Discovery of a Simple Picomolar Inhibitor of Cholesteryl Ester Transfer Protein

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A novel series of substituted *N*-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-*N*-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanols is described which potently and reversibly inhibit cholesteryl ester transfer protein (CETP). Starting from the initial lead **1**, various substituents were introduced into the 3-phenoxyaniline group to optimize the relative activity for inhibition of the CETP-mediated transfer of [^{3}H]-cholesteryl ester from HDL donor particles to LDL acceptor particles either in buffer or in human serum. The better inhibitors in the buffer assay clustered among compounds in which the phenoxy group was substituted at the 3, 4, or 5 positions. In general, small lipophilic alkyl, haloalkyl, haloalkoxy, and halogen moieties increased potency relative to **1**, while analogues containing electron-donating or hydrogen bond accepting groups exhibited lower potency. Compounds with polar or strong electron-withdrawing groups also displayed lower potency. Replacement of the phenoxy ring in **1** with either simple aliphatic or cycloalkyl ethers as well as basic heteroaryloxy groups led to reduced potency. From the better compounds, a representative series **4a**−**i** was prepared as the chirally pure *R*(+) enantiomers, and from these, the 4-chloro-3-ethylphenoxy analogue was identified as a potent inhibitor of CETP activity in buffer (**4a**, IC_{50} 0.77 nM, 59 nM in human serum). The simple *R*(+) enantiomer **4a** represents the most potent acyclic CETP inhibitor reported. The chiral synthesis and biochemical characterization of **4a** are reported along with its preliminary pharmacological assessment in animals.

Introduction

CETP is a plasma glycoprotein that mediates the transfer of neutral lipids among various plasma lipoproteins.[1,2] CETP facilitates the transfer of cholesteryl ester (CE) from high-density lipoprotein (HDL) to apolipoprotein B-containing lipoproteins such as very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) with a balanced exchange of triglyceride (TG). CETP plays a potential pro-atherogenic role by moving CE from HDL into pro-atherogenic VLDL and LDL particles, thereby lowering atheroprotective HDL-cholesterol (HDLc). Assigning a definitive role for CETP in atherosclerosis has been the subject of considerable debate.[2−5] There is an ongoing need to identify potent, selective, and specific CETP inhibitors that could be used to more clearly define the role of CETP in preclinical models of atherosclerosis and to better understand the overall pharmacology of this system.[2]

CETP also plays a potential antiatherogenic role in reverse cholesterol transport (RCT), a process that helps remove CE from peripheral tissues to the liver.[6−9] By regulating HDLc plasma levels and the size of HDL particles, CETP is an important protein in this RCT pathway. CETP is also expressed in macrophages within atherosclerotic lesions and may initiate the early RCT process.[10] Alternatively, the CETP-mediated transfer of CE from HDL to LDL increases LDL-cholesterol (LDLc) and lowers HDLc. Epidemiological studies have demonstrated an inverse relationship between serum HDLc levels and the incidence of coronary heart disease (CHD).[11] Low levels of HDLc represent a significant independent risk factor in CHD irrespective of whether patients have elevated LDLc.[12] Thus, inhibiting CETP activity should elevate HDLc and provide a potential therapeutic benefit for patients with CHD.

Numerous animal studies support the hypothesis that modulation of CETP activity has a beneficial effect on HDLc levels and attenuates atherosclerosis. For example, administration of TP-2, a CETP-neutralizing monoclonal antibody, to hamsters produced a dramatic reduction in CETP activity with a concomitant elevation of HDLc,[13] and cholesterol fed-rabbits treated with antisense oligodeoxynucleotides designed against CETP had elevated HDLc and displayed significantly reduced aortic lesion areas.[14] Rabbits treated with a covalent modifier of CETP had elevated HDLc, lowered LDLc, and attenuated atherosclerosis.[15,16]

In humans, the effects of inhibiting CETP activity is less clear. In some studies, CETP lowering has been shown to raise HDLc and be atheroprotective. For example, human CETP deficiency results in hyperalphalipoproteinemia, i.e., elevated HDLc, and protection

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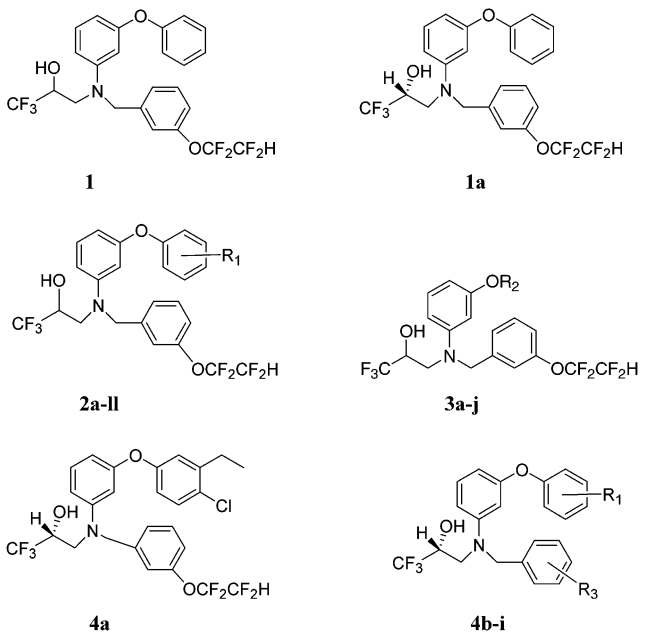
from atherosclerosis.[17] Also, analysis for CETP polymorphism in the Framingham Offspring Study identified a B2B2 allele in men associated with significantly reduced CETP activity, elevated HDLc, and a reduced risk for CHD.[18] Finally, a CETP inhibitor, JTT-705, when given to human subjects with mild hyperlipidemia for 4 weeks, decreased CETP activity by 37% and increased HDLc by 34%.[19] On the other hand, in a recent prospective clinical study of healthy middle-aged US males, carriers of the B2 allele of the Taq1B polymorphism in the CETP gene had higher HDLc, but did not have a lower risk of myocardial infarction.[20] Likewise, those populations exhibiting hyperalphalipoproteinemia were only protected against atherosclerosis below a certain HDLc level,[21] and analysis of a Danish population group associated different CETP mutations with decreased HDLc in both men and women with a possible paradoxical decreased risk of ischemic heart disease in women.[22]

Despite these controversies, there is intense interest in identifying potent and selective CETP inhibitors to determine whether they could represent a new therapeutic approach to improve the HDLc/LDLc ratio and provide an important therapeutic benefit to CHD patients with low HDLc levels.[2,23] While potentially reversible CETP inhibitors from a variety of structural classes are known,[2] they typically exhibit only modest micromolar IC_{50} values for inhibiting CETP-mediated transfer of ^{3}H-CE from HDL to LDL under buffered assay conditions in vitro.[2] Identifying CETP inhibitors that exhibit submicromolar activity when this CETP-mediated transfer process is assayed in the presence of human serum has been especially difficult.[2] However, synthetic studies for a series of tetrahydronaphthalene derivatives with low nanomolar potency in vitro have been described,[24] and related tetrahydoquinoline derivatives have also been reported (activities not given).[25]

We recently reported the discovery of several trifluoro-3-(*tert*-amino)-2-propanols, including **1** and its chiral *R*-enantiomer **1a** as representative of a simple new class of potent CETP inhibitors.[26,27] Here we describe our efforts to optimize the activity of this series through modification and replacement of the aniline 3-phenoxy group in **1**. These efforts produced the substituted phenoxy analogues **2a-ll** and the replacement series **3a**−**j** that incorporated various heterocyclic, benzylic, and cyclic aliphatic ethers in place of the phenoxy group in **1**. Previous studies had demonstrated that an unexpected 10-fold increase in potency was achieved when analogues of **1a** were prepared as their pure chiral *R*-enantiomers.[26,27] Since the substituted phenoxy series displayed the better in vitro potency compared to **1**, a series of related chiral *R*-enantiomers **4a**−**i** were prepared as analogues of **1a**. As a result, **4a** was identified as a simple picomolar CETP inhibitor in buffer with significant nanomolar activity in the presence of human serum.

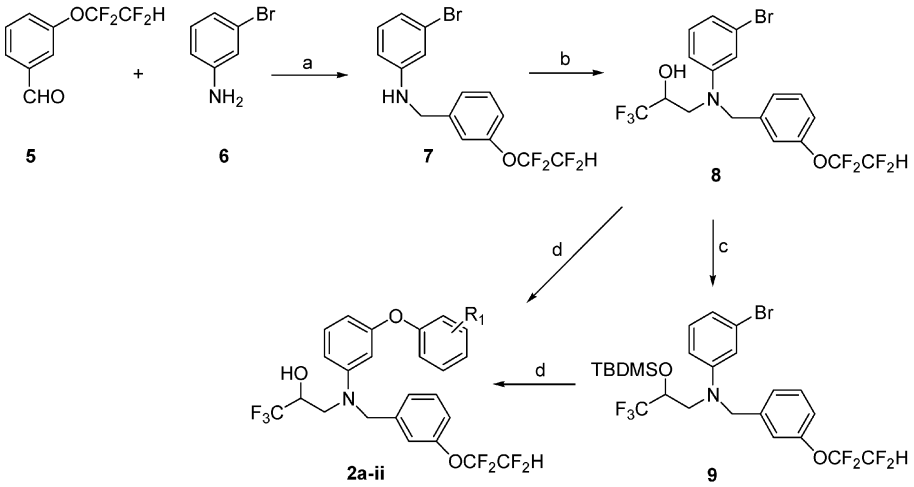
Chemistry

Since the 3-phenoxyaniline moiety provided an important contribution to the potency of **1**,[26] we became interested in chemical approaches that could quickly explore modifications to this key substituent. We chose to explore small focused libraries generated from a highly versatile and easily synthesized intermediate that in one final step could be converted in parallel to many desired compounds. Ideally, each library contained no more than 20 distinct members, and the structure−activity relationship (SAR) developed from these smaller libraries was then used to design subsequent iterations. The recent improvements in new synthetic methods to prepare diaryl ethers developed by Buchwald and Hartwig led us to explore their approaches for library generation.[28] Their versatile cross-coupling methods accommodated both activated and inactivated aryl bromides with a wide range of phenols to give the corresponding diaryl ethers in good yield with a high level of functional group tolerance.[29,30] Initially, our strategy involved exploring functionality changes to optimize potency in analogues of **1** where the enantiomeric purity was less than optimal, and then those substituents that improved activity were incorporated into the chirally pure *R*-enantiomers **4a**−**i** as analogues of **1a**.



