Sulfonylated Benzothiazoles as Inhibitors of Endothelial Lipase

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Supporting Information

ABSTRACT: Endothelial lipase (EL) selectively metabolizes high density lipoprotein (HDL) particles. Inhibition of EL has been shown to increase HDL concentration in preclinical animal models and was targeted as a potential treatment of atherosclerosis. We describe the introduction of an α -sulfone moiety to a benzothiazole series of EL inhibitors resulting in increased potency versus EL. Optimization for selectivity versus hepatic lipase and pharmacokinetic properties resulted in the discovery of **24**, which showed good in vitro potency and bioavailability but, unexpectedly, did not increase HDL in the mouse pharmacodynamic model at the target plasma exposure.

KEYWORDS: Endothelial lipase, HDL, atherosclerosis

Endothelial lipase (EL) is a member of the lipase gene family, which includes hepatic lipase (HL), lipoprotein lipase (LPL), and pancreatic lipase (PL).¹ These lipases modulate lipid levels in circulating plasma by metabolism of phospholipids and triglycerides. EL selectively hydrolyzes phospholipids on the surface of high density lipoprotein (HDL) leading to particle degradation, whereas other lipases in the family are selective for triglycerides.² Epidemiology studies have shown that HDL concentration is inversely correlated with coronary heart disease.^{3,4} This may be due to the ability of HDL to promote cholesterol efflux from atherosclerotic plaque as part of reverse cholesterol transport (RCT).⁵ In addition, HDL has antioxidant and anti-inflammatory effects that are atheroprotective.^{6,7} Although clinical outcomes of increasing HDL by inhibition of cholesterol ester transfer protein (CETP) have shown marginal benefit in the best case,^{8,9} evaluation of alternative biological targets, which raise HDL levels, are an area of ongoing research.^{10,11}

EL knockout studies^{12–14} and anti-EL antibodies¹⁵ in mice demonstrated that inhibiting EL function resulted in increased plasma HDL levels. These studies, together with the epidemiological data, led to targeting small molecule inhibitors of EL for the potential treatment of atherosclerosis.^{16–19} Due to the high sequence homology of the catalytic center for members of this family, selective inhibition of EL has been a historical challenge for small molecules.^{20,21} Inhibition of LPL leads to decreased levels of HDL, and inhibition of HL may lead to increased levels of cholesterol depositing low density lipoprotein (LDL).^{22–25} Recently, a series of anthranilic acid

EL selective inhibitors represented by **1** (reported EL IC₅₀ = 0.24 μ M) was described (Figure 1).²⁶ Compound **1**, referred

Figure 1. Recently disclosed EL inhibitors.

to as XEN445, was found to raise HDLc concentrations by 16% ($p < 0.05$) when dosed for 3 days at 30 mpk *b.i.d.* in wild-type mice (the plasma concentration at 16 h post the last dose was 9.9 μ M with a free fraction corrected exposure of 1.1 μ M).²⁶ We have recently disclosed a series of EL selective inhibitors represented by **2** and found no effect on HDLc concentrations in a mouse model when dosed at 50 mpk for 5

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days *q.d.*²⁷ Subsequently, we developed assays for EL inhibition in the presence of mouse plasma and human serum. Compound **2** did not demonstrate measurable inhibition of EL in these assays at the highest concentration tested of 952 μM providing a possible explanation for the lack of pharmacodynamic effect. Concurrently, a series of benzothiazole EL inhibitors were reported, which have a methylene bridge to a 1,3,4-oxadiazole represented by **3** (reported EL IC_{50} = 6 nM).²⁸ We found compound **3** had encouraging levels of activity in the mouse plasma and human serum assays (IC_{50} = 0.40–0.42 μM), which led to our interest in further exploring the series by substitution at the methylene bridge position.

