1-(2,6-Diisopropylphenyl)-3-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8/7-ylalkyl)ureas as Potential Acyl-CoA:Cholesterol Acyltransferase Inhibitors

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As potential hypocholesterolemics were synthesized 3-(7-alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)- (*I*) and 3-[2-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)ethyl]-1-(2,6-diisopropylphenyl)ureas (*II*) from appropriate 8-(aminomethyl) or 7-(aminoethyl) derivatives and 2,6-diisopropylphenyl isocyanate. Similarly were prepared 3-alkyl/aryl/cycloalkyl-3-(7-alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-ureas (*III*) from appropriate 8-(alkyl-/aryl-/cycloalkylaminomethyl)purine-2,6-diones (*X*). The intermediates *X* were prepared starting from a suitable purine-8-carbaldehyde and primary amines *via* corresponding azomethines and their hydrogenation. The disubstituted and trisubstituted ureas *I*—*III* were evaluated for their ability to inhibit *in vitro* the activity of acyl-CoA:cholesterol acyltransferase, the key enzyme of cholesterol esterification.

Hypercholesterolemia is a primary ischemic heart disease risk factor; heart attack is, in turn, the most frequent death cause in developed industrial countries [1]. The cholesterol level can be lowered not only by inhibiting various stages of its biosynthesis in the body, but also by acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors reducing the intestinal absorption of cholesterol, the secretion of VLDL-cholesterol from the liver and cholesterol accumulation through formation of esters with fatty acids in the arterial walls. The ACAT inhibitors can be categorized into two structure types. The first is the group of ureas substituted at one of the urea nitrogens with an aryl rest or with a substituted aralkyl, a long alkyl, cycloalkyl, heteroaryl or with one of the mentioned groupings at each nitrogen [2—4]. The other class of ACAT inhibitors are anilides of aliphatic or alicyclic more carbon-possessing acids [5, 6].

This paper presents results of a study dealing with di- and trisubstituted ureas as hitherto not described potential inhibitors of ACAT, namely 3-(7-alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)ureas *I*, 3-[2-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)-ethyl]-1-(2,6-diisopropylphenyl)urea (*II*), and 3-substituted 3-(7-alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)ureas *III*. The 3-substituent was a C_5—C_8 cycloalkyl, heptyl or 4-fluorophenyl. The 1-aryl substituent in compounds *I*, *II,* and *III* was selected in accordance with a study [7] comparing ureas with variously substituted *N*-aryl groups (2,4-difluorophenyl, 2,6-diisopropylphenyl, 2,4,6-trimethoxyphenyl). The most effective of the above-mentioned compounds were shown to be 1-(2,6-diisopropylphenyl)ureas.

The 1,3-disubstituted ureas *I*—*III* (Table 1) were synthesized from 2,6-diisopropylphenyl isocyanate (*V*) and the respective primary (*IV* and *VI,* Scheme 1) or secondary (*X*, Scheme 2) aminoalkyl purinediones by refluxing in toluene. The secondary amines *X* reacted considerably slower (12—24 h, *IIIi* up to 30 h) than the primary amines *IV*, *VI* (1.5—2 h) as we expected. Attempts to react the isocyanate *V* with amines *IV* and *VI* in lower-boiling solvents (ethyl acetate [8—10], tetrahydrofuran [11], chloroform [12]) failed.

The required primary amines *IVa*—*IVh* were prepared from the corresponding chloromethyl derivatives employing the Gabriel reaction [13], and the 7-(aminoethyl) derivative *VI* from 7-(cyanomethyl)-1,3-dimethyl-7*H*-purine-2,6-dione by hydrogenation [14]. To obtain the secondary amines *X* (Table 2), the 7-alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehydes *VII* were first reacted with cycloalkylamines, heptylamine or 4-fluoroaniline to afford the respective azomethines *IX*; the water formed in this process was removed either by azeotropic distillation with toluene or with calcium sulfate. Azomethines formed in this way were hydrogenated over a palladium catalyst in ethanol to the required secondary amines *X*. The starting carbaldehydes *VII*

Table 1. Characterization of the Compounds *Ia*—*Ig*, *II*, *IIIa*—*IIIi*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p. ℃
Ia	$C_{22}H_{30}N_6O_3$	61.95	7.09	19.70	89	244—246
	426.5	62.16	7.08	19.67		
Ib	$C_{23}H_{32}N_6O_3$	62.71	7.32	19.08	90	226—227
	440.6	62.52	7.49	19.27		
Ic	$C_{24}H_{34}N_6O_3$	63.41	7.54	18.49	40	215—216
	454.6	63.83	7.51	18.36		
Id	$C_{24}H_{32}N_6O_3$	63.70	7.13	18.57	86	220—221
	452.6	63.87	7.09	18.69		
Ie	$C_{25}H_{36}N_6O_3$	64.08	7.74	17.93	79	228—229
	468.6	64.42	7.74	17.84		
If	$C_{28}H_{34}N_6O_3$	66.91	6.82	16.72	63	210—212
	502.6	67.09	6.81	16.69		
Ig	$C_{24}H_{34}N_6O_3$	63.41	7.54	18.49	86	231—233
	454.6	63.73	7.53	18.44		
II	$C_{22}H_{30}N_6O_3$	61.95	7.09	19.70	75	248—249
	426.5	62.16	7.17	19.48		
IIIa	$C_{31}H_{48}N_6O_3$	67.36	8.75	15.20	75	83—86
	552.8	67.29	8.83	15.39		
IIIb	$C_{31}H_{46}N_6O_3$	67.61	8.42	15.26	81	Very thick sirup
	550.7	67.63	8.03	15.39		
IIIc	$C_{32}H_{48}N_6O_3$	68.05	8.57	14.88	77	167—169
	564.8	68.48	8.39	15.08		
IIId	$C_{31}H_{40}N_6O_3$	68.36	7.40	15.43	53	157—160
	544.7	68.74	7.64	15.21		
IIIe	$C_{35}H_{48}N_6O_3$	69.97	8.05	13.99	79	168—170
	600.8	69.46	7.64	14.17		
IIIf	$C_{33}H_{42}N_6O_3$	69.40	7.42	14.70	59	157—159
	570.7	69.46	7.64	14.84		
IIIg	$C_{35}H_{46}N_6O_3$	70.20	7.74	14.00	49	153—155
	598.8	70.65	8.06	13.82		
IIIh	$C_{36}H_{48}N_6O_3$	70.60	7.89	13.70	48	98—101
	612.8	70.92	8.31	13.56		
IIIi	$C_{34}H_{37}FN_6O_3$	68.44	6.25	14.10	56	100—103
	596.7	68.60	6.51	13.82		