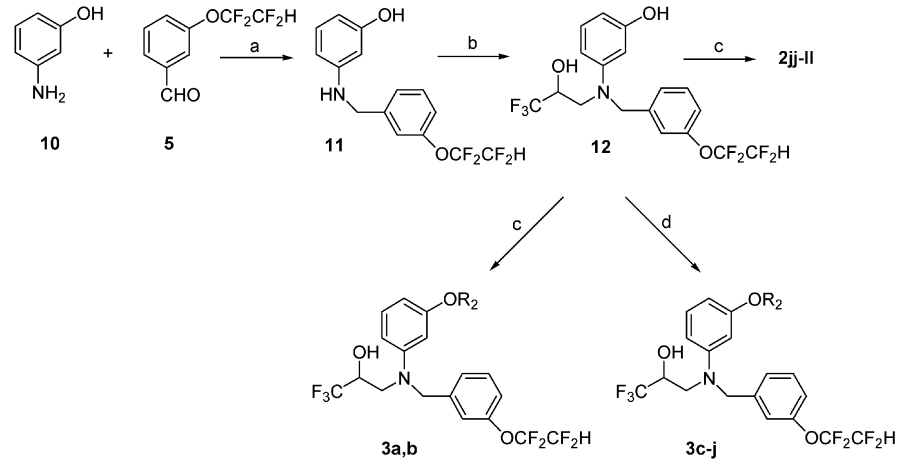
Many of the desired *N*,*N*-disubstituted trifluoro-3-amino-2-propanols **2a-ii** were conveniently prepared in modest to reasonable yield from the cross-coupling reaction of commercially available phenols with protected aryl bromide **9** (Scheme 1). The required *N*-benzyl-3-bromoaniline **7** was conveniently prepared in good yield by standard reductive amination sequences described previously[26] from the reaction of 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde **5** and 3-bromoaniline **6** with sodium triacetoxyborohydride. The ring-opening reaction of *N*-benzyl-3-bromoaniline **7** with commercially available 1,1,1-trifluoro-2,3-epoxypropane of unspecified enantiomeric composition[26] gave the desired trifluoro-3-(*tert*-amino)-2-propanol **8** as the penultimate intermediate. The ring opening of this epoxide under these conditions proceeded with complete regioselectivity, since none of the isomeric 2-amino-3-propanol product was detected. This reaction proceeded smoothly in the presence of catalytic quantities of ytterbium(III) triflate in warm acetonitrile. The ytterbium(III) triflate facilitates the reaction at lower temperature and minimizes the need for large excess quantities of this volatile

Scheme 1[a]



[a] Reagents: (a) $NaBH(OAc)_3$, AcOH, DCE, rt; (b) 1,1,1-trifluoroepoxypropane, $Y(SO_3CF_3)_3$, CH_3CN, 50 °C, 2 h; (c) $TBDMS(SO_3CF_3)$, TEA, DCM, rt, 4 h; (d) appropriate phenol, Cs_2CO_3, $Cu(SO_3CF_3)_2$, naphthoic acid, toluene/DMA, 100 °C, 24−72 h.[29,30]

Scheme 2[a]



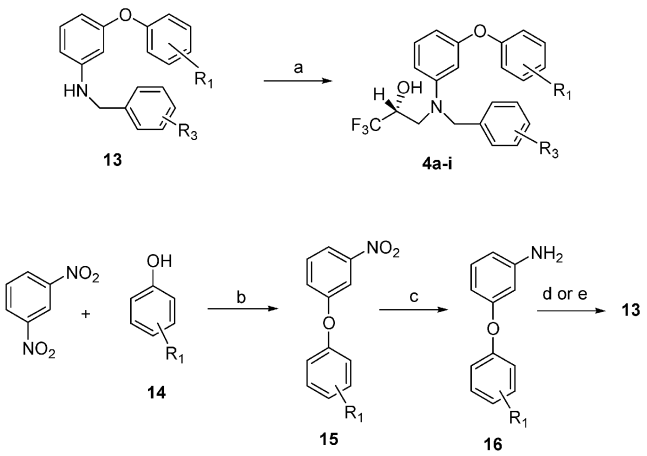
[a] Reagents: (a) $NaBH(OAc)_3$, AcOH, DCE, rt; (b) 1,1,1-trifluoroepoxypropane, $Yb(SO_3CF_3)_3$, CH_3CN, 50 °C, 2 h; (c) appropriate aryl halide, Cs_2CO_3, $Cu(SO_3CF_3)_2$, naphthoic acid, toluene/EtOAc, 100 °C, 24−72 h; (d) alkyl/benzyl halide, Cs_2CO_3, acetone, 60 °C, 18 h or CH_3CN, 50 °C, 48 h.[29,30]

epoxide due to thermal loss. The carbinol group in **8** was protected as the *tert*-butyldimethylsilyl (TBDMS) ether to ensure that no interfering reaction occurred at the propanol center during the subsequent aryl ether cross-coupling reactions. The best yields of **9** were obtained by stirring **8** with *tert*-butyldimethylsilyl triflate in dichloromethane in the presence of triethylamine.

The diaryl ether cross-coupling reactions were carried out in parallel using glass 2-dram vials equipped with mini stir bars. Reaction vials containing a mixture of **9** with the desired phenol, cesium carbonate, copper triflate−benzene complex, and naphthoic acid in a solution of toluene and *N*,*N*-dimethylacetamide were capped and heated with stirring in a Pierce Reacti-Therm system for 24−48 h to give varying yields of **2a-ii**. Reactions of **9** with various phenols usually required 48−72 h to go to completion. The best isolated yields were obtained with phenols bearing 3-alkyl substituents. Reactions of **9** with phenols containing electron-withdrawing groups required either longer reaction times (96 h), or in some cases (e.g., 4-nitro **2ll**) an alternative synthesis. All final products were purified via reverse phase chromatography to greater than 98% purity using a Gilson combichem purification system. Later it was found to be unnecessary to do a separate TBDMS protection/deprotection. The TBDMS protecting group in **9** is lost during the cross-coupling reaction and as a result is not required for efficient cross coupling to occur. Once the cleavage of the TBDMS group was discovered, we utilized **8** to provide analogues of **2** with no loss in yield.

Phenols containing strongly electron withdrawing groups (**2jj**−**ll**) or heteroaryl moieties (**3a**,**b**) failed to give the desired diaryl ethers under these conditions. Consequently, the phenolic trifluoro-3-(*tert*-amino)-2-propanol intermediate **12** (Scheme 2) was utilized with either aryl or heteroaryl bromides to prepare the aryl and heteroaryl ether analogues (**2jj**−**ll**; **3a**,**b**) that could not be synthesized via the original copper-catalyzed cross-coupling reaction sequence (Scheme 1). This functional group switch (Scheme 2) allowed us to further expand our libraries using commercial available starting materials, i.e., substituted aryl bromides. The required *N*-benzyl-3-hydroxy-aniline **11** was conveniently pre-

Scheme 3[a]

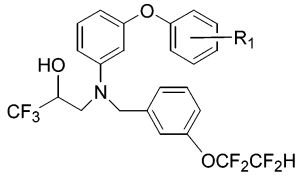


[a] Reagents: (a) (*R*)-(+)-1,1,1-trifluoroepoxypropane, $Yb(OSO_2CF_3)_3$, CH_3CN, 50 °C, 2 h; (b) Cs_2CO_3, DMSO, 100 °C, 18 h; (c) zinc, AcOH, rt, 1 h; (d) appropriate R_3-C_6H_4CHO, $NaBH(OAc)_3$, AcOH, DCE, rt, 2 h; (e) appropriate R_3-$C_6H_4CH_2Br$, cyclohexane, reflux, 24 h.[26]

pared in good yield using a standard reductive amination sequence[26] from the reaction of 3-aminophenol **10** and **5** with sodium triacetoxyborohydride. Intermediate **12** was subsequently prepared from the standard ring-opening reaction of **11** with commercially available 1,1,1-trifluoroepoxypropane of unspecified enantiomeric composition.[26] In a few cases, there were some desired analogues that could not be synthesized using either approach. We were limited particularly in the number of 2- and 3-substitutuents that could be incorporated successfully. To further expand the SAR, we also explored a limited series of simple alkyl, cycloalkyl, and benzylic ether analogues **3c**−**j** (Scheme 2). The alkylation of phenol **11** with the desired alkyl, benzylic, or cycloalkyl halide using cesium carbonate in acetone with heating overnight gave the desired compounds **3c**−**j** in good yield.

The desired chiral *R*-enantiomers **4a**−**i** were prepared in quantities amenable for in vitro testing using previously described procedures[26] from the ring-opening reaction of the appropriately substituted *N*-benzyl-3-phenoxyanilines **13** with the known (*R*)-(+)-1,1,1,-trifluoro-2,3-epoxypropane[31] and catalytic amounts of ytterbium(III) triflate in warm acetonitrile (Scheme 3). Within the limits of detection by chiral HPLC, no racemization of the amino alcohol center was observed under these conditions. When larger quantities of material were desired to support animal testing, an alternative approach to the required substituted *N*-benzyl-3-phenoxyanilines **13** was developed. The substituted (3-nitrophenoxy)benzene **15** was synthesized by heating together 1,3-dinitrobenzene with the appropriately substituted phenol **14** in the presence of cesium carbonate. The nitro group in **15** was reduced using zinc in acetic acid to give the desired substituted 3-phenoxyanilines **16** in good yield. Standard reductive amination procedures[26] were then used to incorporate the necessary benzylic substituents into the *N*-benzyl-3-phenoxyanilines **13** from the reaction of anilines **16** with the appropriately substituted benzaldehyde. The potency of **4a** led us to prepare a limited set of closely related analogues **4f**−**i** varying the benzylic substituent while

Table 1. In Vitro Inhibition of Phenoxy-Substituted *N*-[3-(1,1,2,2-Tetrafluoroethoxy)benzyl]-*N*-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanols Using Recombinant Human CETP in Buffer or in Human Serum[a]



compound	R_1	IC_{50} (μM) in buffer[b]	IC_{50} (μM) in human serum[b,c]
1	H	0.14	6.0
2a	3-isopropyl	0.02	2.3
2b	3-trifluoromethoxy	0.03	3.8
2c	4-fluoro	0.03	4.1
2d	2,3-dichloro	0.03	0.6
2e	4-chloro-3-ethyl	0.03	0.9
2f	3-ethyl	0.06	1.0
2g	3,5-dimethyl	0.07	1.1
2h	3-*tert*-butyl	0.08	3.8
2i	3,4-dimethyl	0.08	6.5
2j	4-fluoro-3-methyl	0.08	3.1
2k	3,4-dichloro	0.08	7.8
2l	3-ethyl-5-methyl	0.08	3.4
2m	3-methyl	0.09	13.3
2n	3,4-$(CH_2)_4$-	0.09	5.2
2o	2,3-difluoro	0.1	ND
2p	4-trifluoromethyl	0.1	6.9
2q	4-methyl	0.1	11.4
2r	4-chloro-3-methyl	0.2	ND
2s	3-trifluoromethyl	0.2	10.3
2t	4-*n*-propyl	0.2	21.3
2u	3,5-difluoro	0.2	11.5
2v	3-*n*,*n*-dimethylamino	0.2	ND
2w	3-methyl-4-isopropyl	0.2	27.2
2x	3-fluoro	0.3	9.7
2y	2-chloro	0.3	ND
2z	4-chloro	0.3	10.0
2aa	4-propoxy	0.4	34.2
2bb	4-isopropyl	0.4	31.3
2cc	4-trifluoromethoxy	0.4	30.1
2dd	4-amino	0.7	9.0
2ee	3-methoxy	1.0	15.6
2ff	4-benzyl	2.4	ND
2gg	4-phenyl	2.5	ND
2hh	4-hydroxy	3.5	ND
2ii	4-thiol	>50	ND
2jj	3-fluoro-2-nitro	0.1	5.6
2kk	2-nitro	0.4	ND
2ll	4-nitro	0.5	29.3

[a] Reference 27. [b] Data represents average of duplicate values. [c] ND, not determined.

maintaining the 3-(4-chloro-3-ethylphenoxy)aniline moiety constant. For one of these, the secondary amine precursor,[26] 1-(bromomethyl)-3-pentafluoroethylbenzene, was prepared by treatment of 3-iodotoluene with sodium pentafluoroethyl propionate at high temperature in the presence of catalytic CuI, followed by bromination with *N*-bromosuccinimide.

Biological Results and Discussion

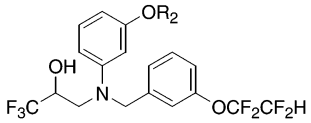
In Vitro Activity and Structure−**Activity Relationships**. Modifications of the 3-phenoxy substituents in **2** were explored to optimize inhibition of CETP-mediated CE transfer in both a buffered in vitro assay using reconstituted reagents as well as in human serum (Table 1).[27,32] The IC_{50} values in human serum are indicative of the inhibitory activity in the target tissue, human blood, when other plasma lipoproteins are also

present. We suspect that the shift to weaker potency in human serum than that observed in buffer is due to nonspecific binding of the inhibitors to nontarget plasma proteins. Results for **2a-ll** and **3a**−**j** were compared to the IC_{50} values observed previously[26,27] for compound **1** in buffer (IC_{50} 0.14 μM) and in serum (IC_{50} 6.0 μM). Notably, inhibitors **2a**−**e** exhibited 6−10-fold higher potency than **1** in the buffer assay, and in particular, inhibitors **2d** and **2e** were about 7−10-fold more potent than **1** in the serum assay.

