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Design and Synthesis of Tricyclic Derivatives as High Density Lipoprotein Cholesterol Enhancers

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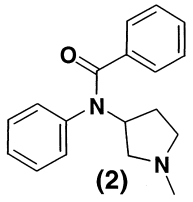
Abstract—A pharmacophore for increasing HDLC was proposed based on common structural features of non-thio-containing compounds with HDLC enhancing properties. A search of the compound database identified various series of these non-thio-containing compounds, including a novel tricyclic imidazoisoquinolone. Preparation of l-aryl-3-oxo-1,3-dihydro-2-benzofuran-1-carboxamides using a novel and widely applicable one-step process from 2-acyl benzoic acids is reported. Reaction of diamines with 1-aryl-3-oxo-1,3-dihydro-2-benzofuran-1-carboxamides and related aza-analogues proceeded with regio-control to furnish imidazoisoquinolones, pyrimidoisoquinolones, and imidazonaphthyridines. NMR studies and X-ray crystallography confirmed the regiochemistry of the products. Compounds of these series increased concentrations of HDLC in test animals following oral administration.

Serum high density lipoprotein cholesterol (HDLC) concentrations have been shown to inversely correlate to both the risk of coronary heart disease (CHD) in humans and the severity of experimental atherosclerosis in animals.[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 antiatherogenic 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 HDLC concentrations would be of utility as anti-atherosclerotic agents useful in the treatment of dyslipoproteinemias and related coronary heart disease. An increase in total serum cholesterol may result from an increase of the HDLC fraction. Data mining for compounds that increased total serum cholesterol in test animals generated a diverse list of compounds. Testing of representative compounds in animal models identified several hits that increase the HDLC without altering other lipid fractions. However, the majority of these agents fell into various thio-containing classes of compounds such as thiohydantoins, thiouracils, thiosemicarbazones, and sulfanyl imidazolidinones.[7] The benzamide series **2** and taclamine **3** were amongst the non-thio-containing hits. These were of interest to our research group (Fig. 1).

These two apparently different classes of compounds carry common structural elements that can be superimposed within a three-dimensional matrix; the tertiary



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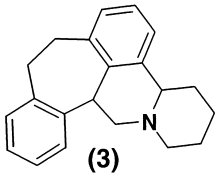

(3)

Figure 1. Structures of non-thio-containing hits with HDLC enhancing properties.

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amine and the two phenyl rings. Due to these commonalities, the three moieties were postulated to define a pharmacophore associated with the HDLC enhancement. Compounds of structure **2** can adopt the conformations of the more rigid taclamine **3**. Taclamine was thus selected as a model for further structure based searching. Both diastereomers (*R,R* and *R,S*) of taclamine were energy minimized (Tripos force field). Average distances between the centroids of the phenyl rings ($a = 5.0$ Å) and the distances between the nitrogen atom and either phenyl ring centroid ($b = 3.8$ Å and $c = 5.2$ Å), were determined based on the geometry of both isomers (Fig. 2). Using these three points and retaining the distance requirement, a 3-D search of the corporate database was performed. The search generated a number of compounds that clustered into several structural series. Of these, the imidazoisoquinolone series **4** was identified as most interesting. In this paper, the synthesis and evaluation of imidazoisoquinolones and the related pyrimidoisoquinolones and imidazonaphthyridines as HDLC enhancing compounds will be discussed.

Synthesis of imidazoisoquinolones **4** required the preparation of 3-carboxamido phthalides **9**. Synthesis of **9** from 2-acyl benzoic acids **5** in a five-step process has been described in the literature.[8] This procedure, as outlined in Scheme 1, involves reduction of the 2-acyl benzoic acid **5** to the lactone **6**. Metalation of the 3-position of **6** and subsequent quenching with carbon dioxide afforded the lactone acid **7**. Conversion of **7** to the corresponding acid chloride **8** followed by treatment with ammonia provided **9**.