Compound **3** was prepared by the general method described (Scheme 1).²⁹ Regioselective sulfonylation gave compounds

Scheme 1. Synthesis of Sulfonyl Compounds^a

^aReagents and conditions: (a) NH_2NH_2 , MeOH (94%); (b) N-BocGly, T3P, DIEA, dioxane, EtOAc, reflux (65%); (c) (1) TFA, DCM (94%); (2) N-TDDSA, DCM (95%); (3) TFA, DCM (74%); (d) (1) NaH or NaHMDS, DMF, 0 $^\circ\text{C}$; (2) RSO_2Cl (yields in parentheses).

7–11, the site of substitution was confirmed by X-ray crystallography. Compound **7** crystallized in the tautomeric form with the double bond in conjugation with the sulfone, imparting a hydrogen bond (pK_a = 7.4) between the benzothiazole and the oxadiazole (Figure 2).

Figure 2. Crystal structure of **7**.

Inhibition of EL and other members of the triglyceride lipase family was evaluated using a fluorogenic substrate assay (Table 1).²⁷ EL activity was also measured in the presence of human serum to account for protein binding and other serum effects, as well as in plasma of the mouse pharmacodynamic model. Methyl sulfone **7** showed very good *in vitro* potency versus EL (IC_{50} < 10 nM) with excellent selectivity versus LPL (IC_{50} =

12 μM) and PL (IC_{50} > 37 μM) albeit relatively poor selectivity versus HL (IC_{50} = 53 nM). High selectivity versus LPL and PL were observed for other compounds tested in this series. In comparison, we found the weight loss drug Orlistat was a potent inhibitor of EL (IC_{50} = 6 nM) as well as HL, LPL, and PL (IC_{50} = 3, 66, and 6 nM, respectively). Compound **7** also demonstrated inhibition of EL in the presence of human serum (IC_{50} = 47 nM) and mouse plasma (IC_{50} = 170 nM). Minimal effect on potency or selectivity was achieved by modifications to the sulfone substituent such as increasing the size (isopropyl **8**), lipophilicity (trifluoropropyl **9**), polarity (methoxyethyl **10**), or by introduction of aromatic groups (benzyl **11**).

The benzyl sulfone **11** was chosen for further SAR development on the C6 phenyl ring based on its improved potency in mouse plasma (IC_{50} = 77 nM) while maintaining similar potency in human serum (IC_{50} = 76 nM). To efficiently explore SAR at the C6 position of the benzothiazole, the sequence of steps was altered to enable Suzuki cross coupling as the final step to generate compounds **15–19** (Scheme 2).

Substitution of chlorine at the meta or meta and para positions (**15**, **16**) maintained potency but did not improve selectivity versus HL (Table 1). The methyl carbamate in the para position (**17**) had modest selectivity. The most selective compound versus HL was dimethyl amide **18**, but a significant amount of EL potency was lost in the presence of human serum and mouse plasma. Morpholine amide **19** had the best balance of selectivity and activity while maintaining potency in the presence of human serum but showing reduced potency in the mouse plasma assay.

With encouraging activity and selectivity for the series, we next determined if the mechanism of EL inhibition was reversible. Compound **11** and EL were preincubated to form an enzyme–inhibitor complex at serial concentrations. Subsequent dialysis and activity determination of the free enzyme was measured at 24 and 48 h time points (Figure 3). It was found that the activity increased with time and dilution of **11** (52% recovered enzyme activity at 48 h with 3 μM concentration of **11**), indicating the inhibition of EL to be reversible.

Having established potency, selectivity, and reversibility, the series was advanced to mouse pharmacokinetic studies to determine exposures (Table 2). To target IC_{90} coverage, we projected a target plasma through concentration of five times the mouse plasma IC_{50} to maintain EL inhibition. Oral dosing of the sulfamides **7** and **11** (mouse plasma EL IC_{50} = 0.17 and 0.077 μM , respectively) at a 10 mpk dose gave exposures between 0.01 and 0.02 μM at the 7 h time point. These exposure levels did not meet target concentrations for **7** and **11** (>0.8 and >0.4 μM , respectively). The dose of 10 mpk was at the limit of solubility in the vehicle, and *b.i.d.* dosing was not expected to provide target plasma concentrations. Further modifications to the series were therefore required to attain target exposure.