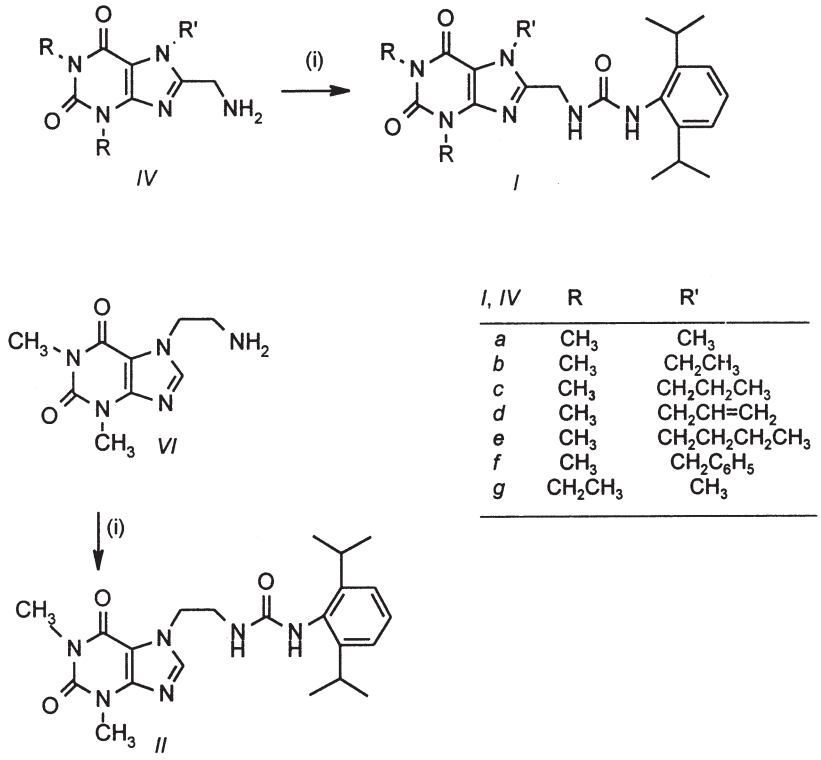
were produced by oxidation of 7-alkyl-1,3-dimethyl-8-(hydroxymethyl)-3,7-dihydropurine-2,6-diones [13] with manganese dioxide in dioxane at elevated temperature, or alternatively, in dichloromethane at room temperature.

Structures of the final ureas *I*—*III*, azomethines *IXa*—*IXi,* and secondary amines *Xa*—*Xi* were first corroborated by appearance of molecular ion-radical peaks in their mass spectra. The ^{1}H NMR spectra of ureas *I*—*III* showed characteristic signals of methyl groups of the 2,6-diisopropylphenyl grouping as follows: for compounds *Ia*—*Ig*, two singlets at $\delta = 1.14$—1.18; for *II* at $\delta = 1.13$—1.16; for *IIIa*—*IIIc* and *IIIe*—*IIIh* at $\delta = 1.17$—1.26; for *N*-isopropyl derivative *IIId* and *N*-(fluorophenyl) derivative *IIIi* at $\delta = 1.09$, 1.11 and 1.12, 1.15, respectively. Similarly, azomethines *IXa*—*IXh* revealed indicative signals of a CH═N— group at $\delta = 8.25$—8.35 and for *IXi* up to 8.54. Secondary ammonium chlorides *Xa*—*Xh* showed characteristic signals of C-8-CH_2 and N^+H groups at $\delta = 4.44$—4.54 and 9.30—9.73, respectively. The ^{1}H NMR and mass spectrum of secondary amine *Xi* was measured as a base (C-8-CH_2 at $\delta = 4.55$).

At the determination of the inhibition of ACAT disubstituted ureas *I* and *II* were less effective than trisubstituted ureas *III* (Table 3). The most active trisubstituted compounds were *IIIg* and *IIIh* with cycloheptyl and cyclooctyl substituent. Unfortunately no urea under investigation showed greater activity than reference substances.

EXPERIMENTAL

Primary amines, palladium catalyst, 2,6-diisopropylphenyl isocyanate, and activated manganese dioxide were commercial products (Acros, Avocado, Merck—Schuchardt). The ACAT inhibitors DUP-128 (duPont—Merck) and CI-976 (Parke—Davis) were



I, IV	R	R'
a	CH_3	CH_3
b	CH_3	CH_2CH_3
c	CH_3	$CH_2CH_2CH_3$
d	CH_3	$CH_2CH{=}CH_2$
e	CH_3	$CH_2CH_2CH_2CH_3$
f	CH_3	$CH_2C_6H_5$
g	CH_2CH_3	CH_3

Scheme 1

reference substances. All solvents were purified and dried in accordance with common procedures.

Melting points were determined on a Boetius micro hot-stage. The NMR spectra measured with a Bruker AM-300 (300 MHz for ^{1}H) apparatus were recorded at 25 °C in deuterochloroform (compounds *I*—*III*, *VII*) or hexadeuterodimethyl sulfoxide (compounds *IX*, *X*), tetramethylsilane being the internal reference. Chemical shifts are reported in δ-scale. The electron-impact mass spectra were taken with a Finigan MAT SSQ 710 instrument by ionization technique (100—210 °C, 70 eV) and are presented as m/z (relative intensity I_r in %). The reaction course and purity of all products were monitored by TLC (Silufol $UV_{254,366}$, Kavalier, Votice, Czech Republic) in chloroform—methanol (φ_r = 9:1 or 10:0.4). Column chromatography was performed on silica gel (40—100 μm) in ethyl acetate—cyclohexane (φ_r = 1:1).

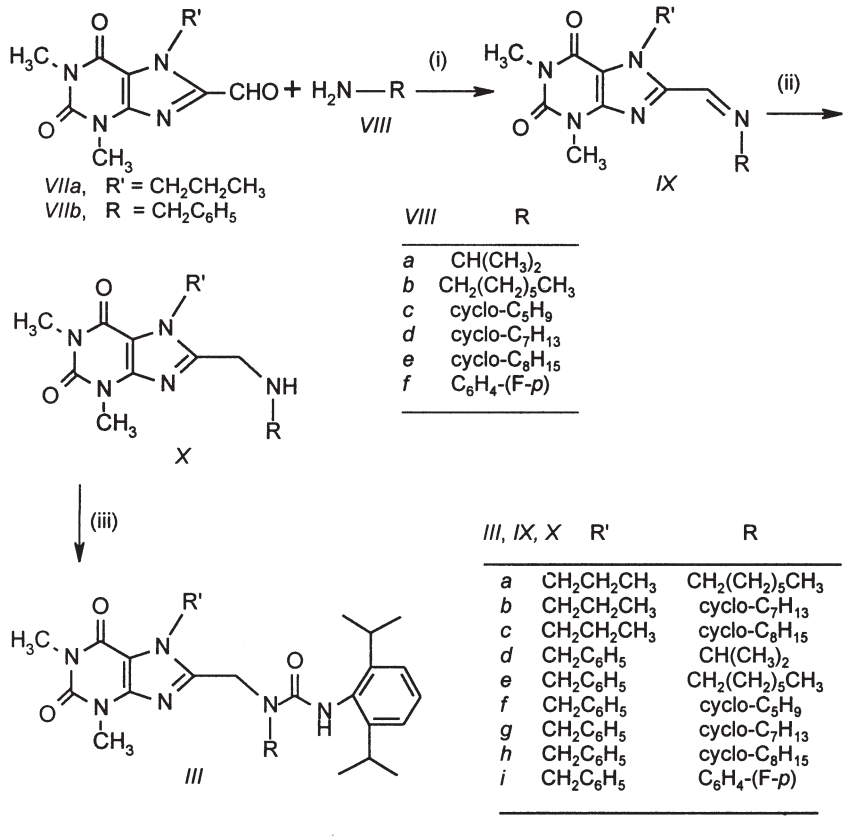
1,3-Dimethyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehyde (*VIIa*)