In the course of our studies, we developed a simplified, novel, and widely applicable one-step conversion of 2-acyl benzoic acids **5** to the corresponding 3-carboxamido phthalides **9** (Scheme 1). In this process, 2-acyl benzoic acids and potassium cyanide are heated in acetic acid at atmospheric pressure or in a stoppered pressure bottle to yield the desired compounds **9**. Using this one-step process, various 3-carboxamido phthalides were prepared. Representative examples are shown in Table 1.

Reaction of **9** with diamines in refluxing toluene afforded the tricyclic derivatives **1** (Scheme 2). Reaction of **9** with ethylenediamine provided the imidazoisoquinolones, and with 1,3-propanediamine afforded the pyrimidoisoquinolones. Reaction of **9b** with 2-methyl-1,2-propane diamine furnished dimethylimidazoisoquinolone as a single regioisomer **1d** (Scheme 3).

Attempts to elucidate the regiochemical outcome of the reaction using ^{1}H–^{13}C NMR correlation experiments were unsuccessful. Alternatively, hydride reduction of compound **1d** provided the hexahydroimidazoisoquinolinol **12** allowing for structural determination by NOE experiments. The induction of NOE intensity increases between the C-3 and C-5 proton resonances of **12** supported the formation of regioisomer **1d** rather than **11** (Scheme 3). Compound **1d** is the expected product from the attack of the less hindered amine at the lactone carbonyl of **9b**.

To further confirm the generality of the regiocontrol of the reaction, 1,2-propanediamine was reacted with 1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-1-carboxamide **9b**.[9] The reaction afforded a mixture of two diastereomers **1f** and **1g** that were separated and crystallized. X-ray crystal structures of both isomers were obtained (Figs. 3 and 4) and their relative stereochemistry was unambiguously assigned.[10]

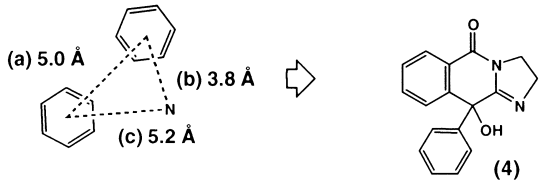
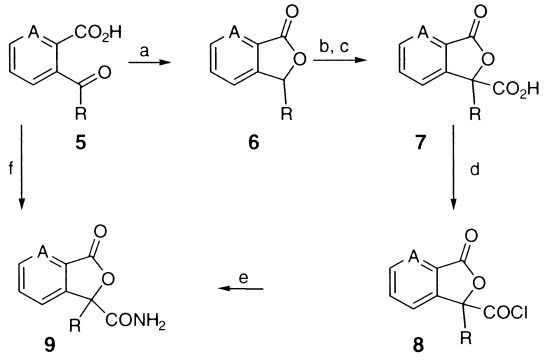


Figure 2. Proposed three-point pharmacophore and the discovery of imidazoisoquinolones as HDLC enhancers.

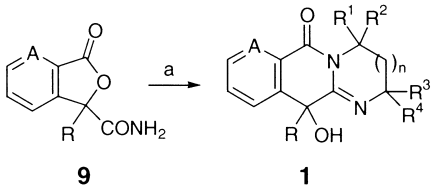


Scheme 1. Conversion of 2-acyl benzoic acids (**5**) to 3-carboxamido phthalides (**9**): (a) Zn, AcOH; (b) (Na/K/Li) NH_2, NH_3; (c) CO_2; (d) $SOCl_2$; (e) NH_3; (f) KCN, AcOH, heat.

Table 1. One-step conversion of *o*-acyl benzoic acids (**5**) to 3-carboxamido phthalides (**9**)

Compd	A	R	Reaction time (h)	Yield[c] (%)
9a	CH	Phenyl	70[a]	54
9b	CH	4-Fluoro-phenyl	48[a]	50
9c	CH	4-Chloro-phenyl	9[b]	36
9d	N	4-Chloro-phenyl	48[a]	71
9e	CH	3-Bromo-phenyl	68[a]	80
9f	CH	Methyl	48[a]	70
9g	CH	Hydrogen	17[a]	41

[a]Reaction run in a pressure bottle.
[b]Reaction run at atmospheric pressure.
[c]Unoptimized isolated yield.

