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Effects of 2-(Substituted-sulfanyl)-3,5-dihydro-imidazole-4-one and 2-(Substituted-sulfanyl)-1*H*-imidazole-4,5-dione Derivatives on Serum HDL-cholesterol

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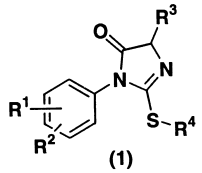
Abstract—A series of 2-substituted sulfanyl-3,5-dihydro-imidazole-4-ones and 2-substituted sulfanyl-1*H*-imidazole-4,5-diones was prepared and shown to increase high density lipoprotein cholesterol over other lipid fractions. Compound **1f** showed efficacy in additional animal models. The major metabolite of **1f** was isolated and its synthesis is reported. The effects of the metabolite on the lipid profile in rats were investigated. © 2000 Elsevier Science Ltd. All rights reserved.

Numerous studies have demonstrated that both the risk of coronary heart disease (CHD) in humans and the severity of experimental atherosclerosis in animals are inversely correlated with serum High Density Lipoprotein-Cholesterol (HDL-C) concentrations.[1] Atherosclerosis is the process of accumulation of cholesterol within the arterial wall that results in the occlusion, or stenosis, of coronary and cerebral arterial vessels and subsequent myocardial infarction and stroke. Angiographical studies have shown that elevated levels of some HDL particles appear to be correlated to a decreased number of sites of stenosis in the coronary arteries of humans.[2] HDL may protect against the progression of atherosclerosis through several mechanisms. In vitro studies have shown that HDL is capable of removing cholesterol from cells.[3] Data of this nature suggest that one anti-atherogenic property of HDL may lie in its ability to deplete tissues of excess free cholesterol and eventually lead to the delivery of this cholesterol to the liver.[4] This has been supported by experiments showing efficient transfer of cholesterol from HDL to the liver.[5]

In addition, HDL may serve as a reservoir in the circulation for apoproteins necessary for the rapid metabolism of triglyceride-rich lipoproteins.[6] Accordingly, agents that increase serum HDL cholesterol concentrations would be of utility as anti-atherosclerotic agents useful in the treatment of dyslipoproteinemias and coronary heart disease.

Based on the HDL-C elevating properties of an earlier series of thio-containing compounds,[7] a series of 2-substituted sulfanyl-3,5-dihydro-imidazole-4-ones (**1**) was designed and evaluated for their effects on the lipid profile in animal models. Compounds of this series selectively increased HDL-C over other lipid fractions such as LDL-C and VLDL-C.



(1)

Compounds **1** were prepared[8] according to Scheme 1. Reaction of an isothiocyanate with an amino acid or an amino acid ester affords 2-thioxo-imidazolidin-4-ones (**3**). Alkylation of **3** with methyl iodide proceeds in poor yield to afford the corresponding *S*-methyl product (**4**). The product is difficult to purify and the reaction does not work with higher alkyl halides. Alternatively, in a preferred general procedure, the reaction of an isothiocyanate with an amino acid amide under basic conditions

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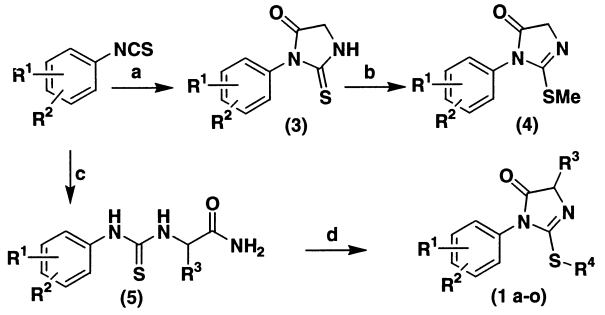
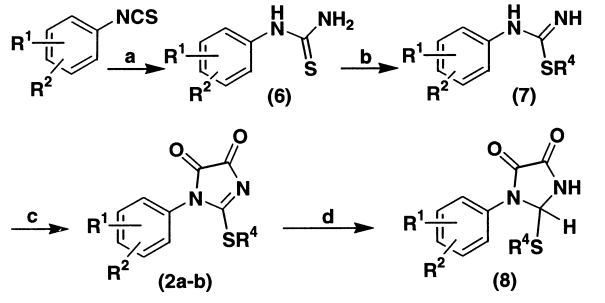
in methylene chloride or chloroform afforded the thiourea amide (**5**). Reaction of **5** with 2 equiv of an alkyl halide or arylalkyl halide in ethanol at reflux effected the *S*-alkylation followed by the cyclization to the desired target compounds. In the case where $R^3 = O$ (**2a**–**b**), the compounds were prepared according to reaction Scheme 2. An isothiocyanate was reacted with ammonia to form the thiourea (**6**). Alkylation of **6**, as described above, yielded *S*-alkyl/*S*-arylalkyl isothiourea (**7**). Reaction of **7** with oxalyl chloride or ethyl oxalyl chloride in chloroform or methylene chloride afforded the desired compounds (**2a**–**b**).

