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Sulfonylated Benzothiazoles as Inhibitors of Endothelial Lipase

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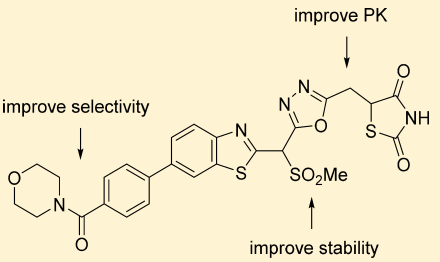
Supporting Information

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 antibodies[15] 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 IC_{50} = 0.24 μM) was described (Figure 1).[26] Compound **1**, referred 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 μM with a free fraction corrected exposure of 1.1 μM).[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

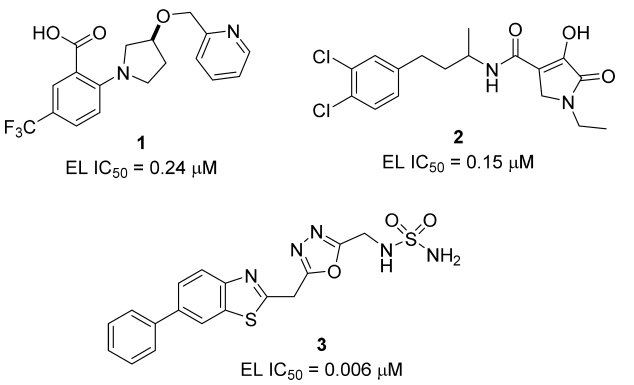


Figure 1. Recently disclosed EL inhibitors.

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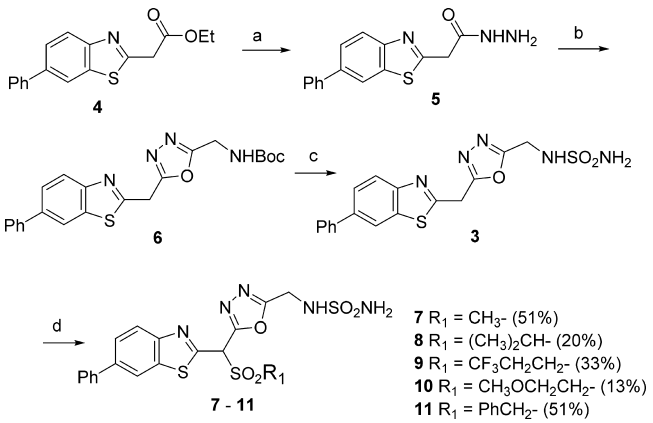
days *q.d.*[27] Subsequently, we developed assays for EL inhibition in the presence of mouse plasma and human serum. Compound **2** did not demonstrate measurable inhibition of EL in these assays at the highest concentration tested of 952 μM providing a possible explanation for the lack of pharmacodynamic 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]



[a]Reagents 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 °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).

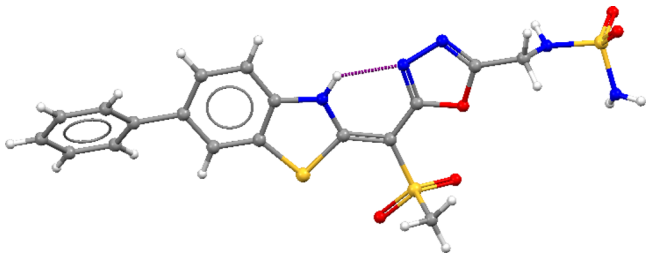


Figure 2. Crystal structure of **7**.

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 hydantoins and thiazolidinediones by utilizing the requisite acids in the oxadiazole cyclization step (Scheme 3).[30,31] Single isomers of hydantoins **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.