As summarized below, several key structural changes provided insights into the general SAR of this series (Table 1). The better inhibitors in the buffer assay appeared to cluster with phenoxy having substituents in the 3, 4, and 5 positions. In general, small, lipophilic alkyl, haloalkyl, and haloalkoxy moieties appeared to increase potency at the 3 and 5 positions while better activity was usually observed with halogen substituents in the 2, 3, or 4 positions. The best single substituent changes incorporated branched alkyl groups at the 3-position and appeared to be optimal with a 3-isopropyl moiety as in **2a** (IC_{50} 0.02 μM). The related analogues incorporating either a 3-methyl group as in **2m** (IC_{50} 0.09 μM), a 3-ethyl group as in **2f** (IC_{50} 0.06 μM), or a 3-*tert*-butyl group as in **2h** (IC_{50} 0.08 μM) were all more potent than **1**, but not as potent as **2a**. Surprisingly, moving the bulky isopropyl group in **2a** to the 4-position as in **2bb** (IC_{50} 0.4 μM) dramatically reduced potency by more than 20-fold, whereas the activity of the 3-methyl analogue **2m** (IC_{50} 0.09 μM) was comparable to that of the 4-methyl isomer **2q** (IC_{50} 0.1 μM). The addition of more extended groups at the 4-position such as the 4-*n*-propyl analogue **2t** (IC_{50} 0.2 μM), the 4-benzyl analogue **2ff** (IC_{50} 2.4 μM), or the 4-phenyl **2gg** (IC_{50} 2.5 μM) all led to lower potencies relative to **1** and suggested that a spatial constraint on the CETP protein was present limiting activity at this position. A similar trend was observed with the nonplanar[26,33] trifluoromethoxy substituent where the 3-isomer **2b** (IC_{50} 0.03 μM) had 10-fold higher potency than the corresponding 4-isomer **2cc** (IC_{50} 0.4 μM). In contrast, the analogue **2s** (IC_{50} 0.2 μM), with an in-plane 3-trifluoromethyl substituent, displayed potency comparable to the 4-isomer **2p** (IC_{50} 0.1 μM). However, while both the 3-methyl analogue **2m** (IC_{50} 0.09 μM) and 4-methyl analogue **2q** (IC_{50} 0.1 μM) displayed potencies similar to **1**, the cyclic tetrahydronaphthyl analogue **2n** (IC_{50} 0.09 μM) had only similar, but not dramatically increased potency (Table 1).

Whereas the addition of single halogen substituents such as 2-chloro **2y** (IC_{50} 0.3 μM), 4-chloro **2z** (IC_{50} 0.3 μM), or 3-fluoro **2x** (IC_{50} 0.3 μM) generally reduced potency relative to **1**, the smaller 4-fluoro analogue **2c** (IC_{50} 0.03 μM) had nearly 5-fold better potency than **1**. Interestingly, a dihalogenated analogue incorporating 2,3-dichloro groups **2d** (IC_{50} 0.03 μM) actually exhibited nearly 5-fold higher potency than **1** (Table 1). Compound **2d** exhibited improved activity than either the corresponding 3,4-dichloro analogue **2k** (IC_{50} 0.08 μM) or the 2,3-difluoro analogue **2o** (IC_{50} 0.1 μM). Even more surprising was the observation that the combination of a 4-chloro and 3-ethyl substituent as in **2e** (IC_{50} 0.03 μM) displayed greater potency than **1** as well as higher potency than the single 3-ethyl group alone as in **2f** (IC_{50} 0.06 μM) or the single 4-chloro moiety as in **2z** (IC_{50} 0.3 μM). In contrast, the combination of 4-chloro and 3-methyl substituents as in **2r** (IC_{50} 0.2 μM) did not improve the potency of the single 3-methyl group as in **2m** (IC_{50} 0.09 μM).

Table 2. In Vitro Inhibition of Phenoxy-Replacement Groups in *N*-[3-(1,1,2,2-Tetrafluoroethoxy)benzyl]-*N*-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanols Using Recombinant Human CETP in Buffer or in Human Serum[a]



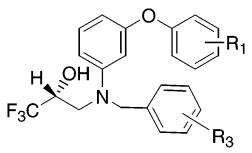
compound	R_2	IC_{50} (μM) in buffer[b]	IC_{50} (μM) in human serum[b,c]
3a	2-pyridyl	>100	ND
3b	3-pyridyl	1.3	ND
3c	3-trifluoromethoxybenzyl	0.06	5.7
3d	3-trifluoromethylbenzyl	0.09	7.7
3e	cyclohexylmethyl	0.2	ND
3f	benzyl	0.2	12.1
3g	4-trifluoromethoxybenzyl	0.3	39.4
3h	isopropyl	0.3	ND
3i	cyclopentyl	0.4	ND
3j	cyclohexyl	2.6	ND

[a] Reference 27. [b] Data represents average of duplicate values. [c] ND, not determined.

In general, the presence of electron-donating or hydrogen-bond accepting groups led to lower potency. For example, the 3-$N(CH_3)_2$ analogue **2v** (IC_{50} 0.2 μM), 4-propoxy analogue **2aa** (IC_{50} 0.4 μM), and 3-methoxy analogue **2ee** (IC_{50} 1.0 μM) had lower potency than **1**. Similarly, hydrogen-bond donating groups at the 4-position such as 4-amino **2dd** (IC_{50} 0.7 μM), 4-hydroxy **2hh** (IC_{50} 3.5 μM), or 4-thiol **2ii** (IC_{50} >50 μM) all dramatically reduced potency relative to **1**. In this series, potency decreased significantly as the acidity of the substituent increased (Table 1).

Analogues containing polar and strongly electron-withdrawing groups, such as 2-nitro as in **2kk** (IC_{50} 0.4 μM) or 4-nitro as in **2ll** (IC_{50} 0.5 μM), also had dramatically reduced potency relative to **1** (Table 1). However, the negative effect of a 2-nitro substituent could be partially overcome by adding a 3-fluoro group as in **2jj** (IC_{50} 0.1 μM). This contribution by the 3-fluoro group in combination with a 2-nitro moiety is unexpected given the relative lack of potency displayed by the 3-fluoro substituent alone as in **2x** (IC_{50} 0.3 μM). Replacing the 3-phenoxy group with basic heteroaryl moieties such as the 3-pyridyl analogue **3b** (IC_{50} 1.3 μM) reduced potency relative to **1** by nearly 10-fold, but an even more dramatic effect was observed for the 2-pyridyl isomer **3a** (IC_{50} >100 μM) which displayed a >500-fold potency reduction relative to **1** (Table 2). The contrast in activity between **1** and **3a** is particularly striking and confirms the sensitivity within the CETP binding site for basic groups. These results are not surprising given the highly hydrophobic environment expected within the CETP CE-binding site. Since CETP recognizes only natural substrates containing weak hydrogen bond acceptors such as present in the TG or CE substrates, the paucity of hydrogen bond interactions likely present at that site should disfavor substituents containing strong hydrogen bond acceptors or donors.

Table 3. In Vitro Inhibition of Chiral *R*-Enantiomers of Phenoxy-Substituted *N*-[3-(1,1,2,2-Tetrafluoroethoxy)benzyl]-*N*-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanols Using Recombinant Human CETP in Buffer or in Human Serum[a]



compound	R_1	R_3	IC_{50} (nM) in buffer[b]	IC_{50} (nM) in human serum[b]
1a	H	3-(1,1,2,2-tetrafluoroethoxy)	16 ± 4	640 ± 140
4a	4-chloro-3-ethyl	3-(1,1,2,2-tetrafluoroethoxy)	3.0 ± 1.3[c] 0.77 ± 0.08[d]	59 ± 5
4b	3-ethyl	3-(1,1,2,2-tetrafluoroethoxy	1.2 ± 0.2	72 ± 16
4c	3-trifluoromethoxy	3-(1,1,2,2-tetrafluoroethoxy)	4.0 ± 1.2	190 ± 20
4d	4-methyl	3-(1,1,2,2-tetrafluoroethoxy)	8.1 ± 2.7	620 ± 60
4e	3-isopropyl	3-(1,1,2,2-tetrafluoroethoxy)	12 ± 4	110 ± 30
4f	4-chloro-3-ethyl	3-trifluoromethoxy	35 ± 14	790 ± 130
4g	4-chloro-3-ethyl	3-pentafluoroethyl	45 ± 15	440 ± 120
4h	4-chloro-3-ethyl	2-fluoro-5-trifluoromethyl	49 ± 17	770 ± 270
4i	4-chloro-3-ethyl	2-fluoro-4-trifluoromethyl	40 ± 11	590 ± 140

[a] Reference 27. [b] Data represents the mean ± SEM ($n = 3-5$). [c] Standard buffer conditions. [d] Assayed with lower [CETP] (<1 nM) and 18 h assay time.

Replacement of the 3-phenoxy group in **1** with either a simple aliphatic isopropyl ether as in **3h** (IC_{50} 0.3 μM), and cycloalkyl ether moieties such as cyclopentyl **3i** (IC_{50} 0.4 μM) or cyclohexyl **3j** (IC_{50} 2.6 μM) all reduced potency relative to **1**, while the cyclohexylmethyl ether **3e** (IC_{50} 0.2 μM) and benzyl ether **3f** (IC_{50} 0.2 μM) had activity comparable to **1** (Table 2). The substituted benzyl ethers such as **3c** (IC_{50} 0.06 μM) and **3d** (IC_{50} 0.09 μM) showed somewhat greater potency than **1** in the buffer assay, but this increased activity failed to translate to the serum assay (Table 2). Interestingly, the same spatial preference for 3-trifluoromethoxy-substituted ring systems was observed for the benzylic ethers as that described earlier for the corresponding meta-substituted aryl ethers. A 5-fold preferential interaction was observed for the 3-trifluoromethoxybenzyl ether **3c** (IC_{50} 0.06 μM) versus its 4-trifluoromethoxy isomer **3g** (IC_{50} 0.3 μM).

For the most part, compounds that showed significantly better potency than **1** in the buffer assay also tended to exhibit qualitatively better potency in the presence of human serum (Tables 1 and 2), but the quantitative effects were difficult to predict. In some cases the correlation in improved activity between buffer and serum was nearly quantitative. For example, the 4-chloro-3-ethylphenoxy analogue **2e** exhibited 5-fold better potency than **1** in buffer and 7-fold better potency than **1** serum. On the other hand, the 3-ethylphenoxy analogue **2f** displayed 2-fold better potency than **1** in buffer, but 6-fold greater potency than **1** in serum. Similarly, the 2,3-dichlorophenoxy analogue **2d** exhibited 5-fold better potency than **1** in buffer and 10-fold better potency than **1** in serum. In contrast, the 3-isopropylphenoxy compound **2a** was 7-fold more potent than **1** in buffer, but only 3-fold more potent in serum. Similar reduced relative activity in serum versus buffer was also observed for the 3-trifluoromethoxy analogue **2c**, the 4-fluorophenoxy analogue **2b** and the 4-methylphenoxy analogue **2q**.

The desire to identify compounds for evaluation in pharmacological models led us to focus on those analogues **2a**−**f** that had the potential to inhibit CETP activity preferentially at low or sub-micromolar concentrations in serum. Previous studies[26] have shown that the chirally pure *R*-enantiomers in this series produced an unexpected potency improvement of nearly 10-fold. This led us to prepare and evaluate the chiral *R*-enantiomers of a limited subset of the better compounds in Table 1 and compare their efficacy versus *R*-enantiomer **1a** (IC_{50} buffer 16 nM, serum IC_{50} 650 nM). The resulting chiral compounds **4a**−**e** all exhibited better potency than **1a** (IC_{50} 1−12 nM) in the buffer assay (Table 3). These compounds displayed IC_{50} values in the low nM range, under conditions where the CETP protein concentration typically was about 8 nM, effectively titrating the protein under these assay conditions.[27] Modification of the buffered assay conditions by extending the assay time to 18 h permitted the use of lower protein concentrations, below 1 nM. Under these extended conditions, the potency of the 4-chloro-3-ethylphenoxy compound **4a** was improved from an IC_{50} of 3.0 nM to 0.77 nM (Table 3, Figure 1A). The chiral compounds **4a**−**e** thus represent some of the most potent inhibitors of CETP reported to date.