A mixture of 8-(hydroxymethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione [13] (12.7 g; 50 mmol) and activated manganese dioxide (49.0 g) in dry dioxane (400 cm^3) was heated and stirred at 80 °C for 4.5 h. Manganese oxides were filtered off, washed with hot dioxane (2 × 150 cm^3) and the filtrate was evaporated under reduced pressure. The distillation residue was crystallized from ethyl acetate (60 cm^3). Yield 8.5 g (68 %), m.p. = 134—136 °C. ^{1}H NMR spectrum, δ: 0.96 (t, 3H, $CH_2CH_2C\underline{H}_3$), 1.87 (sextet, 2H, $CH_2C\underline{H}_2CH_3$), 3.44 (s, 3H, N-1-CH_3), 3.63 (s, 3H, N-3-CH_3), 4.77 (t, 2H, $C\underline{H}_2CH_2CH_3$), 9.92 (s, 1H, CH=O). EI MS, m/z (I_r/%): 250 ($M^{+\bullet}$, 89), 235 (10), 221 (32), 207 (85), 194 (9), 180 (10), 164 (10), 151 (100), 136 (32), 123 (29).

7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehyde (*VIIb*)

Method A: The title product was obtained analogously to *VIIa*, starting from 7-benzyl-8-(hydroxymethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione [13] (15.1 g; 50 mmol), in 67 % yield.

Method B: A mixture of 7-benzyl-8-(hydroxymethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (9.1 g; 30 mmol) and activated manganese dioxide (49.0 g) in dichloromethane (320 cm^3) was stirred at room temperature for 18 h. Manganese oxides were removed by filtration, the filtrate was adsorbed on a short silica gel (10 g) column and eluted with chloroform. The solvent from the eluate was distilled off under diminished pressure and the residue was crystallized from methanol in the presence of charcoal. Yield



VIII	R
a	$CH(CH_3)_2$
b	$CH_2(CH_2)_5CH_3$
c	cyclo-C_5H_9
d	cyclo-C_7H_{13}
e	cyclo-C_8H_{15}
f	C_6H_4-(F-*p*)

III, IX, X	R'	R
a	$CH_2CH_2CH_3$	$CH_2(CH_2)_5CH_3$
b	$CH_2CH_2CH_3$	cyclo-C_7H_{13}
c	$CH_2CH_2CH_3$	cyclo-C_8H_{15}
d	$CH_2C_6H_5$	$CH(CH_3)_2$
e	$CH_2C_6H_5$	$CH_2(CH_2)_5CH_3$
f	$CH_2C_6H_5$	cyclo-C_5H_9
g	$CH_2C_6H_5$	cyclo-C_7H_{13}
h	$CH_2C_6H_5$	cyclo-C_8H_{15}
i	$CH_2C_6H_5$	C_6H_4-(F-*p*)

(i) (*A*) toluene, 120 °C, azeotropic distillation or (*B*) DME, anhydrous $CaSO_4$, reflux;
(ii) H_2-Pd/C, ethanol, r.t.;
(iii) 2,6-diisopropylphenyl isocyanate (*V*), toluene, reflux.

Scheme 2

6.4 g (72 %), m.p. = 141—143 °C (Ref. [17] gives m.p. = 142—143 °C).

7-Alkyl-8-(alkyl-/cycloalkyl-/arylimino-methyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-diones *IXa*—*IXi*

Method A: From a stirred solution of carbaldehyde *VIIa* or *VIIb* (3.0 mmol) and primary amine *VIIIb*—*VIIIf* (3.3—3.9 mmol) water was removed by azeotropic distillation with toluene for 15—30 h. The solvent was then distilled off under reduced pressure and the solid residue was crystallized from an appropriate solvent: *IXa*, *IXb*, *IXe*, *IXg*, *IXh* from tetrahydrofuran—isohexane, *IXc* from toluene—isohexane, *IXf* from toluene—diethyl ether, and *IXi* from ethanol—diethyl ether.

Method B: A stirred solution of carbaldehyde *VIIa* or *VIIb* (3.0 mmol), primary amine *VIIIb*—*VIIIf* (4.5 mmol), and anhydrous calcium sulfate (0.612 g; 4.5 mmol) in 1,2-dimethoxyethane (25 cm^3) was refluxed for 6—13 h. Calcium sulfate was removed from the hot solution and the latter was evaporated *in vacuo*. The solid distillation residue was crystallized from a mixture of suitable solvents: *IXb*, *IXc* from tetrahydrofuran—isohexane, *IXe*, *IXf* from 1,2-dimethoxyethane—isohexane, *IXa* from diethyl ether—isohexane, *IXg* from toluene—diethyl ether, *IXh* from ethanol—diethyl ether.

The (isopropylimino)methyl derivative *IXd* was synthesized from aldehyde *VIIb* (3 mmol) and anhydrous isopropylamine (*VIIIa*, 30 mmol) in 1,2-dimethoxyethane (30 cm^3). The product was crystallized from tetrahydrofuran—isohexane.

^{1}H NMR spectra of compounds prepared by methods *A* and *B* are identical. The following compounds were synthesized (their melting points, elemental analyses, and yields are given in Table 2):

8-(Heptyliminomethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXa*): ^{1}H NMR spectrum, δ: 0.82, 0.86 (2 × t, 6H, $CH_2CH_2C\underline{H}_3$ and $(CH_2)_6C\underline{H}_3$), 1.23—1.28 (m, 8H, $CH_2(C\underline{H}_2)_4CH_2CH_3$),

