	−50[d]	+38[d]

[a] Groups of 10 rats were used to test all the compounds. [b] For all the variables the activity was expressed as percent difference from control. [c] Statistically significant ($p < 0.05$) according to Dunnett's test. [d] Statistically highly significant ($p < 0.01$) according to Dunnett's test.

shown in Table II chromanols (**40**, **41**) and tetralols (**44**) retain the activity of the corresponding ketones (**5**, **28**), but when the alcoholic group is alkylated (**42**, **43**) or when the oxygenated function adjacent to the imidazolyl residue is removed (**45**), the activity disappears.

The *N*-imidazolyl residue plays a key role for activity, which is completely destroyed by the simple introduction of a methyl group on the imidazole ring (**46**) or the replacement of imidazole by pyrazole (**47**, **48**).

Finally replacement of the phenyl moiety of the tetralone with the isosteric thienyl ring[13] results in loss of activity (**49**).

In order to elucidate the profile of activity, two selected compounds, **5** and **40**, were tested in normocholesterolemic rats as described in the Experimental Section. The biological results, reported in Table III, confirm the hypolipidemic trend of activity: compounds **5** and **40** significantly lowered triglycerides and total cholesterol, the hypocholesterolemic effect being particularly strong on LDL so that the HDL/LDL ratio was markedly raised. In this test, the reference hypolipemic compounds pirinixil (BR 931),[14] clofibrate, and procetofene showed a different and less favorable effect on the HDL/LDL ratio because of a highly significant decrease of the HDL fraction. Liver weight again increased in rats treated with active compounds.

Most lipid lowering agents in rodents are known to induce hepatomegaly, proliferation of hepatic peroxisomes, and, as a consequence of this proliferation, a high frequency of hepatic tumors in long term treated animals.[15] On the other hand, hepatic microsomal inducers such as barbiturates cause hepatomegaly in rodents associated with proliferation of the liver endoplasmatic reticulum, while both in rodents and humans significantly raise HDL.[16,17]

For these reasons, early in the course of this study, we decided to investigate in rats the effects of the active compound **5**, chosen as a model, on liver weight and on enzymatic activities associated either with microsomal induction or with peroxisomal proliferation. As reported in the Experimental Section, phenobarbital, a classical microsomal inducer, and pirinixil,[14] a hypolipemic agent known to cause strong peroxisome proliferation,[18] were

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(14) 2-[[4-Chloro-6-(2,3-xylidino)-2-pyrimidinyl]thio]-*N*-(2-hydroxyethyl)acetamide; BE 852.401; *Chem. Abstr.* **1978**, *88*, 50907.

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Table IV. Hepatic Peroxisomal Proliferation Effect in Male Rats Treated for 7 Days with Compound 5 (50 mg/kg per day) and Reference Compound Pirinixil[a]

group	liver/body wt ratio, %	hepatic proteins, mg/g of liver	catalast act.[b]/mg of protein	carnitine acetyl transferase act.[c]/mg of protein	palmitoyl-CoA oxidation act.[d]/mg of protein
control	3.34 ± 0.08	227 ± 5	42.9 ± 2.3	3.6 ± 0.3	5.1 ± 0.2
5	4.36 ± 0.13[e]	216 ± 5	42.1 ± 2.3	2.9 ± 0.2	4.1 ± 0.0
pirinixil	5.31 ± 0.19[d]	237 ± 4	58.8 ± 3.3[d]	69.8 ± 3.9[d]	16.2 ± 0.8[d]

[a] The values are the means ± SEM of three rats. Enzymatic activities are expressed as: [b] K, in sec^{-1} according to Aebi;[28] [c] nmol of CoASH produced/min; [d] nmol of NAD^+ reduced/min. [e] Significantly different from control ($p < 0.01$) according to Dunnett's test.