Target compounds were evaluated in an in vivo assay for their effects on the lipid profile.[10] HDL cholesterol concentrations in serum are determined by separating the lipoprotein classes using a modification of Kieft's[11] method.

The changes in HDL-C concentration following treatment with 2-substituted sulfanyl-3,5-dihydro-imidazole-4-one and 2-substituted sulfanyl-1*H*-imidazole-4,5-dione derivatives are presented in Table 1. In general, optimal increases in HDL-C were observed with 2-methyl-5-chloro-phenyl analogues (compounds **1c**, **1f**, **1o**, and **2a**). Moving the chlorine to the 6, 3, or 4 position of the phenyl ring (compounds **1g**, **1i**, and **1j**) diminished activity. While the 2-methyl-5-fluoro-phenyl analogue (compound **1h**) had no significant effect on HDL-C, the 4-fluoro-phenyl analogue (compound **1l**) significantly

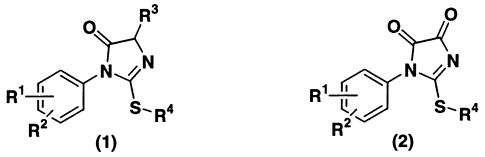


Scheme 1. Synthesis of 2-substituted sulfanyl-3,5-dihydro-imidazole-4-one derivatives:[9] (a) $H_2NCH_2CO_2R$, $CHCl_3$; (b) MeI, MeOH, Heat; (c) $H_2NCH(R^3)CONH_2$, $CHCl_3$ or CH_2Cl_2; (d) R^4I, R^4Br, or R^4Cl, EtOH, Heat.



Scheme 2. Synthesis of 2-substituted sulfanyl-1*H*-imidazole-4,5-dione derivatives and 2-substituted sulfanyl-1*H*-imidazolidine-4,5-dione derivatives: (a) NH_4OH; (b) R^4I, R^4Br, or R^4Cl, EtOH, Heat, basic work up; (c) $(COCl)_2$ or EtO_2CCOCl, $CHCl_3$ or CH_2Cl_2; (d) 5% Pd/C, H_2, EtOH.

increased HDL-C by 140% over controls. The effect of adding a substituent in the 5-position of the dihydro-imidazole ring was also explored. An oxygen in the 5-position (compounds **2a** and **2b**) led to moderate increases in HDL-C. A mono methyl in the 5-position yielded a potent compound (compound **1o**); however, compounds with this substitution were not further pursued due to undesirable side effects, namely reduction in body weight gain and significant elevation of liver enzymes (SGOT and SGPT). None of the compounds exhibiting a significant increase in HDL-C produced a significant increase in LDL-C and only compound **1e** induced a significant increase in VLDL-C (78%).



Based on the overall efficacy and safety profile, compound **1f** was further tested in additional animal models (normal chow-fed rats, cholesterol-fed hamsters and primates). Compound **1f** effectively increased HDL-C in these animal models without increasing other lipid fractions and had a favorable safety profile. The effects of compound **1f** on altering the lipid profile of male cynomolgus monkeys following oral treatment at a dose of 10 mg/kg/day for 4 weeks are illustrated in Figure 1. Significant increases in HDL-C were observed at 2 and 4 weeks with comparable increases in total cholesterol. There were no significant changes in VLDL-C, LDL-C or triglycerides.