Table 2. Characterization of the Intermediates *IXa*—*IXi* and *Xa*—*Xi*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield % (Method)	M.p. °C
IXa	$C_{18}H_{29}N_5O_2$	62.22	8.41	20.16	50 (*A*)	60—62
	347.5	62.49	8.23	20.39	73 (*B*)	
IXb	$C_{18}H_{27}N_5O_2$	62.58	7.88	20.27	79 (*A*)	112—114
	345.4	62.85	7.83	20.63	46 (*B*)	
IXc	$C_{19}H_{29}N_5O_2$	63.48	8.13	19.48	62 (*A*)	78—80
	359.5	63.26	8.23	19.48	35 (*B*)	
IXd	$C_{18}H_{21}N_5O_2$	63.70	6.24	20.64	61 (*B*)	136—137
	339.4	63.52	6.30	20.48		
IXe	$C_{22}H_{29}N_5O_2$	66.81	7.39	17.71	73 (*A*)	98—99
	395.5	66.53	7.24	17.99	75 (*B*)	
IXf	$C_{20}H_{23}N_5O_2$	65.73	6.34	19.16	81 (*A*)	134—135
	365.4	65.87	6.37	18.95	73 (*B*)	
IXg	$C_{22}H_{27}N_5O_2$	67.15	6.92	17.80	86 (*A*)	170—171
	393.5	67.41	6.96	17.58	82 (*B*)	
IXh	$C_{23}H_{29}N_5O_2$	67.79	7.17	17.19	91 (*A*)	171—173
	407.5	67.59	7.25	16.96	68 (*B*)	
IXi	$C_{21}H_{18}FN_5O_2$	64.44	4.64	17.89	90 (*A*)	178—179
	391.4	64.44	4.68	17.56		
Xa	$C_{18}H_{32}ClN_5O_2$	56.02	8.36	18.15	46	180—183
	385.9	56.33	8.33	18.13		
Xb	$C_{18}H_{30}ClN_5O_2$	56.31	7.88	18.24	88	233—236
	383.9	56.75	7.90	18.02		
Xc	$C_{19}H_{32}ClN_5O_2$	57.35	8.11	17.60	84	231—234
	397.9	57.43	8.21	17.95		
Xd	$C_{18}H_{24}ClN_5O_2$	57.21	6.40	18.53	42	213—216
	377.9	57.55	6.56	18.15		
Xe	$C_{22}H_{32}ClN_5O_2$	60.89	7.43	16.14	66	185—188
	434.0	60.46	7.52	16.24		
Xf	$C_{20}H_{26}ClN_5O_2$	59.47	6.49	17.34	75	217—219
	403.9	59.76	6.59	17.53		
Xg	$C_{22}H_{30}ClN_5O_2$	61.17	7.00	16.21	60	231—234
	432.0	61.30	7.05	16.26		
Xh	$C_{23}H_{32}ClN_5O_2$	61.94	7.23	15.70	78	233—236
	445.99	61.75	7.25	15.41		
Xi	$C_{21}H_{21}ClFN_5O_2$	58.70	4.29	16.30	61	186—188
	429.88	58.62	5.23	16.45		

1.64 (m, 2H, $(CH_2)_5C\underline{H}_2CH_3$), 1.76 (sextet, 2H, $CH_2C\underline{H}_2CH_3$), 3.35 (s, 3H, N-1-CH_3), 3.53 (s, 3H, N-3-CH_3), 3.59 (t, 2H, $C\underline{H}_2CH_2CH_3$), 4.72 (t, 2H, =N—CH_2), 8.25 (s, 1H, CH=N). EI MS, m/z (I_r/%): 347 ($M^{+\bullet}$, 100), 332 (6), 318 (50), 302 (36), 291 (74), 276 (70), 262 (17), 249 (50), 234 (47), 220 (38), 194 (56), 112 (22).

8-(Cycloheptyliminomethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXb*): ^{1}H NMR spectrum, δ: 0.94 (t, 3H, $CH_2CH_2C\underline{H}_3$), 1.6—1.85 (m, 14H, $(C\underline{H}_2)_6$ and $CH_2C\underline{H}_2CH_3$), 3.42 (s, 3H, N-1-CH_3), 3.44 (quintet, 1H, CH in cycloheptyl), 3.60 (s, 3H, N-3-CH_3), 4.82 (t, 2H, $C\underline{H}_2CH_2CH_3$), 8.29 (s, 1H, CH=N). EI MS, m/z (I_r/%): 345 ($M^{+\bullet}$, 100), 316 (10), 302 (26), 285 (13), 248 (21), 235 (28), 220 (13), 193 (23), 122 (8), 110 (19).

8-(Cyclooctyliminomethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXc*): ^{1}H NMR spectrum, δ: 0.93 (t, 3H, $CH_2CH_2C\underline{H}_3$), 1.61—1.87 (m, 16H, $(C\underline{H}_2)_7$ and $CH_2C\underline{H}_2CH_3$), 3.42 (s, 3H, N-1-CH_3), 3.47 (quintet, 1H, CH in cyclooctyl), 3.59 (s, 3H, N-3-CH_3), 4.81 (t, 2H, $C\underline{H}_2CH_2CH_3$), 8.29 (s, 1H, CH=N). EI MS, m/z (I_r/%): 359 ($M^{+\bullet}$, 100), 316 (41), 302 (7), 276 (6), 248 (20), 235 (36), 207 (17), 193 (24), 150 (6), 136 (7), 124 (23).

7-Benzyl-8-(isopropyliminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXd*): ^{1}H NMR spectrum, δ: 1.23, 1.25 (2 × s, 6H, $CH(C\underline{H}_3)_2$), 3.41 (s, m, 4H, N-1-CH_3 and $C\underline{H}(CH_3)_2$), 3.60 (s, 3H, N-3-CH_3), 6.15 (s, 2H, CH_2Ph), 7.23—7.35 (m, 5H, H_{arom}), 8.35 (s, 1H, CH=N). EI MS, m/z (I_r/%): 339 ($M^{+\bullet}$, 98), 296 (66), 262 (21), 248 (49), 231 (66),

Table 3. ACAT Inhibition *in vivo*

Compound	Inhibition fraction/% at the concentration			
	20 μmol dm^{-3}	2 μmol dm^{-3}	2 μmol dm^{-3}	0.2 μmol dm^{-3}
	Rat liver ACAT		Rabbit intestinal ACAT	
Ia	44	–	0	–
Ib	67	7	0	–
Ic	84	42	40	–
Id	85	43	40	–
Ie	66	45	50	–
If	76	56	44	–
Ig	60	21	46	–
II	48	–	46	–
IIIa	–	30	–	27
IIIb	–	39	–	20
IIIc	–	35	–	15
IIId	–	0	–	–
IIIe	–	42	–	35
IIIf	–	14	–	11
IIIg	–	59	–	16
IIIh	–	62	–	17
IIIi	–	6	–	–
DuP-128	–	77	67	–
CI-976	–	70	62	–

91 (100).

7-Benzyl-8-(heptyliminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXe*): ^{1}H NMR spectrum, δ: 0.88 (t, 3H, $CH_2(CH_2)_5C\underline{H}_3$), 1.26, 1.66 (2 × m, 2H, 8H, =CH($C\underline{H}_2)_4C\underline{H}_2CH_3$), 3.41 (s, 3H, N-1-$CH_3$), 3.60 (s, 3H, N-3-$CH_3$), 3.64 (t, 2H, =N—$CH_2$), 6.13 (s, 2H, $PhCH_2$), 7.27—7.30 (m, 5H, H_{arom}), 8.33 (s, 1H, =CH—). EI MS, m/z (I_r/%): 395 ($M^{+\bullet}$, 100), 318 (13), 304 (83), 296 (12), 281 (17), 220 (9), 202 (8), 181 (17).

7-Benzyl-8-(cyclopentyliminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXf*): ^{1}H NMR spectrum, δ: 1.68—1.88 (m, 8H, $(CH_2)_4$), 3.42 (s, 3H, N-1-CH_3), 3.61 (s, 3H, N-3-CH_3), 3.78 (quintet, 1H, CH in cyclopentyl), 6.15 (s, 2H, CH_2Ph), 7.26—7.29 (m, 5H, H_{arom}), 8.34 (s, 1H, CH=N). EI MS, m/z (I_r/%): 365 ($M^{+\bullet}$, 70), 296 (28), 274 (100), 257 (5), 220 (10), 193 (5), 161 (2), 117 (3).

