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Design and synthesis of boronic acid inhibitors of endothelial lipase

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ABSTRACT

Endothelial lipase (EL) and lipoprotein lipase (LPL) are homologous lipases that act on plasma lipoproteins. EL is predominantly a phospholipase and appears to be a key regulator of plasma HDL-C. LPL is mainly a triglyceride lipase regulating (V)LDL levels. The existing biological data indicate that inhibitors selective for EL over LPL should have anti-atherogenic activity, mainly through increasing plasma HDL-C levels. We report here the synthesis of alkyl, aryl, or acyl-substituted phenylboronic acids that inhibit EL. Many of the inhibitors evaluated proved to be nearly equally potent against both EL and LPL, but several exhibited moderate to good selectivity for EL.

Heart disease is the most common cause of death in the United States.[1] High density lipoprotein (HDL) cholesterol represents the component among the lipid populations that protects against coronary artery disease (CAD) and cardiac events. Whereas serum concentrations of low density lipoprotein (LDL) cholesterol and triglycerides are positively correlated with risks for developing CAD, concentrations of HDL-cholesterol are negatively correlated. As such, it is now estimated that each 1 mg/dL increase in HDL-C levels is accompanied by a corresponding decrease of cardiovascular risk of 2% in women and 3% in men.[2] Studies have also shown low HDL-C to be an independent risk factor for coronary heart disease, which includes death by cardiac events, as well as myocardial infarction and silent infarct.[3] Additionally, there is evidence that HDL-C may play a direct role in protecting from atherosclerosis. Much of this protection may be the result of HDL-C's role in the reverse cholesterol transport pathway. This generally provides that cholesterol from peripheral tissues may be loaded onto HDL via ABCA1 channels to be transported back to the liver either directly or through CETP-mediated shuttling onto LDL. To this end, factors that affect the circulating levels of HDL-C are important components of the cardiac risk factor mosaic. Included in this list are therapeutic agents such as niacin and torcetrapib, as well as enzymes of the triglyceride lipase gene family.

The triglyceride lipase gene family is a subset of the α/β hydrolase family. Endothelial lipase (EL) is the most recently discovered member of the triglyceride lipase family, sharing 44% sequence identity to human lipoprotein lipase (LPL) and 41% sequence identity to human hepatic lipase (HL).[4,5] The catalytic center, consisting of a classic serine hydrolase aspartate–histidine–serine motif, is conserved among these proteins. Additionally, the putative lipid binding pockets appear conserved as well, indicating that EL likely interacts with lipid substrate in much the same way that HL and LPL do. Before interacting with potential substrate, EL remains in a closed conformation, whereby a 10-amino acid disulfide-linked lid blocks entrance to the active site. Upon binding lipid, this lid domain undergoes significant conformational change, to allow substrate access to the relatively buried catalytic residues.[6] While all three proteins contain a lid, EL appears to have a lid region that is significantly distinct from the other proteins.[7] This suggests that EL may have a different substrate specificity than either HL or LPL, and indeed, EL has considerably greater preference for HDL over other lipoproteins; moreover, HDL is modulated by EL more than by any other lipase.[8] EL preferentially hydrolyses fatty acid esters from the phospholipid components of HDL. Comparing hydrolysis of triglyceride substrates to phospholipid substrates, EL demonstrates a clear preference for phospholipids. In contrast, LPL prefers hydrolysis of triglyceride substrate to phospholipid substrate over 200-fold more than EL.[9]

That HDL-C concentration is greatly influenced by EL is clear in studies that have manipulated its expression levels in vivo. In gene knock-out studies, mice that have an altered EL genetic profile have significantly increased levels of HDL-cholesterol: 57% in the EL −/− model, 25% in the EL +/− model.[8] Infusion of wild-type mice with an anti-EL antibody lead to an increase of HDL-C by 30–50% over 48 h.[10] Perhaps most striking is the effect that EL depletion

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has on the atherosclerotic ApoE −/− mouse model. ApoE −/− mice were bred with EL −/− animals to generate a double knockout strain. In comparison to the ApoE −/− model, the double knockouts had higher levels of HDL-C and (V)LDL, but nonetheless had significantly reduced atherosclerotic lesion areas at the aortic root.[11] In this model, then, the abrogation of EL-dependent depletion and modification of HDL effectively rescued the atherosclerotic profile. These last results have been disputed[12] to the extent that the EL −/− reversed the atherosclerotic lesion; both studies, however, are in agreement with respect to the increased HDL-C effect.