In the presence of serum, the quantitative improvement of activity observed in buffer for **4a**−**e** over **1a** was again variable (Table 3). For example, the 4-methylphenoxy analogue **4d** was more potent than **1a** in buffer, but the activity of **4d** in serum did not improve relative to **1a**. In contrast, the 3-ethylphenoxy analogue **4b** was 16-fold more active than **1a** in buffer and about 9-fold more active than **1a** in serum. The most potent compound in serum, **4a** (Table 3, Figure 1C) (although statistically the same potency as **4b**), contained the 4-chloro-3-ethylphenoxy substituent. Compound **4a** (IC_{50} buffer 0.77 nM, IC_{50} serum 59 nM) was 20-fold more potent than **1a** in buffer and 10-fold more potent than **1a** in serum. Similar excellent potency was also observed for **4a** in serum from both hamster (hamster serum IC_{50} 73 nM) and rabbit (rabbit serum IC_{50} 80 nM). The total CE concentration in the buffer assay estimated from the total CE present in LDL plus HDL was approximately 100 μM. Consequently, the concentration of **4a** needed to inhibit CE transfer by 50% (0.77 nM) was about 125 000-fold lower than the concentration of CE, or 0.0008 mol % inhibitor relative to CE.

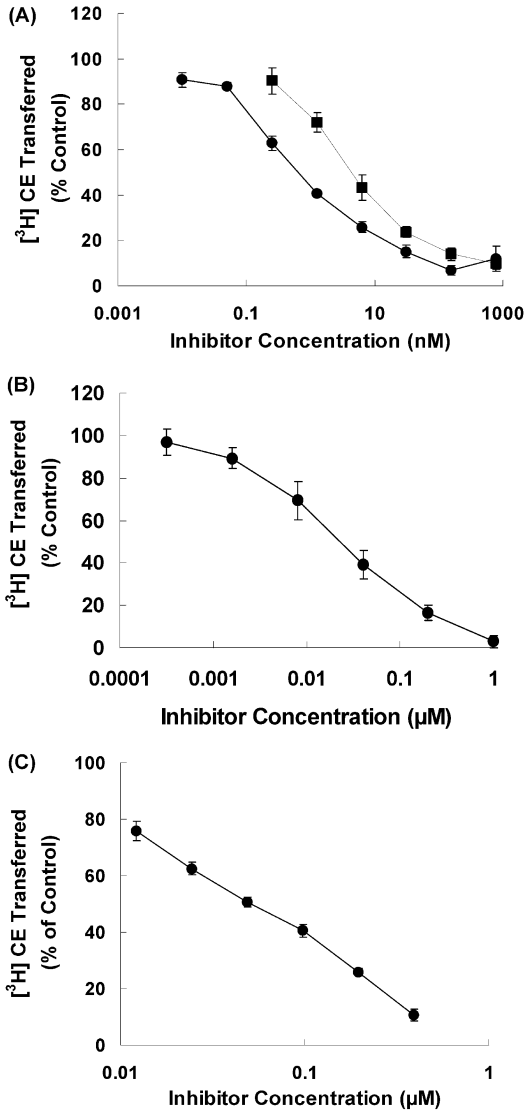


Figure 1. Inhibition of CETP-mediated neutral lipid transfer by compound **4a** in buffer. (A) Inhibition of [^{3}H]CE transfer in the reconstituted HDL/LDL assay, when [CETP] = 8 nM (■) and < 1 nM (●). The amount of CE transferred during the incubation was compared with control samples without added inhibitor. The assay in which [CETP] = 8 nM was incubated for 2 h, while the assay in which [CETP] < 1 nM required an incubation of 16 h. All samples contained donor HDL particles labeled with [^{3}H]CE, acceptor LDL particles, and CETP. (B) Inhibition of [^{3}H]TG transfer in the reconstituted HDL/LDL assay with purified CETP. The experiment was performed as in panel A, except that [^{3}H]TG-HDL was used. (C) Inhibition of CETP-mediated transfer of [^{3}H]CE from HDL to LDL in human serum. [^{3}H]CE-HDL was added to plasma at a final concentration of 25 μg/mL cholesterol. The indicated concentrations of inhibitor were added to plasma containing [^{3}H]CE-HDL and incubated for 4 h at 37 °C. The CETP plasma transfer assay was used to measure the CETP-mediated transfer of [^{3}H]CE from HDL to LDL.

Thus, CETP has a highly specific ability to recognize and interact with **4a** in the presence of relatively high CE concentrations.

Having identified the 4-chloro-3-ethylphenoxy moiety as an optimized aniline substituent in **4a**, we briefly investigated the modification of the 3-(1,1,2,2-tetrafluoroethoxy)benzyl group to give analogues **4f-i** to broaden the SAR of this series. Shortening the benzylic substituent to a 3-trifluoromethoxy group as in **4f** significantly reduced the potency relative to **4a**, particularly in serum. The amplitude of this reduction in activity was similar to that observed previously when the 3-trifluoromethoxy group was introduced into analogues of **1**.[26] Likewise, removing the ether linkage at the benzylic 3-substituent as in the 3-pentafluoroethyl analogue **4g** also reduced activity by approximately 10-fold relative to **4a**. The introduction of *m*- and *p*-trifluoromethyl substituents in combination with an *o*-fluorine as in respectively **4h** and **4i** also significantly reduced the activity in both buffer and serum relative to **4a**. Thus, as observed previously in the SAR of the series developed from **1**,[26,33] the 3-(1,1,2,2-tetrafluoroethoxy)benzyl moiety also appears to be the optimum benzylic substituent in this chiral **4a** series.

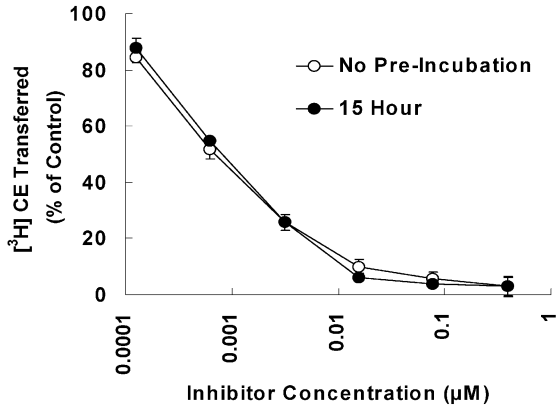


Figure 2. Time dependence of inhibition by **4a**. Purified CETP was incubated in the presence of the indicated concentrations of compound **4a** for 15 h prior to the measurement of [^{3}H]CE transferred in the reconstituted HDL/LDL assay described in Figure 1A. The amount of CE transferred during the HDL/LDL assay was compared with similar samples that did not undergo the 15 h incubation. The amount of CE transferred during the incubations was compared with control samples without added inhibitor.

Biochemical Characterization of 4a. On the basis of its excellent activity in serum, compound **4a** was selected as a prototype of this series for further biochemical and pharmacological characterization using methods previously reported for **1** and **1a**.[27] The results of these efforts demonstrate that like **1a**, compound **4a** is a potent reversible inhibitor of CETP-mediated CE and TG transfer (Figures 1A, 1B, and 1C), and there is no additional time-dependent effect on the inhibitory activity (Figure 2). The plots of activity versus inhibitor **4a** concentrations are virtually superimposable in the presence or absence of preincubation. These results for **1a** and **4a** are consistent with a reversible mode of action and stand in sharp contrast to the recently reported covalent modifiers of CETP.[15,34] Like **1a**, the CETP inhibitory activity of **4a** is not only specific, but is also highly selective since **4a** does not block phospholipid transfer protein (PLTP, IC_{50} > 100 μM) or lecithin cholesterol acyl transferase (LCAT, IC_{50} > 100 μM) at concentrations more than 100 000-fold higher than its IC_{50} for CETP.

Like **1a**, **4a** associates with both LDL and HDL, but does not effect the overall structural integrity of these lipoprotein particles (Figure 3). At concentrations up to 1000-fold higher than its CETP serum IC_{50}, **4a** had no effect on the overall integrity of either LDL or HDL. Competition experiments using size-exclusion chroma-

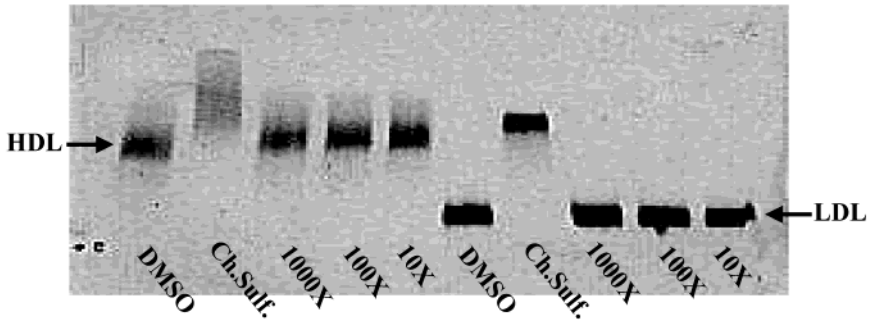


Figure 3. Effects of **4a** on lipoprotein integrity. Compound **4a** was incubated with purified lipoproteins at concentrations up to 1000× its IC_{50} (as determined by in vitro assay) for 2 h at 37 °C prior to subjecting the mixture to buffered agarose gel electrophoresis. Cholesteryl sulfate (Ch. Sulf.), a compound previously shown to alter LDL and HDL structures, was included as a positive control.[27] The gel was fixed to film and stained to visualize the migration of lipoproteins. Lane 1, HDL + DMSO (control); lane 2, HDL + cholesteryl sulfate (100 μM); lane 3, HDL + **4a** (800 nM); lane 4, HDL + **4a** (80 nM); lane 5, HDL + **4a** (8 nM); lane 6, LDL + DMSO (control); lane 7, LDL + cholesteryl sulfate (100 μM); lane 8, LDL + **4a** (800 nM); lane 9, LDL + **4a** (80 nM); lane 10, LDL + **4a** (8 nM).

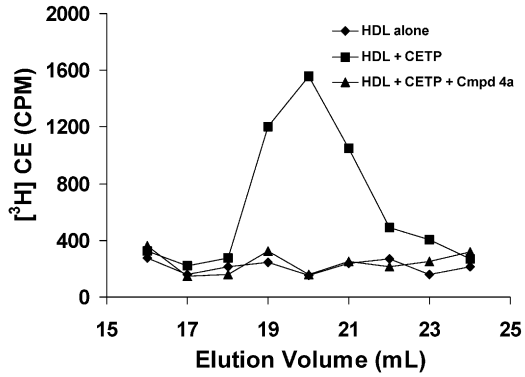


Figure 4. Inhibition of cholesteryl ester binding to CETP by **4a**. [^{3}H]CE HDL was incubated alone, with 60 μg of CETP, or with 60 μg of CETP and 100 μM of **4a** for 2 h at 37 °C. The samples were applied to a Superose 12 size-exclusion column and the radioactivity in each fraction measured by liquid scintillation spectrometry. The elution of CETP, determined by ELISA, was in fractions 18−22. The presence of radiolabel in the CETP fractions indicates the association of [^{3}H]CE with CETP.

tography[27] (Figure 4) demonstrated that **4a**, like **1a**, completely blocked the binding of [^{3}H]CE to purified recombinant human CETP. These results are again consistent with a reversible and competitive biochemical mode of action for **4a**.

Pharmacokinetic Characterization of 4a. Pharmacokinetic studies of **4a** were conducted in the C57/Bl mouse and Syrian golden hamster (Table 4). A single oral dose in the hamster ($n = 6$) at 30 mg/kg gave an average C_{max} at 60 min of >1 μM or 15-fold above the in vitro hamster serum IC_{50} for CETP inhibition. Plasma levels at 24 h in hamster approximated the IC_{50}. In the mouse ($n = 6$), similar results were obtained with a 30 mg/kg dose where the average C_{max} was >3 μM or 60-fold above the human serum IC_{50}, and at the 24 h level, the average C_{max} was twice the human serum IC_{50}. In these two species there was an apparent increase in terminal plasma $t_{1/2}$ after oral dosing, as compared to the β phase plasma $t_{1/2}$ determined from iv dosing. This suggests that **4a** is absorbed sufficiently slowly over the 24 h of the experiment to yield a plasma concentration greater than would be predicted from the iv dosing kinetics. This slow absorption process would support maintenance of plasma levels in excess of the efficacy target IC_{50} with only qd dosing.