7-Benzyl-8-(cycloheptyliminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXg*): ^{1}H NMR spectrum, δ: 1.55—1.72 (m, 12H, $(CH_2)_6$), 3.38 (s, m, 4H, N-1-CH_3 and CH in cycloheptyl), 3.57 (s, 3H, N-3-CH_3), 6.13 (s, 2H, CH_2Ph), 7.22—7.26 (m, 5H, H_{arom}), 8.28 (s, 1H, CH=N). EI MS, m/z (I_r/%): 393 ($M^{+\bullet}$, 72), 316 (7), 302 (100), 296 (32), 285 (53), 281 (15), 245 (7), 220 (11), 193 (11).

7-Benzyl-8-(cyclooctyliminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXh*): ^{1}H NMR spectrum, δ: 1.50—1.75 (m, 14H, $(CH_2)_7$), 3.36 (quintet, 1H, CH in cyclooctet), 3.38 (s, 3H, N-1-CH_3), 3.57 (s, 3H, N-3-CH_3), 6.12 (s, 2H, CH_2Ph), 7.20—7.26 (m, 5H, H_{arom}), 8.30 (s, 1H, CH=N). EI MS, m/z (I_r/%): 407 ($M^{+\bullet}$, 49), 316 (100), 299 (25), 296 (20), 281 (10), 239 (3), 220 (4), 193 (8).

7-Benzyl-8-[(4-fluorophenyl)iminomethyl]-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (*IXi*): ^{1}H NMR spectrum, δ: 3.43 (s, 3H, N-1-CH_3), 3.63 (s, 3H, N-3-CH_3), 6.26 (s, 2H, CH_2Ph), 7.07—7.36 (m, 9H, H_{arom}), 8.54 (s, 1H, =CH—). EI MS, m/z (I_r/%): 391 ($M^{+\bullet}$, 95), 314 (11), 305 (6), 281 (57), 270 (16), 211 (10), 185 (21), 91 (100).

7-Alkyl-8-(alkyl-/aryl-/cycloalkylaminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-diones *Xa*—*Xi*

Azomethine *IX* (2.7 mmol) in ethanol (100 cm^3) was shaken with palladium over charcoal (30 mg, 10 %) in hydrogen atmosphere for 5—8 h. After the hydrogenation was finished, the catalyst was filtered off and the filtrate was evaporated to dryness under diminished pressure. The crude base of the secondary amine was found to be sufficiently pure for the synthesis of ureas *III*. For analytical purposes the base was crystallized from dry ethanol (*Xi*), or dissolved in anhydrous ethanol to which 5 % hydrogen chloride-containing anhydrous ethanol was added; the volatiles were removed *in vacuo* and the solid chloride was crystallized from suitable dry solvents: *Xb*—*Xh* from ethanol—diethyl ether, *Xa* from ethanol—isohexane. Yields relate to analytically pure compounds. The following compounds were obtained (their melting points, elemental analyses, and yields are given in Table 2).

8-(Heptylaminomethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xa*): ^{1}H NMR spectrum, δ: 0.97 (t, 6H, $CH_2CH_2C\underline{H}_3$ and $(CH_2)_6C\underline{H}_3$), 1.38 (m, 8H, $CH_2(C\underline{H}_2)_4CH_2CH_3$),

1.83 (m, 4H, $CH_2C\underline{H}_2CH_3$ and $CH_2(CH_2)_4C\underline{H}_2CH_3$), 3.14 (m, 2H, $C\underline{H}_2(CH_2)_4CH_2CH_3$), 3.34 (s, 3H, N-1-$CH_3$), 3.56 (s, 3H, N-3-$CH_3$), 4.38 (t, 2H, $C\underline{H}_2CH_2CH_3$), 4.54 (s, 2H, 8-CH_2), 9.58 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 349 ($M^{+\bullet}$, 5), 262 (6), 250 (7), 236 (100), 221 (14), 208 (10), 194 (96), 137 (10), 114 (11).

8-(Cycloheptylaminomethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xb*): ^{1}H NMR spectrum, δ: 0.96 (t, 3H, $CH_2CH_2C\underline{H}_3$), 1.58—1.82 (m, 12H, $(CH_2)_6$), 2.18 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.34 (s, 3H, N-1-CH_3), 3.46 (m, 1H, CH in cycloheptyl), 3.56 (s, 3H, N-3-CH_3), 4.35 (t, 2H, $C\underline{H}_2CH_2CH_3$), 4.53 (s, 2H, 8-CH_2), 9.30 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 347 ($M^{+\bullet}$, 2), 304 (2), 276 (5), 250 (4), 235 (91), 221 (12), 194 (100), 137 (9), 112 (87).

8-(Cyclooctylaminomethyl)-1,3-dimethyl-7-propyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xc*): ^{1}H NMR spectrum, δ: 0.98 (t, 3H, $CH_2CH_2C\underline{H}_3$ in propyl), 1.56—1.65, 1.83—1.90 (2 × m, 14H, $(CH_2)_7$), 2.12 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.34 (s, 3H, N-1-CH_3), 3.51 (m, 1H, CH in cyclooctyl), 3.56 (s, 3H, N-3-CH_3), 4.41 (t, 2H, $C\underline{H}_2CH_2CH_3$), 4.53 (s, 2H, 8-CH_2), 9.57 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 362 (M + 1; 14), 236 (34), 237 (39), 126 (100).

7-Benzyl-8-(isopropylaminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xd*): ^{1}H NMR spectrum, δ: 1.37 (d, 6H, $CH(C\underline{H}_3)_2$), 2.83 (m, 1H, $C\underline{H}(CH_3)_2$), 3.34 (s, 3H, N-1-CH_3), 3.59 (s, 3H, N-3-CH_3), 4.48 (s, 2H, 8-CH_2), 5.78 (s, 2H, CH_2Ph), 7.33—7.43 (m, 5H, H_{arom}), 9.42 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 341 ($M^{+\bullet}$, 2), 284 (100), 208 (2), 193 (44), 136 (4), 116 (2), 91 (50).

7-Benzyl-8-(heptylaminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xe*): ^{1}H NMR spectrum, δ: 0.97 (t, 3H, $(CH_2)_6C\underline{H}_3$), 1.36, 1.73 (2 × m, 10H, $(CH_2)_5$), 3.08 (m, 2H, $C\underline{H}_2(CH_2)_5CH_3$), 3.34 (s, 3H, N-1-$CH_3$), 3.58 (s, 3H, N-3-$CH_3$), 4.48 (s, 2H, 8-$CH_2$), 5.77 (s, 2H, CH_2Ph), 7.32—7.42 (m, 5H, H_{arom}), 9.57 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 398 (M + 1; 4), 306 (4), 284 (100), 281 (6), 193 (45), 136 (3), 114 (16), 91 (38).