Lipoprotein lipase (LPL) is another member of the lipase gene family involved in lipoprotein metabolism, particularly of VLDL and chylomicrons. It is primarily responsible for the liberation of fatty acids to be utilized as energy by muscle or stored by adipose. There is a positive correlation between HDL-C levels and LPL activity.[13,14] The hydrolytic action of LPL releases lipids that are transferred to immature HDL particles. The CETP-mediated exchange between (V)LDL triglycerides and HDL cholesterol esters is in part regulated by the relative concentrations of each of these lipid components. As such, increased LPL activity extends the half-life of HDL particles by diminishing the concentration of triglyceride-rich particles available for a CETP-mediated interaction.[15] For these reasons, LPL is viewed as a powerful protector against both development of atherosclerosis and decreasing levels of HDL-C. LPL shares considerable sequence, and presumably structural, homology with other members of this family, such as EL and HL.[16] Therefore, cross-inhibition of LPL would be detrimental to the goals of increasing levels of HDL-C or decreasing risks of CAD.

Two assay systems were used to explore the inhibition of EL and LPL. A vesicle-based system[9] allowed for the exploration of the inhibition of these enzymes as they would undergo interfacial catalysis, as would be expected under physiological conditions. The micelle assay,[17] on the other hand, permitted the exploration of effects of inhibition directly at the active sites, as the mechanism of interfacial catalysis is effectively removed under such conditions.[18] Derivatives of palmitic acid containing various electrophilic traps known to inhibit hydrolases that utilize Asp-His-Ser triads in their active sites were synthesized according to literature precedents. Table 1 illustrates that among these compounds, the boronic acid **1f** demonstrated the greatest potency at our screening concentration of 50 μM, inhibiting 90% of EL activity. The trifluoromethyl ketone **1e** was the second most potent, at 56% EL inhibition. No other electrophile demonstrated significant inhibition. While not selective, these data substantiated an exploration of boronic acids as a class of inhibitory molecules. Indeed, boronic acids have been shown to be reversible active site inhibitors of many serine hydrolases.[19]

Phenylboronic acid derivatives were then tested as inhibitors. Derivatization was accomplished with Suzuki coupling reactions using *O*-triflate nitrobenzene (Scheme 1, compounds **2–4**) as starting materials. Coupling of the triflate with an alkylboronic acid using $Pd(OAc)_2$ with the S-PHOS ligand[20] produced the corresponding alkylnitrobenzene (**5c–5q**) in quantitative yield by GC–MS. These were reduced with H_2 over Pd/C to produce the corresponding aniline (**6c–6q**) in high yield.[21] The amino group was converted to an iodide through diazonium formation with $NaNO_2$ and H_2SO_4, followed by displacement with KI,[22] forming iodobenzene compounds **7c–7q**.