Pharmacology of 4a. Using a single oral dose of 30 mg/kg, **4a** inhibited 38% of the CETP-mediated transfer of ^{3}H-CE-HDL to LDL after 30 min in human-CETP transgenic B57/Bl mice (h-CETP mice) ($n = 6$). Similarly after a single oral dose of 30 mg/kg, **4a** inhibited the CETP-mediated transfer of ^{3}H-CE-HDL to LDL after 4 h in hamsters ($n = 6$) by about the same amount (Figure 5). Thus, **4a** modulates CETP activity ex vivo to about the same extent as observed previously for **1** and **1a**,[26] and the 10-fold improvement in potency of **4a** over **1a** in the human serum assay does not translate into improved activity ex vivo for either hCETP mice or hamsters.

Multiple oral dosingof **4a** at 30 mg/kg qd for 5 days in hCETP mice ($n = 6$) produced a statistically significant 12% elevation of HDL, a 12% reduction in LDL, and a 22% reduction in VLDL. Plasma levels taken 4 h after the final oral dose were about 100-fold above the human serum IC_{50}. Multiple oral qd dosing of **4a** at 3 and 30 mg/kg for 5 days in hamsters ($n = 6$) produced a small elevation of HDL (6.2% and 5.4%, respectively), along with no significant change in LDL or VLDL. Thus, the efficacy of **4a** for raising HDLc and lowering LDLc

Table 4. Pharmacokinetics Data for **4a** in Mouse and Hamster[a]

species	% BA	$t_{1/2}$ (α) iv h	$t_{1/2}$ (β) iv h	$t_{1/2}$ obsd hours	AUC/dose iv μg·h/mL·kg	Cl mL/h/kg	V_{ss} mL/kg
mouse ($n = 6$)	22.0[b]	0.042	0.51	16.0	0.382	7842	1957
hamster ($n = 6$)	10.0[b]	0.18	4.4	5.1	19.7	210	480

[a] After iv or oral dose of 30 mg/kg in both species. Area under the curve (AUC) calculations were performed using the linear trapezoidal rule. Bioavailability (BA) was calculated as the ratio of dose-normalized oral to iv AUC's for the same time frame. The half-life ($t_{1/2}$) is the amount of time to eliminate half the concentration of compound from the plasma and is given for the initial (α) and final (β) elimination phases from the iv dose and also from the elimination phase determined for the oral dose. Clearance (Cl) is the rate at which a given amount of plasma is totally cleared of unbound compound. Volume of distribution (V_{ss}) is an approximation of the volume that the compound would occupy at steady state. [b] Oral dosing vehicle EtOH/0.5% methylcellulose.

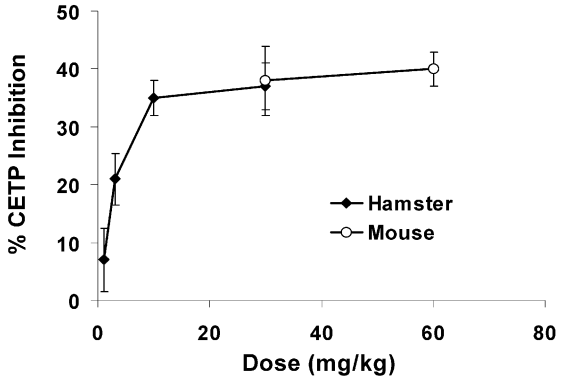


Figure 5. Single dose modulation of CETP activity by **4a** in hamsters and transgenic human-CETP mice as measured ex vivo. [^{3}H]CE-HDL was added to hamster or transgenic human-CETP plasma at a final concentration of 25 μg/mL cholesterol and incubated for 4 h at 37 °C. The ex vivo CETP plasma transfer assay was used to measure the CETP-mediated transfer of [^{3}H]CE from HDL to LDL.

occurs at similar levels to that observed previously for **1**,[26] and the 100-fold improvement in potency of **4a** over **1** in the human serum assay does not translate into significantly improved activity in vivo for either hCETP mice or hamsters. This may be partially due to the known tight affinity that members of this series have exhibited for other plasma proteins, particularly serum albumin,[26] or due to other factors present in the animal serum. The strong association of **4a** with human serum albumin ($K_d \leq 0.01$ μM) was confirmed independently using ^{19}F NMR methods (data not shown). Thus, the unfavorable interaction of **4a** with other plasma proteins may limit their overall in vivo efficacy.

In conclusion, we have discovered additional examples of chiral *N*,*N*-disubstituted trifluoro-3-amino-2-propanols as a new simple class of potent acyclic CETP inhibitors. Several analogues in this series exhibited low nanomolar potency and represent the most potent acyclic CETP inhibitors reported to date. However, further optimization is needed to improve the relatively poor oral exposure and in vivo efficacy of this series.

Experimental Section

General Methods. All reagents were purchased from commercially available sources and used without further purification. Column chromatography was carried out on flash silica gel (Merck 230−400 mesh). Reverse phase chromatography was carried out on a Gilson automated chromatography system (254 nM) using a YMC ODS-A column (50 × 20 mm, 5um, 120A, 50−90% acetonitrile in water (spiked with 0.05% trifluoroacetic acid)). All isolated final purified products were routinely analyzed for purity by reverse-phase HPLC and met a minimum of 90% purity as determined by reverse-phase HPLC monitoring with UV detection (220, 254, and 285 nM). ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were collected on a Varian VXR-400 or VXR-300 spectrometer. The samples were dissolved in $CDCl_3$, C_6D_6, or DMSO-d_6 100 atom % (MSD Isotopes, St. Louis, MO) at a concentration of 0.3−0.7 wt % and placed in 5 mm NMR tubes (Wilmad Glass, Buena, NJ). Mass spectrometry was performed using a SCIEX (Thornhill, Ontario, Canada) API−III mass spectrometer utilizing an electrospray interface. High-resolution mass spectra were obtained by electron impact on a MAT 90 instrument using Electro Calibration with PEG and samples dissolved in H_2O/CH_3CN (50:50). UV absorption spectra were taken on a Hewlett-Packard 8451A diode array spectrophotometer. The chiral purity of individual enantiomeric products was determined with HPLC using a Chiralpak AD 10 μ analytical column. Typically, a mobile phase of 10%/90% 2-propanol/heptane, a flow rate of 1.0 mL/min, and detection at 250 nm provided the optimum chromatography conditions for separation of the individual enantiomers. For each chirally pure product, the achiral mixture was used as a standard to ensure complete separation and detection of each enantiomer. Optical rotations of individual enantiomers were obtained on a Perkin-Elmer 241 polarimeter using a 1.0 mL microcell and CH_3OH as solvent.

3-Bromo-*N*-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]aniline (7). To a solution of 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (2.00 g, 9.0 mmol) in 1,2-dichloroethane (30 mL) were added 3-bromoaniline (0.98 mL, 9.0 mmol), $NaB(OAc)_3H$ (2.48 g, 11.7 mmol), and acetic acid (0.57 mL, 10 mmol). The cloudy mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhyd $MgSO_4$, and evaporated to yield **7** (3.27 g, 96%) as a brown oil which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, 1H), 7.25 (m, 2H), 7.11 (m, 2H), 6.45 (t 1H), 6.56 (m, 2H), 5.90 (tt, 1H), 4.34 (s, 2H). MS *m*/*z* 377 [M$^+$].

3-{(3-Bromophenyl)[3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (8). To a dichloromethane (9 mL) solution of **7** (3.27 g, 8.65 mmol) were added 1,1,1-trifluoro-2,3-epoxypropane (0.968 mL, 11.3 mmol) and $Yb(OTf)_3$ (0.536 g, 0.86 mmol). The cloudy mixture was stirred at room temperature for 24 h, then diluted with diethyl ether. The organic layer was washed with water and brine, dried over anhyd $MgSO_4$, and evaporated to yield 4.20 g (99%) of the title compound as a pale brown oil which can be used without further purification. The formation of the desired product was confirmed by the presence of the alcohol peak (δ 1.5, d) in the ^{1}H NMR spectrum (C_6D_6). An analytical sample was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to give **8** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, 1H), 7.09 (m, 3H), 7.06 (s, 1H), 6.92 (m, 2H), 6.66 (dd, 1H), 5.92 (tt, 1H), 4.69 (s, 2H), 4.36 (m, 1H), 3.88 (dd, 1H), 3.55−3.63 (m, 1H). FABMS *m*/*z* 490 [M + H]$^+$.

***N*-(3-Bromophenyl)-*N*-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,3,3-trifluoropropyl]-3-(1,1,2,2-tetrafluoroethoxy)benzenemethanamine (9).** To a dichloromethane (10 mL) solution of **8** (4.20 g, 8.57 mmol) were added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.0 mL, 13.1 mmol) and triethylamine (2.40 mL, 17.3 mmol). The resulting solution was stirred at room temperature for 4 h. The reaction mixture was diluted with dichloromethane and washed sequentially with saturated $NaHCO_3$ and brine. The organic layer was dried over anhyd $MgSO_4$ and evaporated to an oil. Purification by flash chromatography on silica eluting with 2.5% ethyl acetate in hexane gave **9** (3.0 g, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, 1H), 6.89 (m, 2H), 6.81 (m, 2H), 6.68 (t, 1H), 6.61 (d, 1H), 6.33 (dd, 1H), 5.10 (tt, 1H), 4.12 (q, 1H), 4.11 (s, 2H), 3.38 (m, 2H), 0.88 (s, 9H), −0.06 (s, 3H), −0.19 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −78.5 (d, 3F), −88.2 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{30}BrF_7NO_2Si$ 604.1112 [M + H]$^+$, found 604.1128.

General Procedure for Aryl Ether Couplings with 9. 3-{[3-(4-Chloro-3-ethyl-phenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2e). A solution of **9** (75 mg, 0.124 mmol), cesium carbonate (81 mg, 0.248 mmol), 4-chloro-3-ethylphenol (44 mg, 0.358 mmol), copper triflate benzene complex (6.24 mg, 10 mol %), 1-naphthoic acid (43 mg, 0.248 mmol) in 2:1 toluene, and dimethylacetamide (3.0 mL) was heated at 105 °C for 48 h. The reaction mixture was filtered through Celite, and the solvent was evaporated. The residue was purified by reverse phase chromatography eluting with 50−90% acetonitrile in water to afford **2e** (16.2 mg, 23%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0−7.34 (m, 5H), 6.87 (d, 1H), 6.69 (dd, 1H), 6.48 (dd, 1H), 6.32−6.40 (m, 2H), 5.84 (tt, 1H), 4.63 (s, 2H), 3.87 (dd, 1H), 4.28−4.39 (m, 1H), 3.50−3.61 (m, 1H), 2.69 (q, 2H), 1.18 (t, 3H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.6

(m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{24}ClF_7NO_3$ 566.1332 $[M + H]^+$, found 566.1332.

3-{[3-(3-Isopropylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2a). Tan oil, yield 7.0 mg (10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.20−7.08 (m, 4H), 7.02 (bs, 1H), 6.97 (d, 1H), 6.88 (t, 1H), 6.74 (dd, 1H), 6.53 (dd, 1H), 6.46−6.44 (m, 2H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.34 (m, 1H), 3.84 (dd, 1H), 3.61−3.53 (m, 1 H), 2.86 (m, 1H), 1.21 (d, 6H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.4 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{27}H_{27}F_7NO_3$ 546.1879 $[M + H]^+$, found 546.1878.

3-{[3-(3-Trifluoromethoxyphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2b). Tan oil, yield 9.2 mg (12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.27 (t, 1H), 7.20 (t, 1H), 7.11 (d, 2H), 7.01 (bs, 1H), 6.92 (dd, 1H), 6.86−6.81 (m, 2H), 6.56 (dd, 1H), 6.45 (dd, 1H), 6.39 (t, 1H), 5.87 (tt, 1H), 4.65 (s, 2H), 4.33 (m, 1H), 3.86 (dd, 1H), 3.62−3.54 (m, 1H).^{19}F NMR ($CDCl_3$) δ −58.3 (s, 3F), −79.2 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{20}F_{10}NO_4$ 588.1232 $[M + H]^+$, found 588.1236.

3-{[3-(4-Fluorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2c). Tan oil, yield 1.19 g (64%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, 1H), 7.21−7.10 (m 3H), 7.15−6.89 (m, 5H), 6.49 (dd, 1H), 6.38 (dd, 1H), 6.33 (m, 1H), 5.92 (tt, 1H), 4.67 (ABq, 2H), 4.37 (m, 1H), 3.91 (dd, 1H), 3.59 (dd, 1H), 2.48 (d, 1H). ^{19}F NMR (300 MHz, $CDCl_3$) δ −79.2 (d, 3F), −88.5 (m, 2F), −120.3 (m, 1F), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{20}F_8NO_3$ 522.1315 $[M + H]^+$, found 522.1297.