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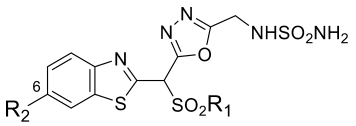
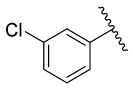
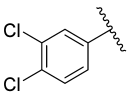
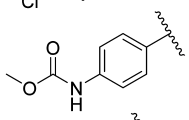
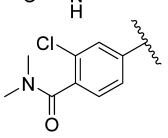
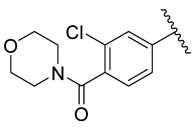
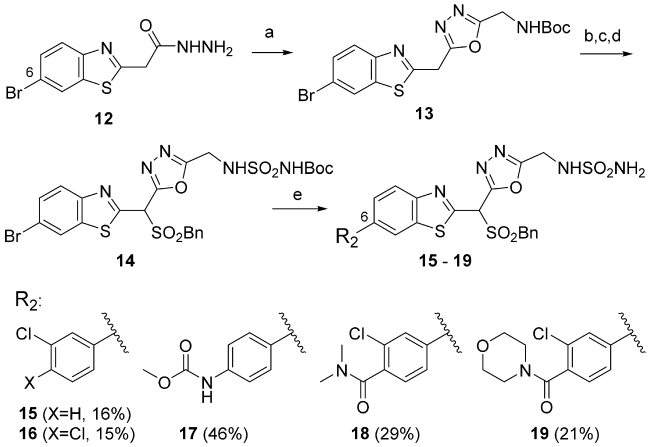
Table 1. Sulfone and C6 Phenyl SAR[a]



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	$(CH_3)_2CH_2$-	Ph	<0.010	<0.010	0.62	0.36
9	$CF_3CH_2CH_2$-	Ph	<0.010	<0.010	0.058	0.10
10	$CH_3O(CH_2)_2$-	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

[a]Inhibition is measured in duplicate at three concentrations, and the mean values are used to calculate the IC_{50} values.

Scheme 2. Substitution of C6 Phenyl[a]



[a]Reagents 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) $BnSO_2Cl$ (45%); (e) (1) boronic acid, $Pd(PPh_3)_4$, 2N Na_2CO_3, dioxane, 90 °C; (2) TFA, DCM (yield over two steps in parentheses)

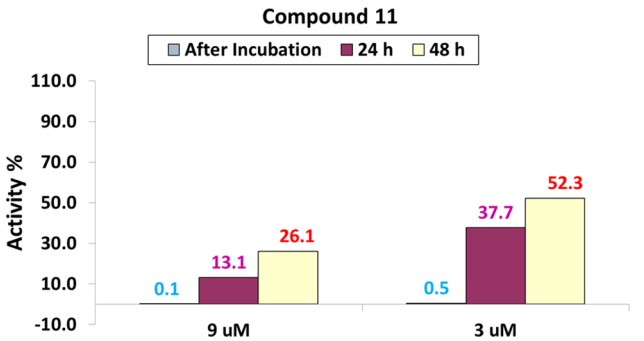


Figure 3. Reversibility experiments with compound **11**.

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

[a]Data from fasted, male, C57BL/6 mice (n = 3). [b]Vehicle: EtOH/PEG400/Cremophor EL (10/60/30).

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 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

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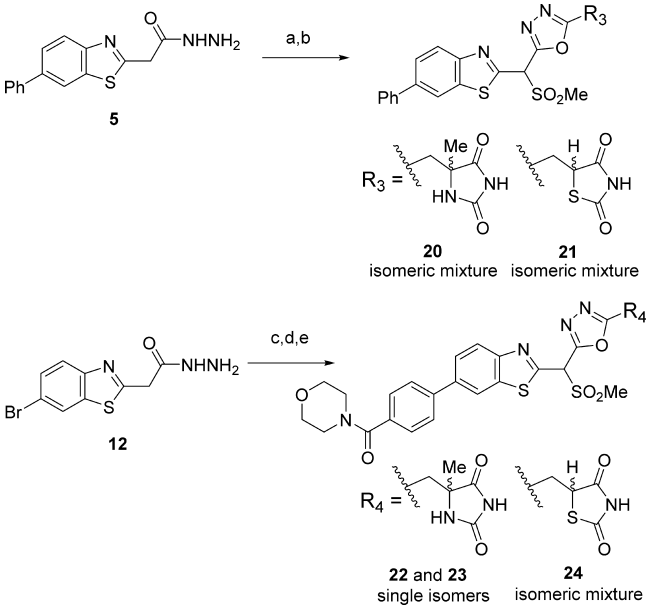
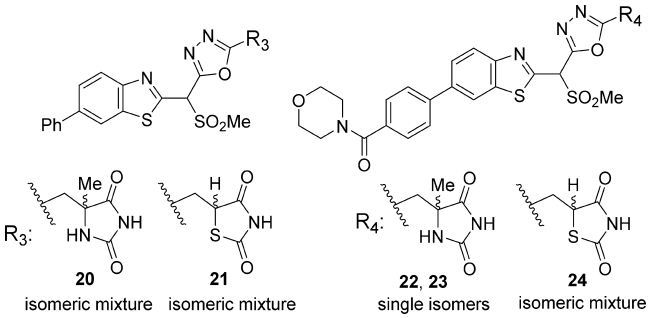
Scheme 3. Sulfamide Replacements[a]