In vitro metabolism of compound **1f** in liver microsomal preparations (rat, dog, monkey, and human) was investigated. A major metabolite was prevalent in all four preparations. The isolated metabolite was assigned the

Table 1. Effect of 2-substituted sulfanyl-3,5-dihydro-imidazole-4-one and 2-substituted sulfanyl-1*H*-imidazole-4,5-dione derivatives on HDL-C in cholesterol-fed male rats

Compds	R^1	R^2	R^3	R^4	HDL-C[a]
1a	2-Cl	6-Cl	H	Et	169[c]
1b	2-MeO	5-Cl	H	Et	66[c]
1c	2-Me	5-Cl	H	$PhCH_2$	102[c]
1d	2-Cl	H	H	Et	74
1e	2-Me	H	H	Et	139[c]
1f	2-Me	5-Cl	H	Et	153[c]
1g	2-Me	6-Cl	H	Et	71
1h	2-Me	5-F	H	Et	32
1i	2-Me	3-Cl	H	Et	26
1j	2-Me	4-Cl	H	Et	39
1k	2-Me	6-Me	H	Et	75
1l	4-F	H	H	Et	140[b,c]
1m	H	H	H	Et	89[c]
1n	3-Cl	4-Me	H	Et	45
1o	2-Me	5-Cl	Me	Et	211[c]
2a	2-Me	5-Cl	—	Et	85[c]
2b	2-Me	H	—	Et	48

[a]Average % HDL-C change in 6 animals (versus control) after treatment for 8 days at a dose of 100 mg/kg/day.
[b]Average % HDL-C change in 6 animals (versus control) after treatment for 8 days at a dose of 80 mg/kg/day.
[c]Statistically significant with $P < 0.05$.

structure of 1-(5-chloro-2-methylphenyl)-2-(ethyl sulfanyl) imidazolidine-4,5-dione (**8**). 2-Substituted sulfanyl-imidazolidine-4,5-dione derivatives are unique and have not been described in the literature. Initial attempts to prepare **8** via hydride reduction of compound **2a** failed to yield the desired product or yielded an intractable mixture of products. Compound **8** was successfully prepared from **2a** by catalytic hydrogenation (5% Pd/C) in ethanol at atmospheric pressure (Scheme 2). The reaction proceeded in good yield and the compound was obtained as a stable solid.

Both the synthetic material and the isolated metabolite were identical as indicated by their HPLC profiles, UV, MS, and ^{1}H NMR spectra (Fig.2). The structure assignment of **8** was based on elemental analysis, mass and ^{1}H NMR spectroscopy.[12] The chemical shift for the S-CH_2 resonance is at 2.5 ppm, upfield from the corresponding S-CH_2 of compound **1f** (3.1 ppm) or that of compound **2a** (3.26 ppm). The resonance at 7.65 ppm shifted to 7.35 ppm when the temperature was raised from 25 °C to 40 °C, indicating a resonance corresponding to an exchangeable proton. The most important structural evidence was derived from a series of NOE experiments.

As expected, saturation of the water resonance transferred saturation to resonance H_a (exchangeable).

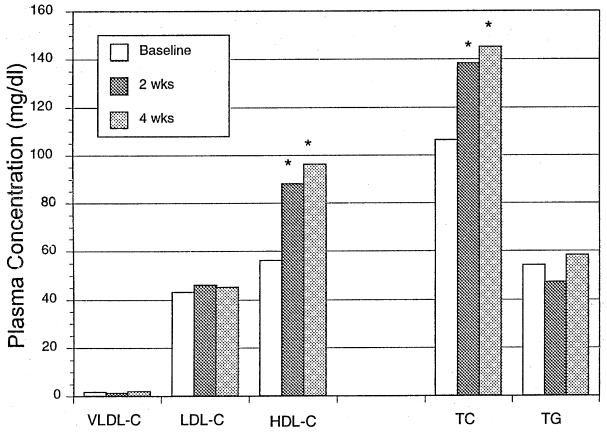


Figure 1. Lipoprotein and lipid effects in cynomolgus monkeys dosed with 10 mg/kg/day orally for 4 weeks. Data represent mean for $n=4$ monkeys at timepoints 0, 2 weeks, and 4 weeks of dosing. VLDL-C = Very low density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, TC = total cholesterol, and TG = triglycerides. *Represents significantly different from baseline at $P<0.05$.

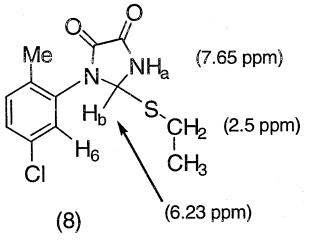


Figure 2. Selected ^{1}H NMR chemical shifts in ($CDCl_3$, 400 MHz) of metabolite **8**.

Saturation of the resonance at 6.23 ppm (H_b) induced an NOE intensity increase in the aromatic methyl resonance, in the aromatic H_6 resonance, and in the S-CH_2 resonance. These close interaromatic distances were confirmed by saturation of the other half of each dipolar coupled pair of resonances.