3-{[3-(2,3-Dichlorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2d). Tan oil, yield 3.1 mg (4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, 1H), 7.18−7.14 (m, 2H), 7.10−7.01 (m, 2H), 6.85 (bs, 1H), 6.77 (t, 1H), 6.70−6.65 (m, 2 H), 6.34 (d, 1H), 5.98 (d, 1H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.35 (m, 1H), 3.88 (dd, 1H), 3.59−3.50 (m, 1H). ^{19}F NMR ($CDCl_3$) d −79.4 (d, 3F), −88.7 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{19}Cl_2F_7NO_3$ 572.0630 $[M + H]^+$, found 572.0653.

3-{[3-(3-Ethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-tri-fluoropropan-2-ol (2f). Tan oil, yield 7.7 mg (12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1 H), 7.22−7.07 (m, 4H), 7.022 (bs, 1H), 6.96−6.87 (m, 1H), 6.84 (bs, 1H), 6.76 (dd, 1H), 6.47 (dd, 1H), 6.41−6.39 (m, 2H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.33 (m, 1H), 3.83 (dd, 1H), 3.60−3.49 (m, 1 H), 2.61 (q, 2H), 1.204 (t, 3H).^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{25}F_7NO_3$ 532.1722 $[M + H]^+$, found 532.1705.

3-{[3-(3,5-Dimethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2g). Tan oil, yield 6.6 mg (10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (m, 1H), 7.02−6.99 (m, 2H), 6.85 (m, 3H), 6.81 (m, 3H), 6.67 (s, 1H), 5.90 (s, 1H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.32 (m, 1H), 3.78 (bs, 1H), 3.55−3.48 (m, 1H), 3.08 (m, 1H), 2.25 (s, 6H). ^{19}F NMR ($CDCl_3$) δ −79.1 (d, 3F), −88.4 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{25}F_7NO_3$ 532.1722 $[M + H]^+$, found 532.1705.

3-{[3-(3-*tert*-Butylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2h). Tan oil, yield 6.8 mg (10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1 H), 7.24−7.16 (m, 1H), 7.15−7.07 (m, 5), 7.02 (bs, 1H), 6.74 (d, 1H), 6.48−6.37 (m, 3H), 5.88 (tt, 1H), 4.64 (d, 2H), 4.32 (m, 1H), 3.85 (dd, 1H), 3.56−3.48 (m, 1H), 1.28 (s, 9H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.5 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{28}H_{28}F_7NO_3$ 560.2035 $[M + H]^+$, found 560.2055.

3-{[3-(3,4-Dimethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2i). Tan oil, yield 38.9 mg (18%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.19−7.04 (m, 4 H), 7.00 (bs, 1 H), 6.77 (d, 1 H), 6.69 (dd, 1H), 6.55 (dd, 1H), 6.49 (dd, 1H), 6.45 (t, 1H), 5.88 (t, 1H), 4.64 (q, 2H), 4.34 (m, 1H), 3.82 (dd, 1H), 3.64−3.55 (m, 1H), 2.23 (s, 3H), 2.21 (s, 3H). HRMS calcd for $C_{26}H_{25}F_7NO_3$ 531.1644 $[M + H]^+$, found 531.1649.

3-{[3-(4-Fluoro-3-methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2j). Tan oil, yield 10.1 mg (15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1H), 7.17−7.09 (m, 2H), 7.00 (bs, 1H), 6.91 (t, 1H), 6.81−6.68 (m, 2H), 6.49 (dd, 1H), 6.39−6.34 (m, 2H), 5.88 (tt, 1H), 4.63 (s, 2H), 4.34 (m, 1H), 3.84 (dd, 1H), 3.61−3.52 (m, 1H), 2.22 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.5 (m, 2F), −120.4 (m, 1F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{22}F_8NO_3$ 536.1471 $[M + H]^+$, found 536.1480.

3-{[3-(3,4-Dichlorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2k). Tan oil, yield 6.0 mg (8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 2H), 7.19 (t, 1H), 7.08 (t, 2H), 7.04−7.01 (m, 3H), 6.76 (dd, 2H), 6.52 (dd, 1H), 5.88 (tt, 1 H), 4.65 (s, 2H), 4.33 (m, 1H), 3.88 (dd, 1H), 3.62−3.54 (m, 1H). ^{19}F NMR ($CDCl_3$) δ −79.4 (d, 3F), −88.7 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{19}Cl_2F_7NO_3$ 572.0630 $[M + H]^+$, found 572.0630.

3-{[3-(3-Ethyl-5-methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2l). Tan oil, yield 2.5 mg (4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (m, 1H), 7.02−6.99 (m, 2H), 6.85 (m, 3H), 6.81 (m, 3H), 6.67 (s, 1H), 5.90 (s, 1H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.32 (m, 1H), 3.78 (bs, 1H), 3.55−3.48 (m, 1H), 3.08 (m, 1H), 2.73 (q, 2H), 2.27 (s, 3H), 1.23 (t, 3H). HRMS calcd for $C_{27}H_{27}F_7NO_3$ 546.1879 $[M + H]^+$, found 546.1899.

3-{[3-(3-Methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2m). Tan oil, yield 39.8 mg (19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, 1H), 7.42−7.22 (m, 5H), 7.09 (t, J = 2 Hz, 2H), 6.98 (bs, 1H), 6.61 (dd, 1H), 6.38 (dd, 1H), 6.29 (t, 1H), 5.85 (tt, 1H), 4.66 (q, 2H), 4.33 (m, 1H), 3.83 (dd, 1H), 3.70−3.58 (m, 1H), 2.70 (s, 3 H). HRMS calcd for $C_{25}H_{23}F_7NO_3$ 517.1488 $[M + H]^+$, found 517.1493.

3-{[3-(5,6,7,8-Tetrahydronaphthalen-2-yloxy)phenyl]-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2n). Tan oil, yield 13.8 mg (20%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1H), 7.18−7.06 (t, 1H), 7.02 (bs, 1H), 6.98−6.95 (m, 1H), 6.72−6.68 (m, 2 H), 6.44 (dd, 1H), 6.38−6.36 (m, 2H), 5.88 (tt, 1H), 4.63 (s, 2H), 4.35 (m, 1H), 3.85 (dd, 1H), 3.56−3.49 (m, 1H), 2.72−2.69 (m, 4H), 1.78−1.76 (m, 4H). HRMS calcd for $C_{28}H_{27}F_7NO_3$ 558.1879 $[M + H]^+$, found 558.1881.

3-{[3-(2,3-Difluorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2o). Tan oil, yield 1.7 mg (2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, 1H), 7.18−7.14 (m, 2H), 7.10−7.01 (m, 2H), 6.85 (bs, 1H), 6.77 (t, 1H), 6.70−6.65 (m, 2 H), 6.34 (d, 1H), 5.98 (d, 1H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.35 (m, 1H), 3.88 (dd, 1H), 3.59−3.50 (m, 1H). HRMS calcd for $C_{24}H_{19}F_9NO_3$ 540.1221 $[M + H]^+$, found 540.1182.

3-{[3-[4-(Trifluoromethyl)phenoxy]phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2p). Tan oil, yield 259 mg (43%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 2H), 7.30 (t 1H), 7.20 (t, 1H), 7.07 (m, 2H), 7.00 (s, 1H), 6.96−6.90 (d, 2H), 6.55 (dd, 1H), 6.43 (dd, 1H), 6.34 (t, 1H), 5.87 (tt, 1H), 4.64 (ABq, 2H), 4.33 (m, 1H), 3.88 (dd, 1H), 3.58 (dd, 1H), 2.43 (d, 1H). ^{19}F NMR (300 MHz, $CDCl_3$) δ −62.2 (s, 3F), −79.2 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{20}F_{10}NO_3$ 572.1282 $[M + H]^+$, found 572.1268.

3-{[3-(4-Methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2q). Tan oil, yield 43.2 mg (20%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.19−7.08 (m, 4H), 7.00 (s, 1H), 6.84 (d, 2H), 6.537−6.40 (m, 3H), 5.87 (tt, 1H), 4.62 (q, 2H), 4.34−4.24 (m, 4H), 3.83 (dd, 1H), 3.59 (m, 1H), 2.32 (s, 3H).^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS Calcd for $C_{25}H_{23}F_7NO_3$ 518.1566 $[M + H]^+$, found 518.1561.

3-{[3-(4-Chloro-3-methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2r). Tan oil, yield 29.3 mg (13%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.24−7.06 (m, 4H), 7.01 (bs, 1H), 6.84 (d, 1H), 6.72 (dd, 1H), 6.55 (dd, 1 H), 6.49 (dd, 1H), 6.45 (t, 1H), 5.88 (tt, 1H), 4.64 (s, 2H), 3.85 (dd, 1H), 3.82 (dd, 1H),

3.64−3.55 (m, 1H), 2.23 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{22}ClF_7NO_3$ 551.1098 $[M + H]^+$, found 551.1101.

3-({3-[3-(Trifluoromethyl)phenoxy]phenyl}[3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino)-1,1,1-trifluoropropan-2-ol (2s). Tan oil, yield 4.6 mg (7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, 2H), 7.32 (m, 2H), 7.21 (s, 1H), 7.12−7.09 (m, 4H), 7.01 (bs, 1H), 6.58 (dd, 1 H), 6.48−6.38 (m, 2H), 5.88 (tt, 1H), 4.66 (s, 2H), 4.34 (m, 1H), 3.86 (dd, 1H), 3.63−3.55 (m, 1H). HRMS calcd for $C_{25}H_{20}F_{10}NO_3$ 572.1283 $[M + H]^+$, found 572.1265.

3-{[3-(4-*n*-Propylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2t). Tan oil, yield 32.9 mg (36%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32 (t, 1H), 7.19−7.03 (m, 5H), 7.00 (s, 1H), 6.87 (d, 2H), 6.48 (dd, 1H), 6.43−6.33 (m, 2H), 5,87 (tt, 1H), 4.64 (s, 2H), 4.37−4.28 (m, 1H), 3.85 (dd, 1H), 3.60−3.48 (m, 1H), 2.53 (t, 2H), 1.68−1.54 (m, 2H), 0.92 (t, 3H). HRMS calcd for $C_{27}H_{27}F_7NO_3$ 545.1801 $[M + H]^+$, found 545.1782.

3-{[3-(3,5-Difluorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2u). Tan oil, yield 4.1 mg (6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 2H), 7.22 (t, 1H), 7.14−7.09 (m, 2H), 7.02 (bs, 1H), 6.61 (dd, 1H), 6.53−6.38 (m, 4H), 5.88 (tt, 1H), 4.66 (s, 2H), 4.32 (m, 1H), 3.86 (dd, 1H), 3.64−3.56 (m, 1H). HRMS calcd for $C_{24}H_{19}F_9NO_3$ 540.1221 $[M + H]^+$, found 540.1217.

3-{[3-(4-*N*,*N*-Dimethylaminophenoxy)phenyl][3-(1,1,2,2)-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2v) Tan oil, yield 1.9 mg, (5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.03 (t, 3H), 6.85 (m, 4H), 6.66 (d, 1H), 6.35−5.93 (m, 4H), 5.44 (tt, 1H), 4.42 (s, 2H), 4.20 (m, 1H), 3.08 (dd, 1H), 3.00 (s, 6H), 2.90 (m, 1H). HRMS calcd for $C_{26}H_{26}F_7N_2O_3$ 547.1831 $[M + H]^+$, found 547.1844.

3-{[3-(4-*iso*-Propyl-3-methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2w). Tan oil, yield 9.7 mg (14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1H), 7.16−7.06 (m, 4H), 7.02 (bs, 1H), 6.77−6.75 (m, 2H), 6.46−6.35 (m, 3H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.32 (m, 1H), 3.84 (dd, 1H), 3.55−3.48 (m, 1H), 3.08 (m, 1H), 2.27 (s, 3H), 1.20 (d, 6H). ^{19}F NMR ($CDCl_3$) δ −79.1 (d, 3F), −88.5 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{28}H_{29}F_7NO_3$ 560.2035 $[M + H]^+$, found 560.2055.