Table V. Enzymatic Induction Effect in Male Rats, Treated for 5 Days with Compounds 5, 38, and Pirinixil (50 mg/kg per day) and Sodium Phenobarbital (75 mg/kg per day)[a]

group	liver/body wt ratio, %	microsomal proteins, mg/g of liver	cytochrome P-450, mmol/mg of protein	aminopyrine N-demethylase act.[b]/g of liver	aniline p-hydroxylase act.[c]/g of liver
control	3.20 ± 0.05	23.5 ± 0.6	0.76 ± 0.07	1.01 ± 0.07	0.56 ± 0.02
5	4.40 ± 0.11[d]	42.5 ± 1.1[d]	2.46 ± 0.15[d]	2.98 ± 0.18[d]	0.93 ± 0.01[d]
38	3.24 ± 0.07	28.0 ± 1.2[d]	0.98 ± 0.06	1.69 ± 0.05	0.67 ± 0.02
pirinixil	4.99 ± 0.14[d]	25.0 ± 0.4	0.82 ± 0.07	0.69 ± 0.03	0.64 ± 0.02
phenobarbital	4.32 ± 0.07[d]	40.6 ± 0.9[d]	1.92 ± 0.05[d]	4.20 ± 0.31[d]	1.15 ± 0.04[d]

[a] The values are the means ± SEM of four rats. Enzymatic activites are expressed as: [b] μmol of HCHO produced/5 min; [c] μmol of p-aminophenol produced/20 min. [d] Significantly different from control ($p < 0.01$) according to Dunnett's test.

taken as reference. As shown in Tables IV and V, compound 5 did not affect either catalase and carnitine acetyltransferase or palmitoyl-CoA oxidation, which are greatly increased by peroxisomal proliferation,[19] but raised microsomal proteins, cytochrome P-450, aminopyrine N-demethylase, and aniline p-hydroxylase, which are markers of microsomal induction.[20]

The finding that hepatomegaly was associated not with peroxisomes proliferation but with microsomal induction prompted us to try to minimize the latter effect. With this aim we placed pairs of substituents on the phenyl ring, one of which was a hydroxyl group, on the basis that one of the main effects of inducing enzymes is hydroxylation on the phenyl ring,[21] and the other a lipophilic group, on the basis that minimal overall lipophilicity could be a requisite for activity. Two compounds belonging to this group, 13 and 38, showed little hepatomegaly while keeping good activity (Table I). Compound 38 actually showed only limited effects on the enzymes associated with microsomal induction (Table V) and was thus chosen for further evaluation.

Finally, in order to gain some information about the mechanism of action of the compounds described, we tested some of them in vitro on cholesterol biosynthesis and on (hydroxymethyl)glutaryl-CoA reductase activity, which is the rate-limiting step in cholesterol biosynthesis, as reported in the Experimental Section. As shown in Table VI, some compounds, e.g. 32 and 33, inhibited acetate incorporation in cholesterol without affecting incorporation in neutral lipids (acting therefore at the squalene cyclization step as reported for N-dodecylimidazole[4]), while others, e.g. 5, 38, and 40, had no effect on acetate incorporation. None of them inhibited HMG-CoA reductase.

In conclusion, among these 3-(1-imidazolyl)chroman-4-ones, 2-(1-imidazolyl)-1-tetralones, and their alcohols a family of hypolipidemic agents with unusual positive features can be identified. In rats on an atherogenic diet, the compounds lowered total cholesterol, clearly lowering LDL and raising HDL. This activity was accompanied by an increase in liver weight, which was correlated, to some degree, with microsomal induction but not with peroxisome proliferation. On the other hand, hypolipidemic and peroxisome proliferator agents (e.g. clofibrate and related compounds) lowered total serum cholesterol but failed, in normolipemic rats, to raise the HDL/LDL ratio to the same large extent as the compounds described here.

Table VI. Inhibition of in Vitro Cholesterol Biosynthesis in Rat Liver Slices[a]

compd[b]	% inhibn of [^{14}C]acetate incorporation in neutral lipids[c]	% inhibn of [^{14}C]acetate incorporation in cholesterol
5	0	0
32	0	74
33	0	55
38	0	0
40	0	0
N-dodecylimidazole	14	66