[a]Reagents and conditions: (a) RCO_2H, T3P, DIEA, dioxane, EtOAc, reflux (26% for **20**, 70% for **21**); (b) (1) NaHMDS, THF, −78 °C; (2) CH_3SO_2Cl (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 $Pd(PPh_3)_4$, K_3PO_4, dioxane, water, 120 °C (64% for **22**, 71% for **23**, 25% for **24**); (e) (1) NaHMDS, THF, −78 °C; (2) CH_3SO_2Cl (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

[a]Inhibition 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 μM at 7 h and 0.17 μM 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_{7h} (μM)	C_{24h} (μM)
24[b]	10	2.0	0.90	0.17
24[b]	50[c]	ND	0.41 @ 8 h	0.17

[a]Data from fasted, male, C57BL/6 mice (n = 3). [b]Vehicle: EtOH/PEG400/Water (10/60/30). [c]Dosed 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 μM 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.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

N-BocGlym, *N*-(*tert*-butoxycarbonyl)glycine; T3P, 1-propanephosphonic acid cyclic anhydride; DIEA, diisopropylethylamine; EtOAc, ethyl acetate; N-TDDSA, *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]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

■ REFERENCES

(1) Jaye, M.; Lynch, K. J.; Krawiec, J.; Marchadier, D.; Maugeais, C.; Doan, K.; South, V.; Amin, D.; Perrone, M.; Rader, D. J. A novel endothelial-derived lipase that modulates HDL metabolism. *Nat. Genet.* **1999**, *21* (4), 424−428.

(2) McCoy, M. G.; Sun, G.-S.; Marchadier, D.; Maugeais, C.; Glick, J. M.; Rader, D. J. Characterization of the lipolytic activity of endothelial lipase. *J. Lipid Res.* **2002**, *43* (6), 921−929.

(3) Martinez, L. O.; Jacquet, S.; Tercé, F.; Collet, X.; Perret, B.; Barbaras, R. New insight on the molecular mechanisms of high-density lipoprotein cellular interactions. *Cell. Mol. Life Sci.* **2004**, *61* (18), 2343−2360.

(4) Gordon, D. J.; Probstfield, J. L.; Garrison, R. J.; Neaton, J. D.; Castelli, W. P.; Knoke, J. D.; Jacobs, D. R., Jr.; Bangdiwala, S.; Tyroler, H. A. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* **1989**, *79* (1), 8−15.

(5) Tall, A. R. An overview of reverse cholesterol transport. *Eur. Heart J.* **1998**, *19* (Suppl A), A31−A35.

(6) Nofer, J. R.; Kehrel, B.; Fobker, M.; Levkau, B.; Assmann, G.; von Eckardstein, A. HDL and arteriosclerosis: beyond reverse cholesterol transport. *Atherosclerosis* **2002**, *161* (1), 1−16.

(7) Soran, H.; Hama, S.; Yadav, R.; Durrington, P. N. HDL functionality. *Curr. Opin. Lipidol.* **2012**, *23* (4), 353−366.

(8) Sheridan, C. CETP inhibitors boost 'good' cholesterol to no avail. *Nat. Biotechnol.* **2016**, *34* (1), 5−6.