Synthesis of the pinacol esters was explored to capitalize on their increased stability relative to free boronic acids. Recent work has suggested that the pinacol boronate group can be directly inserted onto an aryliodide via a transition metal catalyzed reaction. One reported system (CuI/NaH)[23] failed to produce any product in our hands, but a palladium catalyzed system[24] showed much more potential. Since the S-PHOS ligand proved to be so versatile in earlier synthetic steps, we examined the possibility of using the same ligand system to couple pinacolborane here. Indeed, $Pd(OAc)_2$/S-PHOS proved very adept at inserting pinacolborane, often in crude yields of near 80% (**8c–8q**). The remaining 20% resulted from addition of hydride at the aryliodide bond, as determined by GC–MS. Interestingly, this result was not observed for the synthesis of pinacol (2-nonylphenyl)boronate. Repeated attempts failed to produce any boron-containing product. Instead, only unreacted starting aryliodide **7j** was collected. The free boronic acid **9j** could only be synthesized through more traditional lithium-halogen exchange, although the yield was very low (10%). For the remaining alkyl-substituted boronate compounds **8c–8i**, removal of the pinacol protection group was effected by a two step process whereby the ester was first converted to the potassium trifluoroborate salt.[25] This salt was recrystallized from warm acetone and then converted to the free boronic acid by use of a fluorophile, chlorotrimethylsilane. Generally, a 40% overall recovery of free boronic acid from the pinacol ester was obtained via this unoptimized methodology. This was not the case for biarylboronate esters, **8k–8q**, as these compounds showed very low solubility in methanol during the conversion to the trifluoroborate salt. As such, these compounds were not converted to free acids, but rather examined in assays as the pinacol esters.

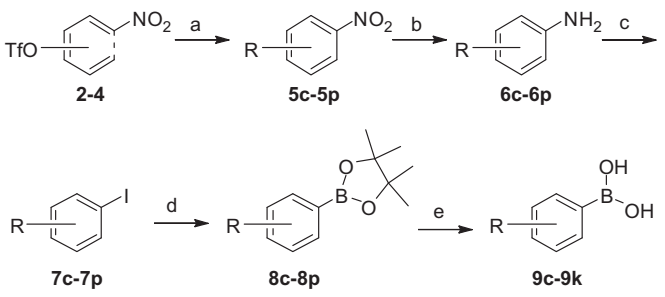
A carboxylate-containing boronate compound was synthesized in the hopes of capitalizing on the different substrate preferences between phospholipid-hydrolyzing EL and triglyceride-hydrolyzing LPL. For this compound, the order of synthetic manipulation was changed to insert the aryliodide before benzylic bromination as illustrated in Scheme 2. Once the enolate condensation reaction had been accomplished, insertion of the pinacol boronate proceeded without loss of the *tert*-butyl ester protection group, effecting compound **15**. This proved a highly fruitful strategy as the last several steps of this synthetic scheme occurred in very satisfactory yields (60% for pinacolboronate insertion, compound **15**, and 70%

Table 1
Inhibition of EL and LPL by electrophilic derivatives of palmitic acid

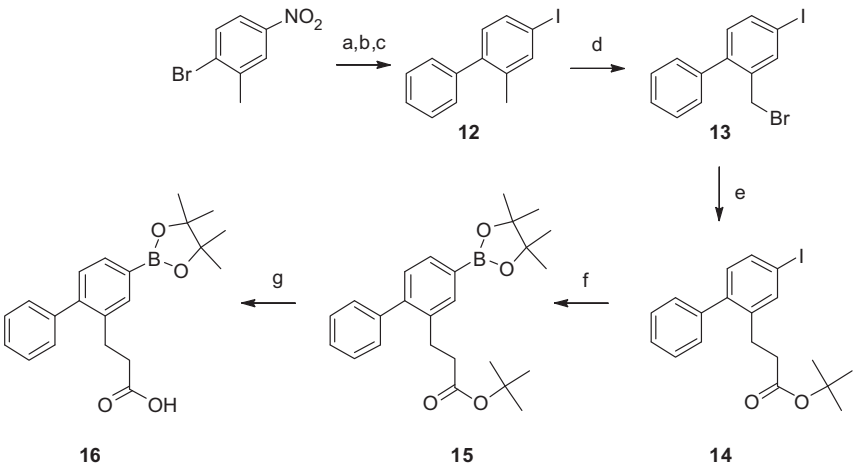
$CH_3-(CH_2)_{14}-X$

Compound	X	% EL inhibition[a]	%LPL inhibition
1a	$C(O)CH_2Cl$	10	−10
1b	CN	4	14
1c	CHO	7	−1
1d	$C(O)CHN_2$	−22	20
1e	$C(O)CF_3$	56	14
1f	$B(OH)_2$	90	63

[a] Percent inhibition of EL or LPL at 50 μM concentration in the vesicle assay. Values are expressed as a percent of activity of each enzyme incubated with DMSO control.