[a] Values are arithmetical means of four determinations. The compounds had no effect on [^{14}C]acetate incorporation in CO_2 and long-chain fatty acids. [b] Except for compound 38 (5×10^{-5} M) and N-dodecylimidazole (10^{-4} M), the compounds were assayed at 2×10^{-4} M concentration. [c] Light petroleum ether (bp 40–60 °C), soluble nonsaponifiable lipids.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Büchi Mel-Temp melting point apparatus and are uncorrected. Elemental analysis were performed on a Carlo Erba 1106 instrument and where analytical results are indicated only by the symbols of the elements, they were within ±0.4% of theoretical values. ^{1}H NMR spectra for all the compounds described were recorded on a Bruker HX 90 instrument with tetramethylsilane as the internal standard and chemical shifts are expressed in parts per million (δ). IR spectra were recorded on a Perkin-Elmer 683 instrument and frequencies are expressed in reciprocal centimeters. Column chromatographic separations were performed by the flash technique on 40–60-μm silica gel (Merck No. 9385). The compounds used as references in pharmacological tests, pirinixil,[14] N-dodecylimidazole,[4] and procetofene,[22] were prepared by us following the literature; phenobarbital was purchased from Co. Farmaceutica Milanese and clofibrate was purchased from Sigma Co.

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Method A. 2-(1-Imidazolyl)-7-methoxy-3,4-dihydro-1-(2*H*)-naphthalenone (28). A solution of 2-bromo-7-methoxy-3,4-dihydro-1(2*H*)-naphthalenone, mp 78–79 °C, prepared according to ref 7, (17.25 g, 0.067 mol), imidazole (23 g, 0.33 mol), and DMF (110 mL) was stirred for 6 h at room temperature. The solution was poured into ice–water and then extracted with CH_2Cl_2. The organic phase, after washing with H_2O, was extracted with a solution of 8% HCl. The acid solution was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed (H_2O, 5% $NaHCO_3$, H_2O), dried ($CaCl_2$), and evaporated under reduced pressure to give 12.6 g (77%) of **28**: mp 113–115 °C; NMR ($CDCl_3$) δ 2.42–2.72 (2 H, m, $CHCH_2CH_2$), 3.02–3.35 (2 H, m, $CHCH_2CH_2$), 3.84 (3 H, s, OCH_3), 4.96 (1 H, dd, $CHCH_2CH_2$), 6.96–7.58 (6 H, m, aromatics); IR (KBr) 1700 cm^{-1}. Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

Method B. General Procedure. The 2-(1-imidazolyl)-2′-hydroxyacetophenones were prepared following this procedure. A solution of 2-bromo-2′-hydroxyacetophenone[10] (28.1 mmol) and imidazole (84.3 mmol) in DMF (50 mL) was heated at 40 °C for 2 h. The solution was poured into water, and the precipitate was filtered off and taken up with 10% HCl solution. The acidic solution was washed with CH_2Cl_2, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The resulting products were purified by crystallization (MeOH).

Method C. 6-Chloro-3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (5). A solution of 2-(1-imidazolyl)-2′-hydroxy-5′-chloroacetophenone (1.18 g, 5.0 mmol) and paraformaldehyde (0.15 g, 5.0 mmol) in glacial AcOH (22.5 mL) was refluxed for 30 min. The solvent was evaporated under reduced pressure and the residue taken up with CH_2Cl_2 (50 mL). The organic layer was washed with water, dried (Na_2SO_4), and filtered, and the filtrate was evaporated to dryness. The residue was crystallized from H_2O–MeOH (1:3) to yield 0.56 g (45%) of **5**: mp 123–125 °C; NMR ($CDCl_3$) δ 4.60–5.10 (2 H, m, OCH_2), 5.84 (1 H, m, OCH_2CH), 6.92–7.84 (6 H, m, aromatics). Anal. ($C_{12}H_9ClN_2O_2$) C, H, Cl, N.

Method D. *trans*-3-(1-Imidazolyl)-2-methyl-2,3-dihydro-4*H*-1-benzopyran-4-one (15). A mixture of 2-(1-imidazolyl)-2′-hydroxyacetophenone (1 g, 4.9 mmol) and acetaldehyde (3 mL) in glacial AcOH (50 mL) was heated at 90 °C for 10 h. The solvent was evaporated under reduced pressure and the residue taken up with CH_2Cl_2 (20 mL). The organic layer was washed with water, dried (Na_2SO_4), and evaporated to dryness. The solid residue was purified by silica gel column chromatography, eluting with $CHCl_3$–MeOH (9:1). The purified product yielded 0.92 g (82%) of **15**: mp 144–146 °C; NMR ($CDCl_3$) δ 1.37 (3 H, d, CH_3), 4.50–4.98 (2 H, m, J = 12 Hz, OCHCH), 7.02–7.95 (7 H, m, aromatics). Anal. ($C_{13}H_{12}N_2O_2$) C, H, N.