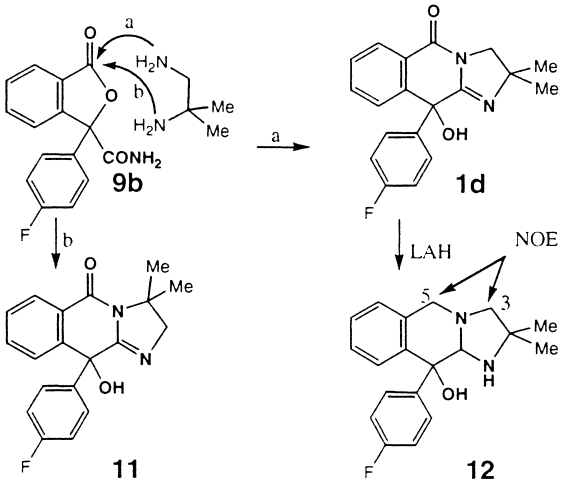


Scheme 2. Synthesis of imidazoisoquinolin-5-ones, pyrimidoisoquinolin-6-ones and imidazonaphthyridin-5-ones (**1**). (a) Diamine, toluene, heat.

Target compounds were evaluated in an in vivo assay for their effects on the lipid profile.[11] HDL cholesterol concentrations in serum were determined by separating the lipoprotein classes using a modification of Kieft's[12] method.

The changes in HDLC concentration following treatment with imidazoisoquinolin-5-one derivatives, pyrimidoisoquinolin-6-one derivatives and imidazonaphthyridin-5-one derivatives are presented in Table 2. Generally, compounds of this series increase HDLC concentrations. Significant increases were found for compounds with the 2-methyl or 2,2-dimethyl substitution **1a**, **1d**, **1f**, and **1g**. Substitution of a fluorine at R^1 significantly enhanced activity in compounds with R^2 and R^3 substitution (**1d** vs **1a**); however, in the absence of R^2 and R^3 substitution, a fluorine substitution exhibits no effect (**1b**). Significant differences in the activities of the two mono-methyl diastereomers **1f** and **1g** were observed. The 2*R*,10*S* isomer **1f** was more potent than the 2*R*,10*R* isomer **1g**. Importantly, none of the compounds tested had any significant effect on the levels of other lipid fractions such as LDLC, VLDLC, triglyceride, or total cholesterol.

In conclusion, database mining led to the discovery of numerous thio-containing and non-thio-containing compounds with HDLC enhancing properties. Based on the common structural elements of the non-thio-containing compounds, a proposed pharmacophore was generated. Using this pharmacophore model, a 3-D search of the database identified the novel tricyclic



Scheme 3. Regiochemistry of addition of diamines to **9b**. Hydride reduction of **1d** to **12**.

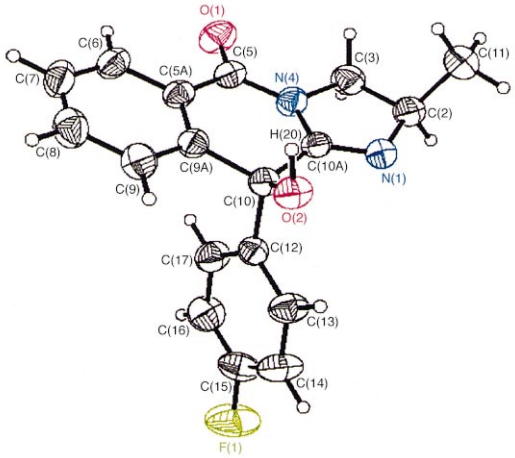


Figure 3. X-ray crystal structure of ±-(2*R*,10*S*)-10-(4-fluorophenyl)-10-hydroxy-2-methyl-2,10-dihydroimidazo[1,2-*b*]isoquinolin-5(3*H*)-one (**1f**), monoclinic, $P2_1/C$, $a = 17.5165(6)$ Å, $b = 10.7125(3)$ Å, $c = 7.8425(3)$ Å, $\beta = 92.026(2)°$, $V = 1470.69(9)$ Å^3, $Z = 4$.