The effect of the synthetic metabolite (**8**) on the lipid profile of test animals was investigated. Compound **8** did not alter the lipid profiles of either the cholesterol-fed rats or the cholesterol-fed hamsters at the test dose of 100 mg/kg/day.

In conclusion, novel 2-substituted sulfanyl-3,5-dihydroimidazole-4-one derivatives and 2-substituted sulfanyl-1*H*-imidazole-4,5-dione derivatives were described. Their effects on increasing serum HDL-C over other lipid fractions were illustrated in animal models. Concerns about the chemical and metabolic stability of these classes of compounds directed our efforts to a related series of *N*-alkyl *N*′-substituted thiohydantoin derivatives.[13] These compounds were also effective in raising HDL-C over other lipid fractions and offered improved stability and metabolic profiles. This series of compounds will be the subject of a future publication.

Acknowledgements

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7. Screening of the compound file in an in vivo based assay (see ref 10) led to the identification of a series of aryl thiosemicarbazones as HDL-C enhancers. For more information see: (a) Commons, T. J.; Musial, C. L.; Christman, S. US

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9. All compounds gave satisfactory spectral data. For example, 3-(5-chloro-2-methylphenyl)-2-ethylsulfanyl-3,5-dihydroimidazol-4-one (**1f**): mp 137–139 °C, Anal. calcd for $C_{12}H_{13}ClN_2OS$: C, 53.63; H, 4.88; N, 10.42. Found: C, 53.58; H, 4.74; N, 10.32. Mass spectrum (EI, $M.^+$) m/z 268/270. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.48 (dd, 1H, J = 8.3, 2.2 Hz), 7.43–7.40 (m, 2H), 4.35 (dd, 2H, J = 42.84, 23.08 Hz), 3.07 (q, 2H, J = 7.27 Hz), 2.1 (s, 3H), and 1.28 (t, 3H, J = 7.3 Hz). 1-(5-Chloro-2-methylphenyl)-2-ethylsulfanyl-1*H*-imidazol-4,5-dione (**2a**): mp 153–155 °C, Anal. calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92; N, 9.91. Found: C, 50.66; H, 3.69; N, 9.70. Mass spectrum (EI, $M.^+$) m/z 282/284. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.59 (d, 1H, J = 2 Hz), 7.54 (dd, 1H, J = 8, 2 Hz), 7.45 (d, 1H, J = 8 Hz), 3.26 (q, 2H, J = 7.2 Hz), 2.18 (s, 3H), and 1.34 (t, 3H, J = 7.2 Hz).
10. Male Sprague–Dawley rats weighing 200–225 g are housed two per cage and fed Purina Rodent Chow Special Mix 5001-S supplemented with 0.25% cholic acid and 1.0% cholesterol and water ad libitum for 8 days. Each test substance is administered to a group of six rats fed the same diet with the test diet mixed in as 0.005–0.1% of the total diet. Body weight and food consumption are recorded prior to diet administration and at termination. Typical doses of the test substances are 5–100 mg/kg/day. At termination, blood is collected from anesthetized rats and the serum is separated by centrifugation. Total serum cholesterol is assayed using the Sigma Diagnostics enzymatic kit for the determination of cholesterol, Procedure No. 352, modified for use with 96-well microtiter plates.
11. (a) Kieft, K. A.; Bocan, T. M. A.; Krause, B. R. *J. Lipid Res.* **1991**, *32*, 859. (b) The relative concentration of each lipoprotein class is calculated as the percent of total absorbance. HDL cholesterol concentration, in serum, is calculated as the percent of total cholesterol as determined by FPLC multiplied by the total serum cholesterol concentration.
12. Analytical data for compound **8**: mp 181–183 °C, Anal. calcd for $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84. Found: C, 50.77; H, 4.54; N, 9.85. Mass spectrum (EI, $M.^+$) m/z 223/225. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.78 (broad s, 1H), 7.55 (broad s, 1H), 7.44–7.38 (m, 2H), 6.71 (broad s, 1H), 2.42 (q, 2H, J = 7.2 Hz), 2.14 (s, 3H) and 1.07 (t, 3H, J = 7.4 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (broad s, 1H), 7.35 (dd, 1H), 7.30 (d, 1H), 7.18 (broad s, 1H), 2.5 (q, 2H), 2.24 (s, 3H) and 1.22 (t, 3H).
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