Scheme 1. Reagents: (a) R-$B(OH)_2$, $Pd(OAc)_2$, S-PHOS, K_3PO_4–H_2O, $PhCH_3$. (b) H_2, Pd/C, EtOH. (c) (1) $NaNO_2$, HCl, ice, H_2O. (2) KI, H_2O. (d) Pinacolborane, $Pd(OAc)_2$, S-PHOS, NEt_3, Dioxane. (e) (1) KHF_2, MeOH. (2) TMSCl, H_2O, CH_3CN.



Scheme 2. Reagents: (a) Ph-B(OH)$_2$, Pd(OAc)$_2$, S-PHOS, K_3PO_4, nBuOH, 100 °C. (b) Pd(C), H_2 5 bars, EtOH. (c) $NaNO_2$, HCl, KI. (d) NBS, AIBN, CCl_4. (e) *tert*-butyl acetate, LDA, THF, −78 °C. (f) Pinacolborane, Pd(OAc)$_2$, S-PHOS, triethylamine, dioxane, 80 °C. (g) TFA, CH_2Cl_2.

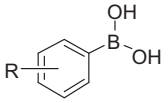
for *tert*-butyl ester deprotection, compound **16**). This reflects the stability of the pinacol ester to anhydrous acidic conditions. This speaks very promisingly for future use of this synthetic route with other functional group moieties.

As shown in Table 2 and 4-substituted phenylboronic acids **9a–9g** were potent inhibitors of both EL and LPL. In the vesicle assay, inhibition of EL increased with increasing chain length, reaching a plateau near a tail of length 7 carbons. Alkyl chains of 7-, 9-, and 11-carbons (**9e–9g**) were comparable in their potency of EL inhibition. In contrast, an inverse relationship between inhibitory prowess and carbon chain length was demonstrated for LPL. From propyl to undecyl (**9c–9g**), the increase in alkyl chain length corresponded with an increase in IC_{50} value against LPL. This lead to an increase in the EL selectivity measure, defined as a ratio of the IC_{50} against LPL to the IC_{50} against EL for a given compound, reaching a maximum of 42-fold with compound **9f**. Because the EL IC_{50} plateaued starting at the 7-carbon chain (**9e**), this increase in EL selectivity was due entirely to the increase in IC_{50} against LPL for compounds of longer chain length. In the micelle assay, these compounds showed increasing potency against EL with increasing chain length, in agreement with the data from the vesicle assay. Unlike in the vesicle assay, these same compounds showed increasing inhibition against LPL as a function of chain length. Longer chain lengths were still associated with increased EL selectivity in the micelle assay, but the magnitude of the effect was muted, as shown by **9f**, being 14-fold selective and thus, three-fold less discriminating than in the vesicle assay.

Phenylboronic acid derivatives substituted at the 2- and 3-position showed considerably less potency against both EL and LPL than similar compounds substituted at the 4-position. Specifically, 3-pentylphenylboronic acid (**9h**) was 13-fold less potent against EL than 4-pentylphenylboronic acid (**9d**) in the vesicle assay and 47-fold less potent against EL in the micelle assay. Substitution at the 2-position, as in 2-nonylphenylboronic acid (**9j**) effected an especially poor inhibitor of both enzymes in both assay systems. This is in direct contract to the moderate inhibitor, 3-nonylphenylboronic acid (**9i**), and the more potent 4-nonylphenylboronic acid (**9f**). These results imply specific patterns for substituents on the ring relative to the boronic acid, in decreasing order of potency: 1,4 > 1,3 > 1,2.