Method E. 6-Hydroxy-2-(1-imidazolyl)-3,4-dihydro-1-(2*H*)-naphthalenone Hydrobromide (30). A solution of **29** (1.5 g, 6.2 mmol) and 48% hydrobromic acid (40 mL) was refluxed for 5 h. The solution was poured into ice–water, and the solid was filtered off, washed with water, and dried, giving 1.3 g (68%) of **30**: mp 298–300 °C; NMR (D_2O–Me_2SO-d_6) δ 2.64 (2 H, m, $CHCH_2CH_2$), 3.22 (2 H, m, $CHCH_2CH_2$), 5.48 (1 H, dd, $CHCH_2CH_2$), 6.88–7.89 (5 H, m, aromatics), 8.84 (1 H, br s, NCHN); IR (KBr) 1660 cm^{-1}. Anal. ($C_{13}H_{13}BrN_2O_2$) C, H, N, Br.

Method F. 6-Bromo-3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-one Hydrochloride (6). Bromine (0.79 g, 50 mmol) was added dropwise to a mixture of **1** (1.07 g, 50 mmol) and $AlCl_3$ (1.7 g, 12.6 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature for 6 h and then poured into a cooled solution of 8% HCl (20 mL). The resulting precipitate was filtered off and crystallized from EtOH to give 1.48 g (90%) of **6**: mp 260–265 °C (dec); NMR (CF_3COOD) δ 5.07 (2 H, m, OCH_2), 5.87 (1 H, dd, OCH_2CH), 7.16–8.11 (5 H, m, aromatics), 9.07 (1 H, br s, NCHN). Anal. ($C_{12}H_9BrN_2O_2$·HCl) C, H, Br, N, Cl^-.

Methyl G. 7-(Dimethylamino)-2-(1-imidazolyl)-3,4-dihydro-1(2*H*)-naphthalenone (33). A solution of **32** (1.3 g, 5.7 mmol), CH_3I (3 mL, 48 mmol), and $(C_2H_5)_3N$ (1.7 mL, 12.1 mmol) in ethanol (100 mL) was refluxed for 20 h. The solvent was evaporated under reduced pressure and the residue was taken up with water. The solution was neutralized with 2 N NaOH and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated under vacuum to give 1.15 g (79%) of **33**: mp 160–162 °C; NMR ($CDCl_3$) δ 2.56 (2 H, m, $CHCH_2CH_2$), 2.98 (6 H, s, $N(CH_3)_2$), 3.15 (2 H, m, $CHCH_2CH_2$), 4.90 (1 H, dd, $CHCH_2CH_2$), 6.92–7.57 (6 H, m, aromatics). Anal. ($C_{13}H_{13}N_3O$) C, H, N.

Method H. *trans*-6-*tert*-Butyl-7-hydroxy-3-(1-imidazolyl)-2-methyl-2,3-dihydro-4*H*-1-benzopyran-4-one (23). A mixture of **17** (1 g, 4.09 mmol) and *tert*-butyl alcohol (2.5 mL) in 15 mL of 85% H_3PO_4 was heated at 70 °C for 5 h. The reaction mixture was poured into ice–water and neutralized with $NaHCO_3$. The resulting precipitate was filtered off and crystallized with MeOH to give 0.73 g (60%) of **23**: mp 266–268 °C; NMR (Me_2SO-d_6) δ 1.21 (3 H, d, CH_3), 1.35 (9 H, s, *t*-Bu), 4.83 (1 H, dq, OCH), 5.20 (1 H, d, J = 12 Hz, OCHC*H*), 6.43–7.63 (5 H, m, aromatics). Anal. ($C_{17}H_{20}N_2O_3$) C, H, N.