7-Benzyl-8-(cyclopentylaminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xf*): ^{1}H NMR spectrum, δ: 1.62—1.79 (m, 8H, $(CH_2)_4$), 3.35 (s, 3H, N-1-CH_3), 3.59 (s, 3H, N-3-CH_3), 3.69 (quintet, 1H, CH in cyclopentyl), 4.45 (s, 2H, 8-CH_2), 5.80 (s, 2H, CH_2Ph), 7.32—7.47 (m, 5H, H_{arom}), 9.73 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 368 (M + 1; 3), 284 (100), 193 (82), 136 (5).

7-Benzyl-8-(cycloheptylaminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xg*): ^{1}H NMR spectrum, δ: 1.53—1.76 (m, 12H, $(CH_2)_6$), 3.30 (s, 3H, N-1-CH_3), 3.41 (s, 1H, CH in cycloheptyl), 3.58 (s, 3H, N-3-CH_3), 4.45 (s, 2H, 8-CH_2), 5.80 (s, 2H, CH_2Ph), 7.32—7.49 (m, 5H, H_{arom}), 9.62 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 395 ($M^{+\bullet}$, 2 %), 304 (5), 284 (88), 232 (3), 208 (2), 193 (53), 136 (6), 112 (70), 91 (100).

7-Benzyl-8-(cyclooctylaminomethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrochloride (*Xh*): ^{1}H NMR spectrum, δ: 1.58—1.86 (m, 14H, $(CH_2)_7$), 2.06 (m, 1H, CH in cyclooctyl), 3.33 (s, 3H, N-1-CH_3), 3.57 (s, 3H, N-3-CH_3), 4.44 (s, 2H, 8-CH_2), 5.80 (s, 2H, CH_2Ph), 7.32—7.47 (m, 5H, H_{arom}), 9.53 (bs, 1H, N^+H). EI MS, m/z (I_r/%): 318 (67; M − $PhCH_2$), 284 (24), 234 (16), 208 (52), 193 (97), 126 (100).

7-Benzyl-8-[(4-fluorophenylamino)methyl]-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (as base) (*Xi*): ^{1}H NMR spectrum, δ: 3.31 (s, 3H, N-1-CH_3), 3.54 (s, 3H, N-3-CH_3), 4.55 (s, 2H, 8-CH_2), 5.76 (s, 2H, CH_2Ph), 6.70, 6.99 (2 × m, 4H, H_{arom} in fluorophenyl), 7.29—7.45 (m, 5H, H_{arom} in benzyl). EI MS, m/z (I_r/%): 393 ($M^{+\bullet}$, 100), 302 (6), 283 (79), 181 (5), 124 (4), 122 (4), 91 (87). For elemental analysis was prepared *Xi*.HCl.

3-(7-Alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)ureas *Ia*—*Ig*

A stirred mixture of 8-(aminomethyl) derivative *IV* (5 mmol), toluene (33 cm^3), and 2,6-diisopropylphenyl isocyanate (*V*, 5.4 mmol, 1.23 g, 90 %, 1.29 cm^3) was refluxed for 1.5—2 h. The mixture dissolved and, after 5—10 min, the product separated. The mixture was left standing at room temperature overnight, the product was filtered off, dried under reduced pressure and crystallized from ethanol. The following compounds were prepared (their melting points, elemental analyses, and yields are given in Table 1):

1-(2,6-Diisopropylphenyl)-3-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)urea (*Ia*): ^{1}H NMR spectrum, δ: 1.14, 1.16 (2s, 12H, 2 × $(C\underline{H}_3)_2CH$), 3.22 (septet, 2H, 2 × $(CH_3)_2C\underline{H}$), 3.38 (s, 3H, N-1-CH_3), 3.44 (s, 3H, N-3-CH_3), 4.03 (s, 3H, N-7-CH_3), 4.47 (d, 2H, $C\underline{H}_2NH$), 4.95 (bs, 1H, $CH_2N\underline{H}$), 6.03 (bs, 1H, CO—NH), 7.19—7.38 (m, 3H, H_{arom}). EI MS, m/z (I_r/%): 426 ($M^{+\bullet}$, 94), 408 (7), 249 (42), 223 (100), 207 (80), 195 (49), 162 (22), 150 (17), 146 (8).

1-(2,6-Diisopropylphenyl)-3-(7-ethyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-urea (*Ib*): ^{1}H NMR spectrum, δ: 1.15, 1.17 (2s, 12H, 2 × $(C\underline{H}_3)_2CH$), 1.43(t, 3H, $CH_2C\underline{H}_3$), 3.22 (septet, 2H, 2 × $(CH_3)_2C\underline{H}$), 3.39 (s, 3H, N-1-CH_3), 3.44 (s, 3H, N-3-CH_3), 4.45 (d, 2H, $C\underline{H}_2CH_3$), 4.48 (d, 2H, $C\underline{H}_2NH$), 5.02 (bs, 1H, $CH_2N\underline{H}$), 5.98 (bs, 1H, CO—NH), 7.19—7.38 (m, 3H, H_{arom}). EI MS, m/z (I_r/%): 440 ($M^{+\bullet}$, 100), 422 (7), 397 (4), 264 (11), 237 (69), 221 (10), 208 (63), 193 (42), 177 (18), 162 (17), 151 (5).

1-(2,6-Diisopropylphenyl)-3-(1,3-dimethyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-urea (*Ic*): ^{1}H NMR spectrum, δ: 0.96 (t, 3H, CH_2CH_2-

C$\underline{H}_3$), 1.15, 1.17 (2s, 12H, 2 × (C$\underline{H}_3$)$_2$CH), 1.83 (sextet, 2H, CH$_2$C$\underline{H}_2$CH$_3$), 3.23 (septet, 2H, (CH$_3$)$_2$C$\underline{H}$), 3.39 (s, 3H, N-1-CH$_3$), 3.43 (s, 3H, N-3-CH$_3$), 4.35 (t, 2H, C$\underline{H}_2$CH$_2$CH$_3$), 4.47 (d, 2H, C$\underline{H}_2$NH), 4.98 (bs, 1H, CH$_2$N$\underline{H}$), 5.94 (bs, 1H, CO—NH), 7.20—7.38 (m, 3H, H$_{arom}$). EI MS, m/z (I_r/%): 454 (M$^{+\bullet}$, 100), 437 (4), 411(4), 278 (9), 251 (84), 235 (52), 208 (54), 193 (50), 188 (52), 177 (54), 162 (52), 146 (17).

3-(7-Allyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-urea (*Id*): ^{1}H NMR spectrum, δ: 1.15, 1.18 (2s, 12H, 2 × (C$\underline{H}_3$)$_2$CH), 3.23 (septet, 2H, 2 × (CH$_3$)$_2$C$\underline{H}$), 3.39 (s, 3H, N-1-CH$_3$), 3.45 (s, 3H, N-3-CH$_3$), 44.43 (d, 2H, C$\underline{H}_2$NH), 5.05 (d, 1H, CH$_{trans}$), 5.12 (d, 2H, C$\underline{H}_2$CH═CH$_2$), 5.19 (d, 1H, CH$_{cis}$), 5.98 (m, 1H, —CH═), 6.27 (bs, 1H, CO—NH), 7.20—7.38 (m, 3H, H$_{arom}$). EI MS, m/z (I_r/%): 452 (M$^{+\bullet}$, 61), 411 (3), 276 (4), 249 (19), 232 (28), 208 (100), 193 (8), 177 (8), 162 (13), 146 (6).