The pinacol boronate esters showed effective potency against both enzymes, as shown in Table 3, and were well correlated with

Table 2
Inhibition of endothelial lipase and lipoprotein lipase by phenylboronic acids



Compound	R	$IC_{50}^{EL,vesicle}$ (μM)[a]	$IC_{50}^{LPL,vesicle}$ (μM)	EL Selectivity, vesicle[b]	$IC_{50}^{EL,micelle}$ (μM)[c]	$IC_{50}^{LPL,micelle}$ (μM)	EL Selectivity, micelle[d]
9a	4-Methyl	17	9	0.5	22	25	1.1
9b	4-Ethyl	11	9	0.3	19	20	1.0
9c	4-Propyl	2.0	8.0	4	4.0	12.5	3.1
9d	4-Pentyl	1.0	15.0	15	0.47	3.8	8.0
9e	4-Heptyl	1.7	30.0	18	0.32	9.0	28
9f	4-Nonyl	1.0	42.0	42	0.1	1.4	14
9g	4-Undecyl	2.0	50	25	0.2	1.5	7.5
9h	3-Pentyl	12.8	50	4	22	85	3.8
9i	3-Nonyl	2.8	>50	>20	5.0	95	19
9j	2-Nonyl	50	≫50	—[e]	11	>500	>50

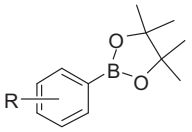
[a] IC_{50} values reported as the average of two independent vesicle based experiments, each performed in duplicate.
[b] EL selectivity, vesicle is defined as the ratio of LPL to EL IC_{50} values as measured in the vesicle assays and is unitless.
[c] IC_{50} values reported as the average of two independent micelle based experiments, each performed in duplicate.
[d] EL Selectivity, micelle is defined as the ratio of LPL to EL IC_{50} values as measured in the micelle assays and is unitless.
[e] Indeterminate.

the free boronic acid. These compounds generally showed excellent inhibition of EL, with IC_{50} values in the low micromolar range. Conversely, their inhibition of LPL varied from the low to mid micromolar range. The most striking difference was between pinacol (4-phenylphenyl)boronate (**8k**) and pinacol (4-(4-fluorophenyl)phenyl)boronate (**8l**), where a 12.5-fold difference in LPL inhibition was seen in IC_{50} values between the fluorinated and non-fluorinated species, leading directly to a 7.7-fold enhancement in selectivity for EL. While the magnitude of the effect was abrogated somewhat in the micelle assay, the difference, 2.5-fold more EL selective with the fluorinated species, was still noted. Interestingly, the heterocyclic boronate esters were also inhibitory against EL and LPL. Compounds **8m–8p** were all modest inhibitors with varying selectivity between the two enzymes, but no one in particular was a specifically outstanding compound. Finally, the carboxyl-containing compound **16** showed little inhibition against either protein, despite the 4-phenyl substituent seen in the comparably much more potent compounds (**8k**) and (**8l**). This result was seen with both assay systems, implying that the result comes from a specific detrimental enzyme–inhibitor interaction, rather than an incompatible inhibitor–assay system interaction. The most likely candidate for this unfavorable interaction is the carboxylate; it remains unknown, however, whether the regiochemistry on the ring, or the charge itself, was the responsible component.

In this study, we attempted to design potent, selective inhibitors of EL. Our vesicle-based assay system indicated that such selectivity is possible, as increases in the chain length of alkyl-substituted phenylboronic acids, particularly at the 4-position, conferred increased EL selectivity. The nature of this trend was not due solely to increasing potency against EL, however. Instead, this selectivity was primarily obtained through the diminishing potency of these inhibitors against LPL with increasing chain length in the 4-position. This clear inverse relationship between inhibitor potency against LPL and alkyl chain length was not observed for the micelle assay. Rather, in the micelle assay, increasing chain length conferred increased potency of inhibitors **9a–9g** against both EL and LPL. Selectivity for EL was still observed, but in the case of **9f**, selectivity was three-fold lower in the micelle assay than in the vesicle assay (14- vs 42-fold, respectively). The additional selectivity in the vesicle assay can be explained in part by the nature of the lipase-substrate interaction. The lid region is made effectively irrelevant by the detergent assay, allowing a compound free access to the active site.[18] With the active site freely accessible, an inhibitor may appear to be potent, but replies upon intrinsic binding differences between the two proteins for selectivity. Thus, compound **9f** is potent against both enzymes' active sites with 14-fold selectivity, as shown by the IC_{50} values in the micelle assay (0.1 and 1.4 μM, respectively). By contrast, in the vesicle system, LPL may fail to undergo proper conformational changes at its lid to allow **9f** access to the LPL active site to the degree seen in the micelle assay,[13] contributing to the increased selectivity for EL in the vesicle assay. Exploiting selective access to the enzyme active site as a means of effecting discriminatory inhibition may prove to be a fruitful strategy for inhibiting such closely related enzymes. When proteins of the same family such as EL and LPL have such homologous active sites, it is essential to move beyond those regions to exploit any possible differences. This lid-based discrimination of the active site may prove to be the most expedient path toward development of potent, selective inhibitors of EL.