Method I. *trans*-6-Chloro-3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-ol (41) and *cis*-6-Chloro-3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-ol (40). $NaBH_4$ (1.0 g, 26.4 mmol) was added portionwise to a solution of **5** (2.7 g, 10.8 mol) in MeOH (70 ml) at 10–15 °C. The mixture, stirred at room temperature for 2 h, was poured into water (300 mL) and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give 2.5 g (91%) of a mixture of **40** and **41**. The isomers were separated by silica gel column chromatography, eluting with $CHCl_3$–MeOH (9:1). The first fraction gave 0.8 g (29%) of **41** (containing traces of **40**): mp 153–160 °C; NMR (Py-d_6) δ 4.40–4.90 (3 H, m, OCH_2CH), 5.18 (1 H, d, J = 6.5 Hz, C*H*OH), 6.96–8.03 (6 H, m, aromatics). Anal. ($C_{12}H_{11}ClN_2O_2$) C, H, Cl, N. Further elution gave 1.5 g (55%) of **40** (containing traces of **41**): mp 60–65 °C; NMR (Py-d_6) δ 4.26–5.00 (3 H, m, OCH_2CH), 5.19 (1 H, d, J = 2.2 Hz, C*H*OH) 7.00–8.12 (6 H, m, aromatics). Anal. ($C_{12}H_{11}ClN_2O_2$) C, H, Cl, N.

Method J. 6-Chloro-3-(1-imidazolyl)-4-(*n*-octyloxy)-2,3-dihydro-4*H*-1-benzopyran Nitrate (43; Cis and Trans Mixture). A solution of 2.0 g (7.9 mmol) of 3-(1-imidazolyl)-6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-ol (cis and trans mixture) in DMF (10 mL) was added to a suspension of NaH (0.21 g, 8.7 mmol) in DMF (5 mL). The reaction mixture was stirred at 40 °C for 30 min and then a solution of octyl bromide in DMF (5 mL) was added. After stirring at room temperature for 4 h, the reaction mixture was evaporated to dryness under reduced pressure and the residue was taken up with water and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in EtOH and treated with 70% HNO_3 to give 1.68 g (50%) of **43**: mp 110–117 °C; NMR (Me_2SO-d_6) δ 0.84 (3 H, t, CH_3), 1.21 (12 H, m, $CH_2(CH_2)_6CH_3$), 3.56 (2 H, t, $CH_2(CH_2)_6CH_3$), 4.45–5.45 (4 H, m, OCH_2CHCH), 6.95–7.71 (5 H, m, aromatics), 9.08 (1 H, br s, NCHN). Anal. ($C_{20}H_{27}ClN_2O_2$·HNO_3) C, H, Cl, N.

Method K. 6-Chloro-3-(1-imidazolyl)-2*H*-1-benzopyran (45). A solution of 5.4 g (21.5 mmol) of 6-chloro-3-(1-imidazolyl)-2,3-dihydro-4*H*-1-benzopyran-4-ol (cis and trans mixture) in glacial AcOH (81 mL) and concentrated H_2SO_4 (27 mL) was heated at 80 °C for 8 h. The reaction mixture was poured into ice water (200 mL), neutralized with NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized with isopropyl alcohol, yielding 3.9 g (78%) of **45**: mp 118–120 °C; NMR ($CDCl_3$) δ 5.11 (2 H, d, OCH_2), 6.49 (1 H, br s, OCH_2CCH), 6.84–7.21 (5 H, m, aromatics), 7.78 (1 H, br s, NCHN). Anal. ($C_{12}H_9ClN_2O$) C, H, Cl, N.

Pharmacology. Experiments on diet-induced hypercholesterolemic rats were carried out as described,[23] with the following modifications. Adult male Wistar Crl: (WI) BR rats, 170–200-g initial body weight, were used. In the hypercholesterolic diet (supplied by Rieper, Vandoies, Italy), liver concentrate powder was replaced by a supplement of choline, inositole, and DL-methionine (respectively 2000, 1000, and 2000 mg/kg diet). Rats fed for 7 days with this hypercholesterolic diet (1.5% cholesterol, 0.5% cholic acid) showed total serum cholesterol 4–6 times higher

(23) Schurr, P. E.; Schultz, H. R.; Day, C. E. "Atherosclerosis and Drug Discovery"; Day, C. E., Ed.; Plenum Press: New York, 1976; p 215.

than that of normal diet fed animals and HDL cholesterol one-fourth that of control animals. The compounds were given orally in the last 4 days of diet treatment. Rats were killed on day 8 after fasting overnight.