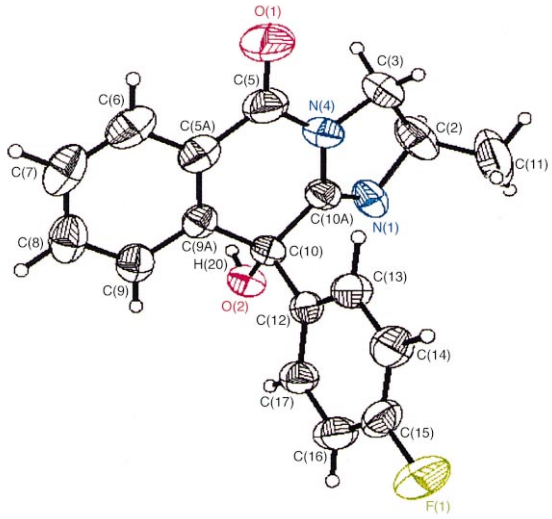
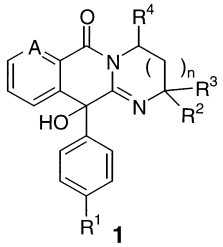


Figure 4. X-ray crystal structure of ±-(2*R*,10*R*)-10-(4-fluorophenyl)-10-hydroxy-2-methyl-2,10-dihydroimidazo[1,2-*b*]isoquinolin-5(3*H*)-one (**1g**), triclinic, P1/C, $a = 13.789(1)$ Å, $b = 15.554(2)$ Å, $c = 16.163(2)$ Å, $\alpha = 114.088(7)°$, $\beta = 104.515(6)°$, $\gamma = 93.864(7)°$, $V = 3006.6(5)$ Å^3, $Z = 8$.

Table 2. Effect of imidazoisoquinolin-5-one derivatives, pyrimidoisoquinolin-6-one derivatives and imidazonaphthyridin-5-one derivatives on HDLC in cholesterol cholic acid-fed male rats



Compd	A	n	R^1	R^2	R^3	R^4	HDLC[a]
1a	CH	0	H	Me	Me	H	55[b]
1b	CH	0	F	H	H	H	0
1c	CH	1	F	H	H	H	22
1d	CH	0	F	Me	Me	H	90[b]
1e	CH	0	F	H	-$(CH_2)_4$-		21
1f	CH	0	F	H	Me(2*R*,10*S*)	H	105[b]
1g	CH	0	F	H	Me(2*R*,10*R*)	H	38[b]
1h	N	0	Cl	H	H	H	49[b]
1i	CH	0	Cl	H	H	H	[c]

[a]Average % HDLC change in six animals (vs control) after treatment for 8 days at a dose of 100 mg/kg/day.
[b]Statistically significant with $P < 0.05$.
[c]Not tested.

imidazoisoquinolone series. Compounds of this series were prepared from the corresponding 3-carboxamido phthalides and diamines with regiochemical control as confirmed by NMR and X-ray crystallography. A novel and widely applicable one-step synthesis of 3-carboxamido phthalides was discovered. Finally, several of these derivatives exhibited potent HDLC enhancing activity in an animal model.