(9) The HPS3/TIMI55−REVEAL Collaborative Group. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N. Engl. J. Med.* **2017**, *377* (13), 1217−1227.

(10) Hafiane, A.; Genest, J. HDL, Atherosclerosis, and Emerging Therapies. *Cholesterol* **2013**, *2013*, 1−18.

(11) Uehara, Y.; Chiesa, G.; Saku, K. High-Density Lipoprotein-Targeted Therapy and Apolipoprotein A-I Mimetic Peptides. *Circ. J.* **2015**, *79* (12), 2523−2528.

(12) Ishida, T.; Choi, S.; Kundu, R. K.; Hirata, K. I.; Rubin, E. M.; Cooper, A. D.; Quertermous, T. Endothelial lipase is a major determinant of HDL level. *J. Clin. Invest.* **2003**, *111* (3), 347−355.

(13) Ishida, T.; Choi, S. Y.; Kundu, R. K.; Spin, J.; Yamashita, T.; Hirata, K. I.; Kojima, Y.; Yokoyama, M.; Cooper, A. D.; Quertermous, T. Endothelial lipase modulates susceptibility to atherosclerosis in apolipoprotein-E-deficient mice. *J. Biol. Chem.* **2004**, *279* (43), 45085−45092.

(14) Edmondson, A. C.; Braund, P. S.; Stylianou, I. M.; Khera, A. V.; Nelson, C. P.; Wolfe, M. L.; DerOhannessian, S. L.; Keating, B. J.; Qu, L.; He, J.; Tobin, M. D.; Tomaszewski, M.; Baumert, J.; Klopp, N.; Döring, A.; Thorand, B.; Li, M.; Reilly, M. P.; Koenig, W.; Samani, N. J.; Rader, D. J. Dense genotyping of candidate gene loci identifies variants associated with high-density lipoprotein cholesterol. *Circ.: Cardiovasc. Genet.* **2011**, *4* (2), 145−155.

(15) Jin, W.; Millar, J. S.; Broedl, U.; Glick, J. M.; Rader, D. J. Inhibition of endothelial lipase causes increased HDL cholesterol levels in vivo. *J. Clin. Invest.* **2003**, *111* (3), 357−362.

(16) O'Connell, D. P.; LeBlanc, D. F.; Cromley, D.; Billheimer, J.; Rader, D. J.; Bachovchin, W. W. Design and synthesis of boronic acid inhibitors of endothelial lipase. *Bioorg. Med. Chem. Lett.* **2012**, *22* (3), 1397−1401.

(17) Goodman, K. B.; Bury, M. J.; Cheung, M.; Cichy-Knight, M. A.; Dowdell, S. E.; Dunn, A. K.; Lee, D.; Lieby, J. A.; Moore, M. L.; Scherzer, D. A.; Sha, D.; Suarez, D. P.; Murphy, D. J.; Harpel, M. R.; Manas, E. S.; McNulty, D. E.; Annan, R. S.; Matico, R. E.; Schwartz, B. K.; Trill, J. J.; Sweitzer, T. D.; Wang, D.-y.; Keller, P. M.; Krawiec, J. A.; Jaye, M. C. Discovery of potent, selective sulfonylfuran urea endothelial lipase inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19* (1), 27−30.

(18) Greco, M. N.; Connelly, M. A.; Leo, G. C.; Olson, M. W.; Powell, E.; Huang, Z.; Hawkins, M.; Smith, C.; Schalk-Hihi, C.; Darrow, A. L.; Xin, H.; Lang, W.; Damiano, B. P.; Hlasta, D. J. A thiocarbamate inhibitor of endothelial lipase raises HDL cholesterol levels in mice. *Bioorg. Med. Chem. Lett.* **2013**, *23* (9), 2595−2597.

(19) Connelly, M. A.; Greco, M.; Ye, H. Preparation of tricyclic indole derivatives useful as endothelial lipase inhibitors. US20130210806A1, 2013.

