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Discovery of potent, selective sulfonylfuran urea endothelial lipase inhibitors

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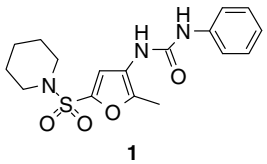
ABSTRACT

Endothelial lipase (EL) activity has been implicated in HDL catabolism, vascular inflammation, and atherogenesis, and inhibitors are therefore expected to be useful for the treatment of cardiovascular disease. Sulfonylfuran urea **1** was identified in a high-throughput screening campaign as a potent and non-selective EL inhibitor. A lead optimization effort was undertaken to improve potency and selectivity, and modifications leading to improved LPL selectivity were identified. Radiolabeling studies were undertaken to establish the mechanism of action for these inhibitors, which were ultimately demonstrated to be irreversible inhibitors.

Endothelial lipase (EL), a serine-phospholipase, is a member of the triglyceride lipase family first cloned in 1999.[1] Unlike other triglyceride lipases, EL has a dramatic difference in substrate preference, possessing predominantly phospholipase activity rather than triglyceride lipase activity.[2] Importantly, a role for EL in the regulation of HDL cholesterol in mice has been well-documented. EL knockout mice have a pronounced elevation in HDL cholesterol relative to wild type mice.[3] Moreover, recent studies suggest that EL may have a proinflammatory effect[4] and may be involved in atherogenesis.[5] Taken together, this evidence suggests that an EL inhibitor could have benefit in the treatment of cardiovascular disease.

A high-throughput screening campaign identified compound **1** as a potent inhibitor of EL (Fig. 1). Although the EL potency of compound **1** was promising, poor lipase selectivity was a concern, since other lipases such as lipoprotein lipase (LPL) and hepatic lipase (HL) also affect lipoprotein metabolism and their inhibition could confound interpretation of in vivo data.[6] Consequently, improving lipase selectivity became a critical goal for the program. Compounds were tested in parallel against both EL and LPL to evaluate lipase selectivity. Since an EL inhibitor would be used for chronic treatment, reversibility was also an important criterion for progression to minimize potential selectivity issues.

Sulfonylfuran ureas were synthesized in a straightforward manner from methyl 2-methyl-3-furancarboxylate (Scheme 1). Sulfonation with chlorosulfonic acid was followed by treatment with PCl_5 to afford the sulfonyl chloride **3**. Reaction of sulfonyl chloride



1

EL IC_{50} = 0.13 uM
LPL IC_{50} = 0.10 uM

Figure 1. Initial sulfonylfuran urea lead.

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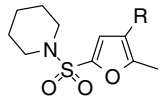
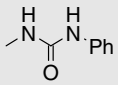
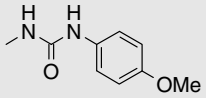
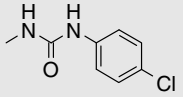
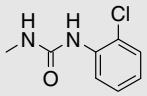
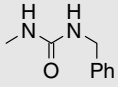
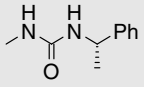
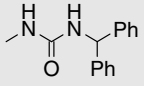
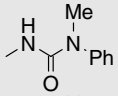
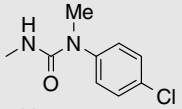
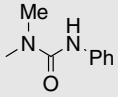
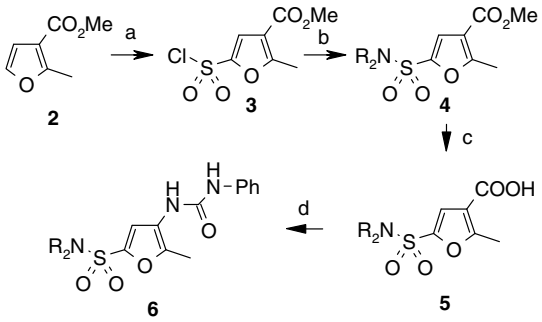
Table 1
Lipase activity for urea analogs and replacements[a,b]



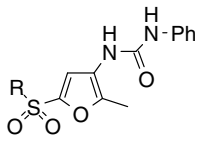
Compound	R	EL IC_{50} (μM)	LPL IC_{50} (μM)
1		0.13	0.10
7		0.13	0.13
8		0.20	0.13
9		0.13	0.32
10		>50	>50
11		0.06	0.40
12		0.16	2.5
13		>50	>50
14		>50	>50
15		25	16
16		>50	>50

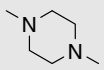
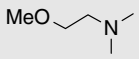
[a] Data represent the average value for two or more measurements. Standard error is typically within two-fold of the reported mean.
[b] Inhibition by the most potent compounds may be driven in part by a covalent interaction between enzyme and inhibitor (vide infra). Although the kinetics for this process are still under investigation, the IC_{50} values were determined after a 15-min preincubation of enzyme with the inhibitor in order to minimize the effects of time-dependent inhibition that may arise from this process.



Scheme 1. Synthesis of sulfonylfuran ureas. Reagents: (a) $ClSO_2OH$, DCM, then pyridine, PCl_5; (b) R_2NH, Et_3N, DCM; (c) NaOH, MeOH; (d) DPPA, Et_3N, toluene, then $PhNH_2$.

Table 2
Lipase activity for sulfonamide analogs[a]



Compound	R	EL IC_{50} (μM)	LPL IC_{50} (μM)
1		0.13	0.10
17		0.13	0.04
18		1.3	0.50
19		0.25	0.05
20		1.0	0.40
21		0.3	0.10

[a] Data represent the average value for two or more measurements. Standard error is typically within two-fold of the reported mean.

3 with amines under standard conditions afforded sulfonamide **4**, which was hydrolyzed to provide acid **5**. Curtius rearrangement and trapping of the intermediate isocyanate with an amine afforded the desired urea products **6**.

Initially, substitution around the phenyl urea was investigated. EL activity and LPL selectivity were relatively insensitive to aryl substitution (Table 1, entries **7–9**), although *ortho*-substitution resulted in a modest improvement in LPL selectivity. An unsubstituted alkyl group (entry **10**) was not tolerated; however, branched alkyl groups (entries **11–12**) markedly improved selectivity against LPL. Additional substitution at the urea nitrogens was not tolerated, and modification of the urea to an amide similarly led to loss of activity (entries **13–16**).

Exploration of the sulfonamide functional group revealed a broad tolerance for substitution. A range of sulfonamides (Table 2, entries **17–21**) maintained activity against EL with little effect on LPL selectivity.

Substitution and replacement of the furan core was also explored. Addition of a methyl group at C3 (**22**, Table 3) resulted in a marked decrease in activity. Similarly, removal of the C5 methyl