To increase oral exposure by reducing the number of rotatable bonds, cyclic isosteres of the sulfamide group were prepared in the form of hydantoin and thiazolidinediones by utilizing the requisite acids in the oxadiazole cyclization step (Scheme 3).^{30,31} Single isomers of hydantoin **22** and **23** could be obtained by separation of the corresponding enantiomers after oxadiazole formation. The chiral center of the thiazolidinedione epimerized readily at room temperature. Therefore, **21** and **24** were tested as mixtures of isomers.

Table 1. Sulfone and C6 Phenyl SAR^a

Compound	R ₁	R ₂	EL IC ₅₀ (μM)	HL IC ₅₀ (μM)	hSerum EL IC ₅₀ (μM)	mPlasma EL IC ₅₀ (μM)
7	CH ₃ -	Ph	<0.010	0.053	0.047	0.17
8	(CH ₃) ₂ CH ₂ -	Ph	<0.010	<0.010	0.62	0.36
9	CF ₃ CH ₂ CH ₂ -	Ph	<0.010	<0.010	0.058	0.10
10	CH ₃ O(CH ₂) ₂ -	Ph	<0.010	<0.010	0.90	0.37
11	PhCH ₂ -	Ph	<0.010	0.021	0.076	0.077
15	PhCH ₂ -		0.010	<0.010	0.053	0.066
16	PhCH ₂ -		0.010	0.010	0.15	0.12
17	PhCH ₂ -		0.021	0.090	0.24	0.30
18	PhCH ₂ -		0.010	0.391	1.19	8.0
19	PhCH ₂ -		0.010	0.121	0.34	4.2

^aInhibition is measured in duplicate at three concentrations, and the mean values are used to calculate the IC₅₀ values.

Scheme 2. Substitution of C6 Phenyl^a

^aReagents and conditions: (a) N-BocGly, T3P, DIEA, dioxane, EtOAc, reflux (73%); (b) TFA, DCM (96%); (c) N-TDDSA, pyridine, DCM (79%); (d) (1) NaHMDS, THF, -78 °C; (2) BnSO₂Cl (45%); (e) (1) boronic acid, Pd(PPh₃)₄, 2N Na₂CO₃, dioxane, 90 °C; (2) TFA, DCM (yield over two steps in parentheses)

Hydantoin **20** and thiazolidinedione **21** were found to have good potency for EL but offered no improvement in selectivity for EL versus HL (Table 3). When the hydantoin was

Figure 3. Reversibility experiments with compound 11.

Table 2. Mouse Oral PK Properties^a

compd	dose (mpk)	C _{max} (μM)	C _{7h} (μM)	C _{24h} (μM)
7 ^b	10	0.30	0.01	<LLQ
11 ^b	10	2.3	0.02	0.01

^aData from fasted, male, C57BL/6 mice (*n* = 3). ^bVehicle: EtOH/PEG400/Cremophor EL (10/60/30).

combined with the C6 phenyl morpholine amide (**22** and **23**), 100-fold selectivity versus HL was obtained. However, both isomers lost significant potency versus EL in the presence of human serum and mouse plasma. Thiazolidinedione **24** had

Scheme 3. Sulfamide Replacements^a

^aReagents and conditions: (a) RCO_2H , T3P, DIEA, dioxane, EtOAc, reflux (26% for 20, 70% for 21); (b) (1) NaHMDS, THF, -78°C ; (2) $\text{CH}_3\text{SO}_2\text{Cl}$ (39% for 20, 26% for 21); (c) RCO_2H , T3P, DIEA, dioxane, EtOAc, reflux (26% for 22 and 24% for 23 after chiral HPLC separation, 72% for 23); (d) (4-(morpholine-4-carbonyl)phenyl)-boronic acid, Siliacat DPP-Pd or $\text{Pd}(\text{PPh}_3)_4$, K_3PO_4 , dioxane, water, 120°C (64% for 22, 71% for 23, 25% for 24); (e) (1) NaHMDS, THF, -78°C ; (2) $\text{CH}_3\text{SO}_2\text{Cl}$ (41% for 22, 49% for 23, 37% for 24).