(20) Hirata, K.-I.; Dichek, H. L.; Cioffi, J. A.; Choi, S. Y.; Leeper, N. J.; Quintana, L.; Kronmal, G. S.; Cooper, A. D.; Quertermous, T. Cloning of a unique lipase from endothelial cells extends the lipase gene family. *J. Biol. Chem.* **1999**, *274* (20), 14170−14175.

(21) Jaye, M.; Lynch, K. J.; Krawiec, J.; Marchadier, D.; Maugeais, C.; Doan, K.; South, V.; Amin, D.; Perrone, M.; Rader, D. J. A novel endothelial-derived lipase that modulates HDL metabolism. *Nat. Genet.* **1999**, *21* (4), 424−428.

(22) Merkel, M.; Eckel, R. H.; Goldberg, I. J. Lipoprotein lipase: Genetics, lipid uptake, and regulation. *J. Lipid Res.* **2002**, *43* (12), 1997−2006.

(23) Goldberg, I. J. Lipoprotein lipase and lipolysis: Central roles in lipoprotein metabolism and atherogenesis. *J. Lipid Res.* **1996**, *37* (4), 693−707.

(24) Santamarina-Fojo, S.; Haudenschild, C.; Amar, M. The role of hepatic lipase in lipoprotein metabolism and atherosclerosis. *Curr. Opin. Lipidol.* **1998**, *9* (3), 211−219.

(25) Brown, R. J.; Lagor, W. R.; Sankaranaravanan, S.; Yasuda, T.; Quertermous, T.; Rothblat, G. H.; Rader, D. J. Impact of Combined Deficiency of Hepatic Lipase and Endothelial Lipase on the Metabolism of Both High-Density Lipoproteins and Apolipoprotein B−Containing Lipoproteins. *Circ. Res.* **2010**, *107* (3), 357−364.

(26) Sun, S.; Dean, R.; Jia, Q.; Zenova, A.; Zhong, J.; Grayson, C.; Xie, C.; Lindgren, A.; Samra, P.; Sojo, L.; van Heek, M.; Lin, L.; Percival, D.; Fu, J.-M.; Winther, M. D.; Zhang, Z. Discovery of XEN445: A potent and selective endothelial lipase inhibitor raises plasma HDL-cholesterol concentration in mice. *Bioorg. Med. Chem.* **2013**, *21* (24), 7724−7734.

(27) Hangeland, J. J.; Abell, L. M.; Adam, L. P.; Jiang, J.; Friends, T. J.; Haque, L. E.; Neels, J.; Onorato, J. M.; Chen, A. Y. A.; Taylor, D. S.; Yin, X.; Harrity, T. W.; Basso, M. D.; Yang, R.; Sleph, P. G.; Gordon, D. A.; Huang, C. S.; Wexler, R. R.; Finlay, H. J.; Lawrence, R. M. PK/PD Disconnect Observed with a Reversible Endothelial Lipase Inhibitor. *ACS Med. Chem. Lett.* **2018**, *9* (7), 673−678.

(28) Masuda, K.; Kida, S.; Yoshikawa, N.; Katou, M.; Kato, T.; Nakajima, M.; Kojima, E.; Yonehara, M. Preparation of oxadiazole derivatives having endothelial lipase inhibitory activity. WO2011074560A1, 2011.

DOI: 10.1021/acsmedchemlett.8b00424
ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX

(29) Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. N-(tert-Butoxycarbonyl)-N-[4- (dimethylazaniumylidene)-1,4- dihydropyridin-1-ylsulfonyl]azanide: A New Sulfamoylating Agent. Structure and Reactivity toward Amines. *Org. Lett.* **2001**, *3* (14), 2241−2243.
(30) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* **2002**, *45* (12), 2615−2623.
(31) Johnson, J. A.; Jiang, J.; Kim, S.-H.; Pi, Z.; Qiao, J. X.; Tora, G. O.; Wang, T. C.; Finlay, H. Preparation of sulfonyl containing benzothiazole inhibitors of endothelial lipase. US20140011799A1, 2014.

DOI: 10.1021/acsmedchemlett.8b00424
ACS Med. Chem. Lett. XXXX, XXX, XXX−XXX