The assay on normal diet fed rats was performed as described[24] with slight modifications. Iva-SDIV (SPF) male rats, 230-260 g initial body weight, were used. The animals were fed Altromin R diet (Rieper, Vandoies, Italy) and given test and reference products by gavage for 4 days. They were killed in a fed state 24 h after the last dose.

In the above tests all compounds were suspended in 0.5% Methocel 4 AC Premium in distilled water and given to rats in a volume of 0.5 mL/100 g of body weight. Doses are reported in the corresponding tables.

Lipid assays were always done on serum obtained by bleeding animals under light CO_2 anesthesia. HDL were isolated[25] by mixing 1 mL of serum with 0.05 mL of 4% sodium heparinate and 0.07 mL of 1 M $MnCl_2$. Samples were centrifuged at 8000 rpm for 15 min at 4 °C in a Beckman Model J 21C centrifuge equipped with a JA-21 rotor. Serum total and HDL cholesterol were determined by a colorimetric enzymatic method[26] with use of a Braun Sistematik Zeiss apparatus.

VLDL + LDL cholesterol was determined from the difference between total and HDL cholesterol. Serum triglycerides were assayed with a colorimetric method.[27]

Hepatic peroxisomal proliferation was studied in OFA-ICO SD (IOPS Caw) male rats, treated orally for 1 week with 50 mg/kg per day of the test compounds. Compound BR-931 was administered as a reference peroxisomal proliferation drug. Liver homogenates were prepared in 0.25 M sucrose–0.01 M phosphate–0.1% ethyl alcohol buffer, pH 7. The homogenates were diluted with the appropriate incubation buffer in the presence of 0.1% Triton X-100 and centrifuged. The supernatants were used for measuring the following enzymatic activities: catalase,[28] carnitine acetyl transferase,[29] and cyanide insensitive fatty acetyl-CoA oxidizing activity (palmitoyl-CoA oxidation).[30]

Hepatic microsomal induction was studied in OFA-ICO SD (IOPS) Caw male rats treated orally for 5 days with 50 mg/kg per day of the test compounds. Sodium phenobarbital, 75 mg/kg per day, was administered as a reference inducer drug. Liver homogenates were prepared in 1.15% KCl–0.01 M phosphate buffer, pH 7.5; from 9000*g* supernatants of liver homogenates, microsomal fractions were prepared by ultracentrifugation at 105000*g*. The microsomal fractions were used to determine the following parameters: cytochrome P-450,[31] aniline *p*-hydroxylation,[32] aminopyrine N-demethylation,[33] hexobarbital hydroxylation,[34] and proteins.[35] In vitro cholesterol synthesis was determined in liver slices (250 mg) prepared from fed male rats. The slices were incubated in 4 mL of Krebs-Ringer bicarbonate buffer, pH 7.4, containing 4 mM [2-^{14}C]acetate and flushed with 95% O_2–5% CO_2. The compounds were added to a maximal final concentration of 2×10^{-4} M. The rate of [^{14}C]acetate incorporation in CO_2 long-chain fatty acids, neutral lipids, and cholesterol was determined according to published methods.[36,37] The compounds were also tested in vitro, at 4×10^{-4} M, on (hydroxymethyl)glutaryl-coenzyme A reductase activity with a liver microsomal fraction prepared from male rats.[38]

Statistical Analysis. All variables were submitted to analysis of variance,[39] and then Dunnett's test was done to compare control groups with each treated group.[40]