Table 3. Hydantoin and Thiazolidinedione Series SAR^a

compd	EL IC_{50} (μM)	HL IC_{50} (μM)	hSerum EL IC_{50} (μM)	mPlasma EL IC_{50} (μM)
20	<0.010	0.053	0.16	0.38
21	<0.010	<0.010	0.91	0.053
22	0.012	1.9	1.5	2.7
23	0.065	1.4	6.0	3.1
24	<0.010	0.45	<0.022	0.094

^aInhibition is measured in duplicate at three concentrations, and the mean values are used to calculate the IC_{50} values.

acceptable selectivity for EL versus HL and maintained potency in human serum and mouse plasma, and was advanced to pharmacokinetic studies.

Oral dosing of thiazolidinedione 24 in mouse at 10 mpk gave exposures of $0.90 \mu\text{M}$ at 7 h and $0.17 \mu\text{M}$ at 24 h corresponding to 40-fold and 7-fold over the mouse plasma IC_{50} , respectively (Table 4). Increasing the dose of 24 to 50 mpk required administration as a suspension and gave similar

Table 4. Mouse Oral PK Properties^a

compd	dose (mpk)	C_{max} (μM)	$C_{7\text{h}}$ (μM)	$C_{24\text{h}}$ (μM)
24 ^b	10	2.0	0.90	0.17
24 ^b	50 ^c	ND	0.41 @ 8 h	0.17

^aData from fasted, male, C57BL/6 mice ($n = 3$). ^bVehicle: EtOH/PEG400/Water (10/60/30). ^cDosed as homogeneous suspension.

exposures to the 10 mpk dose at the 24 h time point, a consequence of the limited solubility.

Attempts to further increase the exposure of 24 using spray dried dispersion techniques were unsuccessful. Nevertheless, sufficient EL inhibition was expected upon administration of thiazolidinedione 24 at a 50 mpk dose over a 24 h time course, and the compound was advanced to the mouse PD model. Wild-type mice were orally dosed with 24 at 50 mpk *q.d.* for 2 days. Blood samples were taken at 6 h post final dose and subjected to FPLC analysis. Compound 24 did not demonstrate any increase in total plasma cholesterol or phospholipids with plasma concentrations of $0.54 \mu\text{M}$ at 30 h. The lack of pharmacodynamic response was unexpected and may indicate a requirement for higher levels of coverage over the IC_{50} than was achieved with compound 24.

In summary, a series of potent, selective, and reversible EL inhibitors was identified with oral bioavailability in mouse. Despite achieving exposure multiples above the IC_{50} , no increase in HDL was observed for compound 24 in the mouse model. Further optimization of physicochemical and pharmacokinetic properties will be the topic of future disclosures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00424.

Synthetic procedures, analytical data, biological and reversibility assay details, pharmacokinetic procedures, and graphical representation of PD results (PDF)

Accession Codes

Cambridge Crystallographic Data Centre (CCDC) number for Compound 7: 1866355.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

N-BocGlym, *N*-(*tert*-butoxycarbonyl)glycine; T3P, 1-propane-phosphonic acid cyclic anhydride; DIEA, diisopropylethylamine; EtOAc, ethyl acetate; N-TDDSA, *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonil]azanide; NaHMDs, sodium hexamethyldisilazane; TFA, trifluoroacetic acid; DCM, dichloromethane; NaH, sodium hydride; THF, tetrahydrofuran; DPP-Pd, diphenylphosphine palladium(II); DMF, dimethylformamide; HPLC, high-performance liquid chromatography; *b.i.d.*, twice a day; *q.d.*, once a day; mpk, milligram of compound per kilogram of body weight; *p.o.*, by mouth; PD, pharmacological dynamics; FPLC, fast protein liquid chromatography

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