3-{[3-(3-Fluorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2x). Tan oil, yield 3.0 mg (5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1 H), 7.21−7.18 (m, 2H), 7.13 (m, 4H), 7.01 (bs, 1H), 6.80−6.56 (m, 3H), 6.49−6.43 (m, 1H), 5.88 (tt, 1H), 4.65 (s, 2H), 4.34 (m, 1H), 3.85 (dd, 1H), 3.64−3.55 (m, 1H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.6 (m, 2F), −120.0 (m 1H) −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{20}F_8NO_3$ 522.1315 $[M + H]^+$, found 522.1337.

3-{[3-(2-Chlorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2y). Tan oil, yield 3.7 mg (7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 1H), 7.27 (m, 1H), 7.20−7.03 (m, 4H), 6.88−6.64 (m, 4H), 6.35 (d, 1H), 6.03 (d, 1H), 5.48 (tt, 1H), 4.42 (s, 2H), 4.18 (m, 1H), 3.09 (dd, 1H), 2.94 (m, 1H). HRMS calcd for $C_{24}H_{20}ClF_7NO_4$ 538.1019 $[M + H]^+$, found 538.1021.

3-{[3-(4-Chlorophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2z). Tan oil, yield 3.1 mg (6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.22 (d, 2H), 7.19−7.08 (m, 3H), 7.00 (bs, 1H), 6.85 (d, 2H), 6.58 (dd, 1H), 6.44 (dd, 1H), 6.40 (t, J = 1 Hz, 1H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.35 (m, 1H), 3.86 (dd, 1H), 3.64−3.59 (m, 1H). HRMS calcd for $C_{24}H_{20}ClF_7NO_3$ 537.0942 $[M + H]^+$, found 537.0944.

3-{[3-(4-*n*-Propoxyphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2aa). Tan oil, yield 4.9 mg (7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1H), 7.16−7.10 (m, 3H), 7.00 (bs, 1H), 6.86 (q, 4H), 6.48 (dd, 1H), 6.40−6.37 (m, 2H), 5.88 (tt, 1H), 4.62 (s, 2H), 4.33 (m, 1H), 3.89 (t, 2H), 3.84 (dd, 1H), 3.60−3.51 (m, 1H), 1.79 (m, 2H), 1.04 (t, 3H). HRMS calcd for $C_{27}H_{27}F_7NO_4$ 562.1828 $[M + H]^+$, found 562.1803.

3-{[3-(4-*iso*-Propylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2bb). Tan oil, yield 9.2 mg (14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, 1H), 7.14 (q, 4H), 7.11 (s, 1H), 7.01 (bs, 1H), 6.88 (d, 2H), 6.48 (dd, 1H), 6.43−6.37 (m, 2H), 5.88 (tt, 1H), 4.63 (s, 2H), 4.33 (m, 1H), 3.84 (dd, 1H), 3.58−3.50 (m, 1H), 2.88 (m, 1H), 1.23 (d, 6H). HRMS calcd for $C_{27}H_{27}F_7NO_3$ 546.1879 $[M + H]^+$, found 546.1899.

3-{[3-(4-Trifluoromethoxyphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2cc). Tan oil, yield 238 mg (62%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t 1H), 7.32 (t, 1H), 7.20−7.09 (m, 4H), 7.03 (s, 1H), 6.94 (d, 2H), 6.54 (dd, 1H), 6.42 (dd, 1H), 6.36 (t, 1H), 5.90 (tt, 1H), 4.67 (ABq, 2H), 4.36 (m, 1H), 3.90 (dd, 1H), 3.61 (dd, 1H), 2.52 (bs, 1H). ^{19}F NMR (300 MHz, $CDCl_3$) δ −58.7 (s, 3F), −79.2 (d, 3F), −88.6 (m, 2F), −137.3 (dt, 2F). HRMS calcd for $C_{25}H_{20}F_{10}NO_4$ 588.1233 $[M + H]^+$, found 588.1241.

3-{[3-(4-Aminophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2dd). Tan oil, yield 13.4 mg (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (t, 1H), 7.36−7.14 (m, 2H), 7.08 (t, 1H), 6.90 (d, 1H), 6.74−6.64 (m, 2H), 6.57−6.39 (m, 2H), 6.36−6.32 (m, 1H), 6.2 (d, 1H), 5.75 (t, 1H), 4.79 (s, 2H), 4.55−4.43 (m, 1H), 3.97 (dd, 1H), 3.64 (dd, 1H). HRMS calcd for $C_{24}H_{22}F_7N_2O_3$ 519.1519 $[M + H]^+$, found 519.1529.

3-{[3-(3-Methoxyphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2ee). Tan oil, yield 2.9 mg (5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.20−7.08 (m, 4H), 7.02 (bs, 1H), 6.97 (d, 1H), 6.88 (t, 1H), 6.74 (dd, 1H), 6.53 (dd, 1H), 6.46−6.44 (m, 2H), 5.88 (tt, 1H), 4.64 (s, 2H), 4.34 (m, 1H), 3.84 (dd, 1H), 3.65 (s, 3H), 3.61−3.53 (m, 1H). HRMS calcd for $C_{25}H_{23}F_7NO_4$ 533.1437 $[M + H]^+$, found 533.1450.

3-{[3-(4-Benzylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2ff). Tan oil, yield 9.3 mg (12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.01 (m, 12H), 6.87 (d, 2H), 6.44 (dd, 1H), 6.38 (dd, 1H), 6.34 (t, 1H), 5.87 (tt, 1H), 4.62 (s, 2H), 4.32 (m, 1H), 3.94 (s, 2H), 3.85 (dd, 1H), 3.57−3.48 (m, 1H). ^{19}F NMR ($CDCl_3$) δ −79.1 (d, 3F), −88.3 (m, 2F), −137.2 (dt, 2F)HRMS calcd for $C_{31}H_{27}F_7NO_3$ 594.1879 $[M + H]^+$, found 594.1906.

3-{[3-(1,1′-Biphenyl-4-yloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2gg). Tan oil, yield 7.2 mg (10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.48 (m, 4H), 7.43 (t, 2H), 7.36−7.26 (m, 2H), 7.184 (t, 1H), 7.09 (m, 2H), 7.024−6.99 (m, 3H), 6.55−6.39 (m, 3H), 5.842 (tt, 1H), 4.65 (s, 2H), 4.37−4.33 (m, 1H), 3.88 (dd, 1H), 3.60−3.52 (m, 1H). HRMS calcd for $C_{30}H_{25}F_7NO_3$ 580.1722 $[M + H]^+$, found 580.1741.

4-{3-[[3-(1,1,2,2-Tetrafluoroethoxy)benzyl](3,3,3-trifluoro-2-hydroxypropyl)-amino]phenoxy}phenol (2hh). Tan oil, yield 82 mg (26%). ^{1}H NMR (C_6D_6, 400 MHz) δ 6.92−6.79 (m, 6H), 6.67 (d, 1H), 6.42−6.38 (m, 4H), 6.17 (d, 1H), 5.10 (tt, 1H), 4.52 (bs, 2H), 4.10 (bs, 1H), 3.44 (d, 1H), 3.18 (q, 1H), 3.09, 3.05 (dd, 1H), 1.96 (d, 1H). HRMS calcd for $C_{24}H_{21}F_7NO_4$ 520.1359 $[M + H]^+$, found 520.1325.

3-{[3-(4-Mercaptophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2ii). Tan oil, yield 3.6 mg (4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.17 (m, 9H), 7.04−6.99 (m, 1H), 6.96−6.82 (m, 2H), 5.88 (tt, 1H), 4.76 (d, 1H), 4.40 (d, 1H), 4.39−4.27 (m, 1H), 3.82−3.65 (m, 2H). ^{19}F NMR ($CDCl_3$) δ −79.4 (d, 3F), −88.7 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{21}F_7NO_3S$ 536.1130 $[M + H]^+$, found 536.1163.

3-{[3-(1,1,2,2-Tetrafluoroethoxy)benzyl]amino}-phenol (11). To a solution of 3-aminophenol (4.91 g, 45.0 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (10.0 g, 45.0 mmol) dissolved in 100 mL of 1,2-dichloroethane were added sodium triacetoxyborohydride (14.28 g 67.5 mmol) and glacial acetic acid (2.7 mL, 47.3 mmol). The reaction mixture was stirred for 6 h, water was added, and the mixture was extracted with dichloromethane. The organics were washed with saturated aqueous sodium bicarbonate then dried over anhyd $MgSO_4$. The dried organic layer was evaporated to give

11 (11.00 g, 78%) as a dark orange oil, that was used below without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, 1H), 7.24−7.27 (m, 2H), 7.11 (dd, 1H), 7.00 (t, 1H), 6.17−6.22 (m, 2H), 6.08 (t, 1H), 5.88 (tt, 1H), 4.32 (s, 2H). HRMS calcd for $C_{15}H_{14}F_4NO_2$ 316.0960 $[M + H]^+$, found 316.0989.

3-{[3-(1,1,2,2-Tetrafluoroethoxy)benzyl](3,3,3-trifluoro-2-hydroxypropyl)amino}phenol (12). A solution of **11** (11.0 g, 34.9 mmol), 3,3,3-trifluoro-1,2-epoxypropane (4.5 mL, 52.4 mmol), and ytterbium trifluoromethanesulfonate (2.2 g, 10 mol %) in 20 mL of acetonitrile was heated at 50 °C in a sealed glass tube for 16 h. The reaction mixture was cooled, water was added, and the reaction mixture was extracted with ether. The ether layer was washed with saturated aqueous sodium bicarbonate and brine, then dried over anhyd $MgSO_4$. The dried organic layer was evaporated to give **12** (8.07 g, 89%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, 1H), 7.07−7.14 (m, 4H), 6.25−6.37 (m, 3H), 5.91 (tt, 1H), 4.68 (s, 2H), 4.39 (m, 1H), 3.88 (dd, 1H), 3.58 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ −79.0 (d, 3F), −88.0 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{18}H_{17}F_7NO_3$ 428.1097 $[M + H]^+$, found 428.1104.

General Procedure for Aryl Ether Couplings with 12. 3-{[3-(2-Nitrophenoxy)-phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino}-1,1,1-trifluoro-2-propanol (2kk). A solution of **12** (100 mg, 0.23 mmol), 1-bromo-2-nitrobenzene (52.4 mg, 0.26 mmol), copper(I) trifluoromethanesulfonate benzene complex (3 mg, 2.5 mol %), and cesium carbonate (100 mg, 0.31 mmol) in toluene (1 mL) and ethyl acetate (1 μL) was heated at 95 °C in a sealed vial for 4 days. The reaction mixture was filtered through Celite, and the solvent was evaporated from the filtrate. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (1:1 to 9:1) to afford **2kk** (14.1 mg, 11%) as an orange oil. ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H), 6.98−7.50 (m, 8H), 6.47−6.67 (m, 3H), 5.90 (tt, 1H), 4.64 (s, 2H), 4.35−4.42 (m, 1H), 3.84 (dd, 1H), 3.63 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ −79.4 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{20}F_7N_2O_5$ 549.1260 $[M + H]^+$, found 549.1235.

3-{[3-(3-Fluoro-2-nitrophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2jj). Tan oil, yield 14.0 mg (10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.69 (m, 1H), 7.41−6.98 (m, 7H), 6.75−6.70 (m, 1H), 6.50−7.42 (m, 2H), 5.91 (tt, 1H), 4.63 (s, 2H), 4.42−4.33 (m, 1H), 3.85 (dd, 1H), 3.64 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ −79.8 (d, 3F), −88.7 (m, 2F), −120.1 (m, 1H), −137.2 (dt, 2F). HRMS calcd for $C_{24}H_{19}F_8N_2O_5$ 567.1166 $[M + H]^+$, found 567.1135.

3-{[3-(4-Nitrophenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (2ll). Tan oil, yield 14.9 mg (11%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16−8.11 (m, 1H), 7.38−7.24 (m, 5H), 7.10 (t, 2H), 7.01 (s, 1H), 6.96 (d, 1H), 6.63 (d, 1H), 6.47 (d, 1H), 6.39 (s, 1H), 5.85 (tt, 1H), 4.66 (s, 2H), 4.42−4.32 (m, 1H), 3.90 (dd, 1H), 3.61 (dd, 1H). HRMS calcd for $C_{24}H_{20}F_7NO_5$ 549.1260 $[M + H]^+$, found 549.1306.