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Registry No. 1, 80930-45-6; **2**, 80929-63-1; **3**, 80929-81-3; **4**, 80930-35-4; **5**, 80930-36-5; **6**, 80929-61-9; **6**·HCl, 80930-18-3; **7**, 80930-38-7; **8**, 80929-66-4; **9**, 80929-68-6; **9**·HCl, 80930-25-2; **10**, 80929-89-1; **10**·HCl, 80928-74-1; 11, 99657-11-1; **12**, 80929-82-4; **12**·HBr, 80929-17-5; **13**, 80930-41-2; **14**, 80930-00-3; **14**·HCl, 80928-88-7; **15**, 85943-22-2; **16**, 85928-36-5; **17**, 85928-38-7; **18**, 85928-41-2; **19**, 99657-12-2; **19**·HCl, 85928-54-7; **20**, 85928-42-3; **21**, 85928-45-6; **22**, 85928-44-5; **23**, 85928-39-8; **24**, 85928-33-2; **25**, 85928-46-7; *trans*-**26**, 85928-47-8; *cis*-**26**, 91515-88-7; **27**, 84391-39-9; **27**·HNO_3, 85928-82-1; **28**, 85928-58-1; **29**, 85928-59-2; **30**, 85928-83-2; **30**·HBr, 85928-73-0; **31**, 85928-61-6; **32**, 85928-76-3; **33**, 85928-77-4; **34**, 85928-64-9; **35**, 85928-66-1; **36**, 99657-13-3; **37**, 85928-68-3; **38**, 85928-70-7; **38**·HCl, 85928-74-1; **39**, 85928-79-6; **40**, 80930-02-5; **41**, 80929-40-4; *cis*-**42**, 99665-38-0; *trans*-**42**, 99657-16-6; *cis*-**43**, 99657-14-4; *trans*-**43**, 99657-17-7; **44**, 85928-71-8; **45**, 89781-59-9; **46**, 91515-82-1; **47**, 99657-15-5; **48**, 99665-53-9; **49**, 86342-66-7; I (Z = O, R = 3-OMe, R′ = H), 66125-08-4; I (Z = O, R = 4-OMe, R′ = H), 80930-46-7; I (Z = O, R = 4-Ph, R′ = H), 99657-18-8; I (Z = O, R = 3-OMe, 4-Br, R′ = H), 99657-19-9; I (Z = O, R = 3-*t*-Bu, 4-Br, R′ = H), 80930-48-9; I (Z = O, R = 3-*t*-Bu, 5-Br, R′ = H), 99657-20-2; I (Z = CH_2, R = H, R = H′), 13672-07-6; I (Z = CH_2, R = 3-OMe, R′ = H), 85928-57-0; I (Z = CH_2, R = 4-OMe, R′ = H), 20933-24-8; I (Z = CH_2, R = 3-NO_2, R′ = H), 3293-67-2; I (Z = CH_2, R = 3-NH_2, R′ = H), 99657-21-3; I (Z = CH_2, R = 3-CO_2H, R′ = H), 89781-53-3; I (Z = CH_2, R = 2-CO_2H, R′ = H), 99657-22-4; I (Z = CH_2, R = 4-Br, R′ = H), 99657-23-5; I (Z = CH_2, R = 3-Ph, R′ = H), 99657-24-6; I (Z = CH_2, R = H, R′ = Me), 99657-25-7; III (R = 4-OMe), 60965-24-4; III (R = 3-CO_2H), 74815-31-9; III (R = 3-Br, 4-OH), 99657-26-8; III (R = 3-CO_2H, 5-Br), 99657-27-9; III (R = 3-Pr, 4-OMe), 99657-28-0; III (R = 3-Pr, 4-OH), 99665-54-0; III (R = H), 2491-36-3; III (R = 3-Cl), 52727-99-8; III (R = 3-Me), 51317-87-4; IV (R = H), 85928-32-1; IV (R = 4-Cl), 80930-53-6; IV (R = 3-Me), 80930-54-7; IV (R = 4-Me), 99657-29-1; IV (R = CO_2H), 91515-98-9; IV (R = 3-Br, 4-OH), 99657-30-4; IV (R = 3-CO_2H, 5-Br), 99657-31-5; IV (R = 3-Pr, 4-OMe), 99657-32-6; IV (R = 3-Pr, 4-OH), 99657-33-7; HCHO, 50-00-0; CH_3CHO, 75-07-0; PrCHO, 123-72-8; PhCHO, 100-52-7; imidazole, 288-32-4; octyl bromide, 111-83-1; 5-bromo-6,7-dihydrobenzo[b]thiophen-4-one, 2513-49-7; nicotinaldehyde, 500-22-1; 2-methylimidazole, 693-98-1; pyrazole, 288-13-1.

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