Goodman et al. have reported the synthesis of a library of EL and LPL inhibitors based on a sulfonylurea backbone.[26] Therein, compounds were described with variable potency against either enzyme, ranging from 0.04 μM to the assay maximum of 50 μM. However, while not extensively discussed, it is clear that obtaining selectivity was also a challenge with this sulfonylurea series, as the most selective compound reported was only 15-fold selective for EL. Clearly, the challenge of EL selective inhibition must be overcome regardless of potency before any molecule would be considered a success. Indeed, both Goodman's 15-fold selective sulfonylurea and our own 42-fold selective boronic acid set the stage for the discovery of increasingly selective inhibitors. The discovery of such a molecule would provide a novel means by which to specifically raise HDL-C. In light of the failure of torcetrapib to be

Table 3
Inhibition of endothelial lipase and lipoprotein lipase by pinacol(phenylboronate) esters



Compound	R	$IC_{50}^{EL,vesicle}$[a] (μM)	$IC_{50}^{LPL,vesicle}$ (μM)	EL Selectivity, vesicle[b]	$IC_{50}^{EL,micelle}$[c] (μM)	$IC_{50}^{LPL,micelle}$ (μM)	EL Selectivity, micelle[d]
8c	4-Propyl	5.0	25	5	6.0	25	4.1
8d	4-Pentyl	2.6	50	19	1.1	21	19
8e	4-Heptyl	3.5	55	16	1.1	19	17
8f	4-Nonyl	2.5	50	20	1.0	15	15
8g	4-Undecyl	4.5	>50	—[e]	1.4	15	11
8h	3-Pentyl	4.2	45	11	35	100	2.8
8k	4-Phenyl	1.0	4.4	4.4	1.0	12	12
8l	4-(4-Fluorophenyl)	1.6	55	34	1.1	33	30
8m	4-Furan-2-yl	1.9	9.6	5	1.3	35	27
8n	4-Thiophen-2-yl	1.9	7	3.7	1.6	40	25
8o	4-Furan-3-yl	2.8	15	5.4	2.9	33	11
8p	4-Thiophen-3-yl	1.3	13	10	3.1	36	12
8q	4-Naphth-2-yl	2.0	22	11	1.7	15	8.8
16	4-Ph-3-$((CH_2)_2CO_2H)$	95	120	1.2	300	~500	1.7

[a] IC_{50} values reported as the average of two independent vesicle based experiments, each performed in duplicate.
[b] EL selectivity, vesicle is defined as the ratio of LPL to EL IC_{50} values as measured in the vesicle assays and is unitless.
[c] IC_{50} values reported as the average of two independent micelle based experiments, each performed in duplicate.
[d] EL Selectivity, micelle is defined as the ratio of LPL to EL IC_{50} values as measured in the micelle assays and is unitless.
[e] Indeterminate

approved as an HDL-C raising therapeutic, new mechanisms such as EL inhibition have become increasingly attractive.

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Supplementary data

Supplementary data (Reference data for known compounds, NMR and MS data for new compounds, and EL and LPL assay.) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.12.043.

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