3-(7-Butyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-urea (*Ie*): ^{1}H NMR spectrum, δ: 0.95 (t, 3H, (CH$_2$)$_3$-C$\underline{H}_3$), 1.15, 1.17 (2s, 12H, 2 × (C$\underline{H}_3$)$_2$CH), 1.38 (sextet, 2H, (CH$_2$)$_2$C$\underline{H}_2$CH$_3$), 1.77 (quintet, 2H, CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 3.23 (septet, 2H, (CH$_3$)$_2$C$\underline{H}$), 3.39 (s, 3H, N-1-CH$_3$), 3.42 (s, 3H, N-3-CH$_3$), 4.38 (t, 2H, C$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 4.47 (d, 2H, C$\underline{H}_2$NH), 5.01 (bs, 1H, CO—NH), 7.20—7.37 (m, 3H, H$_{arom}$). EI MS, m/z (I_r/%): 468 (M$^{+\bullet}$, 100), 450 (2), 425 (3), 394 (2), 291 (13), 265 (41), 235 (25), 208 (17), 193 (9).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-urea (*If*): ^{1}H NMR spectrum, δ: 1.14, 1.16 (2s, 12H, 2 × (C$\underline{H}_3$)$_2$CH), 3.21 (septet, 2H, (CH$_3$)$_2$C$\underline{H}$), 3.40 (s, 3H, N-1-CH$_3$), 3.45 (s, 3H, N-3-CH$_3$), 4.39 (d, 2H, C$\underline{H}_2$NH), 5.00 (bs, 1H, CH$_2$N$\underline{H}$), 5.73 (s, 2H, CH$_2$Ph), 6.02 (s, 1H, CO—NH), 7.19—7.35 (m, 8H, H$_{arom}$). EI MS, m/z (I_r/%): 502 (M$^{+\bullet}$, 21), 411(5), 299 (32), 282 (51), 208 (84), 188 (78), 162 (41), 146 (38), 117 (44), 91 (100).

3-(1,3-Diethyl-7-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-urea (*Ig*): ^{1}H NMR spectrum, δ: 1.15, 1.17 (2s, 12H, 2 × (C$\underline{H}_3$)$_2$CH), 1.19—1.25 (m, 6H, 2 × N—CH$_2$C$\underline{H}_3$), 3.21 (septet, 2H, (CH$_3$)$_2$C$\underline{H}$), 3.95—4.08 (m, 4H, 2 × N—C$\underline{H}_2$CH$_3$), 4.02 (s, 3H, N-7-CH$_3$), 4.46 (d, 2H, C$\underline{H}_2$NH), 5.00 (bs, 1H, CH$_2$N$\underline{H}$), 6.29 (bs, 1H, CO—NH), 7.17—7.32 (m, 3H, H$_{arom}$). EI MS, m/z (I_r/%): 454 (M$^{+\bullet}$, 100), 436 (6), 411 (5), 278 (10), 251 (76), 235 (39), 223 (17), 188 (10), 162 (12).

1-(2,6-Diisopropylphenyl)-3-[2-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-7-yl)-ethyl]urea *(II)*

The title product was obtained analogously to compounds *I*, starting from 7-(2-aminoethyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione [14] (1.12 g; 5 mmol) (melting point, elemental analysis, and yield are given in Table 1). ^{1}H NMR spectrum, δ: 1.13, 1.16 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 3.16 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.31 (s, 3H, N-1-CH$_3$), 3.55 (s, 3H, N-3-CH$_3$), 3.60, 4.43 (2t, 4H, CH$_2$CH$_2$), 4.52 (bs, 1H, CH$_2$N$\underline{H}$), 5.92 (bs, 1H, CO—NH), 7.15—7.33 (m, 3H, H$_{arom}$), 7.55 (s, 1H, H-8). EI MS, m/z (I_r/%): 427 (M − 1, 100), 426 (M$^{+\bullet}$, 90), 383 (13), 250 (42), 224 (22), 203 (86), 177 (71), 162 (43).

3-Alkyl/aryl/cycloalkyl-3-(7-alkyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-ureas *IIIa—IIIi*

A mixture of secondary amine *X* (4 mmol), toluene (33 cm^3), and 2,6-diisopropylphenyl isocyanate (*V*, 6 mmol, 1.36 g, 90 %, 1.43 cm^3) was stirred and refluxed for 12—24 h. The solvent was evaporated under diminished pressure and the residue was purified by column chromatography. The following compounds were synthesized (their melting points, elemental analyses, and yields are given in Table 1):

1-(2,6-Diisopropylphenyl)-3-(1,3-dimethyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-3-heptylurea (*IIIa*): ^{1}H NMR spectrum, δ: 0.88, 0.93 (2t, 6H, CH$_2$CH$_2$C$\underline{H}_3$ and (CH$_2$)$_6$C$\underline{H}_3$), 1.19 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_3$), 1.37 (m, 10H, CH$_2$(C$\underline{H}_2$)$_5$CH$_3$), 1.81 (sextet, 2H, CH$_2$C$\underline{H}_2$CH$_3$), 3.07 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.41 (s, 3H, N-1-CH$_3$), 3.44 (t, 2H, C$\underline{H}_2$(CH$_2$)$_5$CH$_3$), 3.58 (s, 3H, N-3-CH$_3$), 4.37 (t, 2H, C$\underline{H}_2$CH$_2$CH$_3$), 4.75 (s, 2H, 8-CH$_2$N), 6.10 (bs, 1H, CO—NH), 7.15—7.29 (m, 3H, H$_{arom}$). EI MS, m/z (I_r/%): 552 (M$^{+\bullet}$, 40), 509 (5), 249 (100), 306 (11), 250 (66), 204 (23), 193 (16), 137 (10), 141 (18), 141 (18).

3-Cycloheptyl-1-(2,6-diisopropylphenyl)-3-(1,3-dimethyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)urea (*IIIb*): ^{1}H NMR spectrum, δ: 0.97 (t, 3H, CH$_2$CH$_2$C$\underline{H}_3$), 1.20, 1.26 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.77—1.95 (2m, 14H, (CH$_2$)$_6$ and CH$_2$C$\underline{H}_2$CH$_3$), 3.11 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.44 (s, 3H, N-1-CH$_3$), 3.60 (s, 3H, N-3-CH$_3$), 3.95 (quintet, 1H, CH in cycloheptyl), 4.40 (t, 2H, C$\underline{H}_2$CH$_2$CH$_3$), 4.70 (t, 2H, 8-CH$_2$N), 6.42 (bs, 1H, CO—NH), 7.16—7.30 (m, 3H, H$_{arom}$). EI MS, m/z (I_r/%): 550 (M$^{+\bullet}$, 12), 346 (46), 276 (13), 250 (85), 235 (100), 193 (82), 160 (15), 146 (19), 112 (75).