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9. Preparation and spectral data of (2*R*,10*S*)- and (2*R*,10*R*)-10-(4-fluorophenyl)-10-hydroxy-2-methyl-2,10-dihydroimidazo[1,2-*b*]isoquinolin-5(3*H*)-one (**1f** and **1g**): A mixture of 2-(4-fluorobenzoyl)benzoic acid (75 g, 0.307 mol), potassium cyanide (28 g, 0.431 mol), and glacial acetic acid (160 mL) was heated at 115–125 °C in a sealed pressure bottle for 48 h. After cooling to ambient temperature, the mixture was poured into ice water (1.5 L). The solid was collected by filtration and crystallized from ethanol to give 42 g of 1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-1-carboxamide (**9**, R = 4-fluorophenyl, R′ = H) as a white solid, mp 170–173 °C. Mass spectrum (EI, M^+) *m*/*z* 271. Anal. for $C_{15}H_{10}NO_3F$. Calcd: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.06; H, 3.83; N, 5.14. A mixture of 1-(4-fluorophenyl)-3-oxo-1,3-dihydro-2-benzofuran-1-carboxamide (12.5 g, 0.046 mol), 1.2-diamino-propane (13.5 g, 0.182 mol), and toluene (150 mL) was heated at reflux for 18 h in a flask equipped with a water separator. The mixture was evaporated to dryness. The residue was treated with hot ethanol (200 mL). The solids were collected by filtration and dried to give 4.3 g of (2*R*,10*S*)-10-(4-fluorophenyl)-10-hydroxy-2-methyl-2,10-dihydroimidazo[1,2-*b*]-isoquinolin-5(3*H*)-one (**1f**) as a white solid, mp 229–232 °C. Mass spectrum (EI, M^+) *m*/*z* 310. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, 1H, *J* = 7.7 Hz), 7.62 (t, 1H, *J* = 7.3 Hz), 7.51 (t, 1H, *J* = 7.3 Hz), 7.35–7.29 (m, 3H), 7.10 (t, 2H, *J* = 8.8 Hz), 7.04 (s, 1H), 4.16–4.10 (m, 1H), 4.02 (dd, 1H, *J* = 11.2, 11.0 Hz), 3.52 (dd, 1H, *J* = 11.2, 5.93 Hz) 1.20 (d, 3H, *J* = 6.6 Hz). Anal. for $C_{18}H_{15}N_2O_2F$ Calcd: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.86; H, 4.77; N, 9.14. The ethanolic filtrate was evaporated to dryness. The residue was purified by flash chromatography on silica gel using methanol/methylene chloride (8:92). Crystallization from ethyl acetate/hexane gave 2.9 g of (2*R*,10*R*)-10-(4-fluorophenyl)-10-hydroxy-2-methyl-2,10-dihydroimidazo[1,2-*b*]-isoquinolin-5(3*H*)-one (**1g**) as a white solid, mp 142–146 °C. Mass spectrum (EI, M^+) *m*/*z* 310. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, 1H, *J* = 7.91 Hz), 7.61 (t, 1H, *J* = 7.47 Hz), 7.49 (t, 1H, *J* = 6.69 Hz), 7.39 (d, 1H, *J* = 7.91 Hz), 7.36–7.31 (m, 2H), 7.10 (t, 2H, *J* = 9.0 Hz), 6.96 (s, 1H), 4.24–4.38 (m, 1H), 4.14 (dd, 1H, *J* = 11.2, 11.0 Hz), 3.45 (dd, 1H, *J* = 11.0, 6.6 Hz), 1.13 (d, 3H, *J* = 6.6 Hz). Anal. for $C_{18}H_{15}N_2O_2F$. Calcd: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.44; H, 4.84; N, 9.19.
10. Data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC 149545 and CCDC 149546.
11. 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.
12. (a) Kieft, K. A.; Bocan, T. M. A.; Krause, B. R. I. *Lipid Res.* **1991**, *32*, 859. (b) The relative concentration of each lipoprotein class is calculated as the percent of total absorbance. HDLC concentration, in serum, is calculated as the percent of total cholesterol as determined by FPLC multiplied by the total serum cholesterol concentration.