3-Cyclooctyl-1-(2,6-diisopropylphenyl)-3-(1,3-dimethyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)urea (*IIIc*): ^{1}H NMR spectrum, δ: 0.94 (t, 3H, CH$_2$CH$_2$C$\underline{H}_3$), 1.21, 1.24 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.49—1.88 (m, 16H, CH$_2$ in cyclooctyl and CH$_2$C$\underline{H}_2$CH$_3$), 3.08 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.42 (s, 3H, N-1-CH$_3$), 3.58 (s, 3H, N-3-CH$_3$), 4.03 (quintet, 1H, CH in cyclooctyl), 4.37 (t, 2H, C$\underline{H}_2$CH$_2$CH$_3$), 4.70 (s, 2H, 8-CH$_2$N), 6.20 (bs, 1H, CO—NH), 7.15—7.18 (m, 3H, H$_{arom}$). EI MS, m/z

(I_r/%): 564 ($M^{+\bullet}$, 15), 360 (33), 276 (13), 250 (100), 235 (79), 193 (52), 160 (9), 146 (10), 126 (51).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-3-isopropylurea (*IIId*): ^{1}H NMR spectrum, δ: 1.09, 1.11 (2 × s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.16 (d, 6H, N-CH(C$\underline{H}_3$)$_2$), 3.00 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.34 (s, 3H, N-1-CH$_3$), 3.52 (s, 3H, N-3-CH$_3$), 4.19 (septet, 1H, N-C$\underline{H}$(CH$_3$)$_2$), 4.44 (s, 2H, 8-CH$_2$N), 5.66 (s, 2H, CH$_2$Ph), 6.31 (bs, 1H, CO—NH), 7.08—7.24 (m, 8H, H$_{arom}$). EI MS, m/z (I_r/%): 544 ($M^{+\bullet}$, 5), 340 (17), 298 (13), 284 (47), 250 (40), 193 (31), 146 (6), 91 (100).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-3-heptylurea (*IIIe*): ^{1}H NMR spectrum, δ: 0.88 (t, 3H, (CH$_2$)$_6$C$\underline{H}_3$), 1.17, 1.20 (2 × s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.28—1.64 (m, 10H, CH$_2$(C$\underline{H}_2$)$_5$CH$_3$), 3.06 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.42 (s, overlapped t, 5H, N-1-CH$_3$ and N-C$\underline{H}_2$(CH$_2$)$_5$CH$_3$), 3.60 (s, 3H, N-3-CH$_3$), 4.67 (s, 2H, 8-CH$_2$N), 5.72 (s, 2H, CH$_2$Ph), 6.06 (bs, 1H, CO—NH), 7.15—7.29 (m, 8H, H$_{arom}$). EI MS, m/z (I_r/%): 600 ($M^{+\bullet}$, 16), 396 (25), 308 (100), 284 (42), 222 (23), 193 (30), 188 (23), 149 (16).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-3-cyclopentyl-1-(2,6-diisopropylphenyl)urea (*IIIf*): ^{1}H NMR spectrum, δ: 1.17, 1.19 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.68—1.98 (m, 8H, (CH$_2$)$_4$), 3.08 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.43 (s, 3H, N-1-CH$_3$), 3.61 (s, 3H, N-3-CH$_3$), 4.25 (quintet, 1H, CH in cyclopentyl), 4.57 (s, 2H, 8-CH$_2$N), 5.75 (s, 2H, CH$_2$Ph), 6.25 (bs, 1H, CO—NH), 7.15—7.35 (m, 8H, H$_{arom}$). EI MS, m/z (I_r/%): 570 ($M^{+\bullet}$, 3), 366 (9), 283 (79), 193 (49), 146 (11), 91 (100).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-3-cycloheptyl-1-(2,6-diisopropylphenyl)urea (*IIIg*): ^{1}H NMR spectrum, δ: 1.17, 1.19 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.43—1.92 (m, 8H, (CH$_2$)$_6$), 3.08 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.42 (s, 3H, N-1-CH$_3$), 3.59 (s, 3H, N-3-CH$_3$), 3.89 (quintet, 1H, CH in cycloheptyl), 4.56 (s, 2H, 8-CH$_2$N), 5.72 (s, 2H, CH$_2$Ph), 6.38 (bs, 1H, CO—NH), 7.13—7.34 (m, 8H, H$_{arom}$). EI MS, m/z (I_r/%): 598 ($M^{+\bullet}$, 2), 394 (10), 304 (27), 298 (18), 283 (42), 209 (9), 193 (33), 112 (61), 91 (100).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-3-cyclooctyl-1-(2,6-diisopropylphenyl)urea (*IIIh*): ^{1}H NMR spectrum, δ: 1.18, 1.20 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 1.49—1.75 (m, 14H, (CH$_2$)$_7$), 3.07 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.42 (s, 3H, N-1-CH$_3$), 3.60 (s, 3H, N-3-CH$_3$), 4.01 (quintet, 1H, CH in cyclooctyl), 4.59 (s, 2H, 8-CH$_2$N), 5.71 (s, 2H, CH$_2$Ph), 6.21 (bs, 1H, CO—NH), 7.14—7.32 (m, 8H, H$_{arom}$). EI MS, m/z (I_r/%): 612 ($M^{+\bullet}$, 9), 408 (29), 329 (10), 318 (38), 298 (100), 208 (26), 91 (33).

3-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylmethyl)-1-(2,6-diisopropylphenyl)-3-(4-fluorophenyl)urea (*IIIi*): ^{1}H NMR spectrum, δ: 1.12, 1.15 (2s, 12H, 2 × CH(C$\underline{H}_3$)$_2$), 3.00 (septet, 2H, 2 × C$\underline{H}$(CH$_3$)$_2$), 3.41 (s, 3H, N-1-CH$_3$), 3.57 (s, 3H, N-3-CH$_3$), 4.88 (s, 2H, 8-CH$_2$N), 5.54 (bs, 1H, CO—NH), 5.76 (s, 2H, CH$_2$Ph), 7.10—7.57 (m, 12H, H$_{arom}$). EI MS, m/z (I_r/%): 596 ($M^{+\bullet}$, 29), 393 (33), 302 (88), 283 (50), 203 (14), 188 (25), 177 (42), 162 (26), 146 (12), 91 (100).

Inhibition of ACAT

In vitro specific activity of ACAT was measured *in vitro* in microsomal fraction of liver cells of rats [15] to the food of which 1 % of cholesterol was added for 10 days and in mucose of small intestine of rabbits [16] to the food of which 1 % of cholesterol and 10 % of corn oil were added for 28 days. Ureas *I*—*III* were dissolved in dimethyl sulfoxide (final content 1 %). The enzyme-specific activity comparing test was measured in the same solvent. The ACAT activities were determined emploing substrates of endogenous cholesterol and exogenous ^{14}C-oleoylcoenzyme A by measuring the amount of the labelled cholesterol oleate per mg of albumin during 1 min. The effect of tested compounds is presented as fraction of ACAT activity inhibition at given concentration.

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