3-{[3-(Pyridin-2-yloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3a). Tan oil, yield 0.5 mg (1%). ^{1}H NMR ($CDCl_3$, 300 MHz)) δ 8.24 (d, 1H), 7.67(t, 1H), 7.18−7.14 (m, 2H), 7.05 (t, 1H), 6.85 (d, 1H), 6.81 (t, 1H), 6.68 (dd, 1H), 6.72−6.59 (m, 1H), 6.47 (d, 1H), 6.12 (dd, 1H), 5.85(bs, 1H), 5.44 (tt, 1H), 4.68 (s, 2H), 4.36 (bs, 1H), 3.79 (d, 1H), 3.59−3.69 (m, 1H).^{19}F NMR ($CDCl_3$) δ −79.5 (d, 3F), −88.7 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{23}H_{20}F_7N_2O_3$ 505.1362 $[M + H]^+$, found 505.1378.

3-{[3-(Pyridin-3-yloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3b). Tan oil, yield 12.2 mg (14.6%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (d, 2H), 7.79 (d, 1H), 7.63 (s, 1H), 7.32 (t, 1H), 7.20−7.29 (m, 1H), 7.11 (t, 2H), 7.02 (s, 1H), 6.62 (d, 1H), 6.55 (s, 1H), 6.47 (d, 1H), 5.89 (tt, 1H), 4.68 (q, 2H), 4.36 (bs, 1H), 3.79 (d, 1H), 3.59−3.69 (m, 1H). HRMS calcd for $C_{23}H_{20}F_7N_2O_3$ 505.1362 $[M + H]^+$, found 505.1369.

3-{(3-[[3-(Trifluoromethoxy)benzyloxy]phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3c). To a solution of **12** (100 mg, 0.23 mmol) and 3-trifluoromethoxybenzyl bromide (70.0 mg, 0.27 mmol) in 2.5 mL of acetone was added solid cesium carbonate (100 mg, 0.31 mmol). The reaction mixture was heated to 60 °C for 18 h, then cooled. The reaction mixture was filtered through Celite, and the solvent was evaporated from the filtrate. The residue was purified by C_{18} reverse phase HPLC with mobile phase acetonitrile/water (1:1 to 9:1) to afford **3c** (63.3 mg, 45%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04−7.42 (m, 9H), 6.43−6.55 (m, 3H), 5.84 (tt, 1H), 4.98 (s, 2H), 4.62 (s, 2H), 4.32−4.39 (m, 1H), 3.83 (dd, 1H), 3.61 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ −58.1 (s, 3F) −79.3 (d, 3F), −88.4 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{23}F_{10}NO_4$ 602.1389 $[M + H]^+$, found 602.1380.

3-{(3-[[3-(Trifluoromethyl)benzyloxy]phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3d). Tan oil, yield 68.1 mg (48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.44 (m, 4 H), 7.37−7.12 (m, 6H), 6.60−6.52 (m, 2H), 5.86 (tt, 1H), 5.01 (s, 2H), 4.62 (s, 2H), 4.40−4.32 (m, 1H), 3.82 (dd, 1H), 3.63 (dd, 1H). ^{19}F NMR ($CDCl_3$) d −62.1 (s, 3F) −79.3 (d, 3F), −88.5 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{22}F_{10}NO_3$ 586.1440 $[M + H]^+$, found 586.1419.

3-{[3-(Benzyloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)-benzyl]amino}-1,1,1-trifluoropropan-2-ol (3f). Tan oil, yield 69.5 mg (52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.28 (m, 6H), 7.20−7.12 (m, 3H), 7.07 (s, 1H), 6.47 (d, 1H), 6.41−6.39 (m, 2H), 5.91 (tt, 1H), 5.03 (s, 2H), 4.67 (s, 2H), 4.37−4.31 (m, 1H), 3.86 (dd, 1H), 3.56 (dd, 1H). ^{19}F NMR ($CDCl_3$) d −79.1 (d, 3F), −88.5 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{22}F_7NO_3$ 518.1566 $[M + H]^+$, found 518.1578.

3-{[3-(Cyclohexylmethoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3e). Bromomethylcyclohexane (42 μL, 0.30 mmol) and **12** (100 mg, 0.23 mmol) were dissolved in 2 mL of acetonitrile. Cesium carbonate (144 mg, 0.44 mmol) was added, and the stirred solution was warmed to 50 °C for 48 h, at which time HPLC analysis indicated that no phenolic starting material remained. The reaction was quenched with water and filtered through prewetted Celite eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford **3e** (55 mg, 35%) as a brown oil, which was greater than 99% pure by reverse phase HPLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9−1.4 (m, 5H), 1.7−1.9 (m, 6H), 3.6 (m, 3H), 3.9 (dd, 1H), 4.3 (m, 1H), 4.7 (m, 2H), 5.1 (s, 1H), 5.9 (tt, 1H), 6.5 (m, 3H), 7.0−7.4 (m, 5H). ^{19}F NMR ($CDCl_3$) d −79.2 (d, 3F), −88.4 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{30}F_7NO_3$ 524.2036 $[M + H]^+$, found 524.2028.

3-{3-[[4-(Trifluoromethoxy)benzyloxy]phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3g). Tan oil, yield 69.2 mg (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.20 (m, 8H), 7.02 (s, 1H), 6.55−6.42 (m, 3H), 5.88 (tt, 1H), 4.99 (s, 1H), 4.63 (s, 1H), 4.39−4.31 (m, 1H), 3.82 (dd, 1H), 3.59 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ −61.6 (s, 3F). −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{22}F_{10}NO_4$ 602.1389 $[M + H]^+$, found 602.1383.

3-{(3-Isopropoxyphenyl)[3-(1,1,2,2-tetrafluoroethoxy)-benzyl]amino}-1,1,1-trifluoropropan-2-ol (3h). Tan oil, yield 77 mg (59%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (t, 1H), 7.20−7.05 (m, 4H), 6.35 (t, 1H), 6.25 (bs, 1H), 5.90 (tt, 1H), 4.65 (s, 2H), 4.45 (q, 1H), 4.35 (m, 1H), 3.85 (dd, 1H), 3.55 (dd, 1H), 2.55 (bs, 1H), 1.25 (t, 6H). ^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{21}H_{23}F_7NO_3$ 470.1488 $[M + H]^+$, found 470.1565.

3-{[3-(Cyclopentyloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3i). Tan oil, yield 15 mg (13%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (t, 1H), 7.20−7.05 (m, 4H), 6.55−6.3 (m, 3H), 5.90 (tt, 1H), 4.65 (s, 3H), 4.35 (m, 1H), 3.85 (dd, 1H), 3.55 (dd, 1H), 3.05 (bs, 1H), 1.9−1.5 (m, 8H). HRMS calcd for $C_{23}H_{25}F_7NO_3$ 496.1723 $[M + H]^+$, found 496.1719.

3-{[3-(Cyclohexyloxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (3j). Tan oil, yield 1.8 mg (1.5%). HRMS calcd for $C_{24}H_{27}F_7NO_3$ 510.1880 $[M + H]^+$, found 510.1910.

1-Chloro-2-ethyl-4-(3-nitrophenoxy)benzene (15a). To a solution of 1,3-dinitrobenzene (16.8 g, 0.1 mol) and 4-chloro-3-ethylphenol (15.6 g, 0.1 mol) in 200 mL of dimethyl sulfoxide was added cesium carbonate (65 g, 0.2 mol). The reaction mixture was heated at 100 °C under nitrogen overnight, then cooled to room temperature. The reaction mixture was filtered through Celite, then rinsed with diethyl ether and a small amount of water. The filtrate was extracted several times with diethyl ether. The organic layers were combined, washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to give **15a** (21.8 g, 78%) as a dark orange oil, which was greater than 90% pure by reverse phase HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.89 (dd, 1H), 7.72 (t, 1H), 7.46 (t, 1H), 7.27 (dd 1H), 7.30 (dd, 1H), 6.99 (m, 2H), 2.85 (q, 2H), 1.27 (t, 3H). HRMS calcd for $C_{14}H_{13}ClNO_3.NH_4$ 295.0849 $[M + NH_4]^+$, found 295.0862.

3-(4-Chloro-3-ethylphenoxy)aniline (16a). To a solution of **15a** (10 g, 0.036 mol) in 400 mL of glacial acetic acid and 1 mL of water was added zinc metal (20 g, 0.305 mol) at room temperature, and the resultant mixture was stirred for 1 h. The filtrate was neutralized with ammonium hydroxide and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to give **16a** (10 g, 100%) as a dark orange oil, which was greater than 90% pure by reverse phase HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 1H), 7.11 (t 1H), 6.91 (d, 1H), 6.80 (dd, 79), 6.44 (d, 1H), 6.40 (d, 1H), 6.31 (s, 1H), 2.72 (q, 2H), 1.21 (t, 3H). HRMS calcd for $C_{14}H_{15}ClNO$ 248.0842 $[M + H]^+$, found 248.0833.

3-(4-Chloro-3-ethylphenoxy)-*N*-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]aniline (13a). To a solution of **16a** (2.0 g, 8.1 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (1.6 g, 7.3 mmol) in 30 mL of dichloroethane were added sodium triacetoxyborohydride (2.0 g, 9.7 mmol) and glacial acetic acid (0.51 mL, 8.9 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched with water and extracted with diethyl ether. The organic layer was washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to give **13a** (3.5 g, 95%) as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.25 (m 4H), 7.10 (m, 3H), 6.88 (d, 1H), 6.42 (d, 1H), 6.38 (d, 1H), 6.29 (s, 1H), 5.92 (t, 1H), 4.32 (s, 2H), 2.73 (q, 2H), 1.21 (t, 3H). ^{19}F NMR ($CDCl_3$) δ −88.3 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{23}H_{21}ClF_4NO_2$ 454.1197 $[M + H]^+$, found 454.1220.

(2*R*)-3-{[3-(4-Chloro-3-ethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4a). A solution of **13a** (1.8 g, 4.0 mmol), *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.64 g, 5.7 mmol), and ytterbium(III) trifluoromethanesulfonate (0.25 g, 0.4 mmol) in 1.5 mL of CH_3CN was heated at 40 °C in a sealed glass tube for 1 h. The reaction mixture was cooled to room temperature, then diluted with water and diethyl ether and extracted. The ether layer was washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1:7:0.01 of EtOAc:hexane:concentrated NH_4OH to afford **4a** (1.5 g, 66%) as a yellow oil (97% ee by chiral HPLC analysis). $[\alpha]^{25}_{589} = +36.9$ (*c* 1.044 g%, $CHCl_3$), $[\alpha]^{25}_{365} = +189.7$ (*c* 1.044 g%, $CHCl_3$). The refractive index @ 25 °C is 1.5275. ^{1}H NMR ($CDCl_3$) δ 7.30 (t, 1H), 7.20 (d, 1H), 7.15 (t, 1H), 7.08 (t, 2H), 7.00 (s, 1H), 6.86 (d, 1H), 6.68 (dd, 1H), 6.48 (dd, 1H), 6.36 (dd, 1H), 6.34 (t, 1H), 5.81 (tt, 1H), 4.62 (s, 2H), 4.32 (m, 1H), 3.84 (dd, 1H), 3.55 (dd, 1H), 2.67 (q, 2H), 2.45 (bs, 1H), 1.17 (t, 3H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{24}ClF_7NO_3$ 566.1330 $[M + H]^+$, found 566.1323. Anal. Calcd for $C_{26}H_{23}ClF_7NO_3$: C, 55.18; H, 4.10; N, 2.48, found C, 54.92; H, 4.05; N, 2.33.

(2*R*)-3-{[3-(3-Ethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4b). Prepared in a manner similar to **4a** using 3-ethylphenol instead of 4-chloro-3-ethylphenol. Product was a light brown oil (final step 68%). ^{1}H NMR ($CDCl_3$) δ 7.28 (t, 1H), 7.16 (m, 2H), 7.10 (t, 2H), 6.98 (s, 1H), 6.84 (m, 2H), 6.78 (dd, 1H), 6.52 (dd, 1H), 6.40 (dd, 1H), 6.38 (t, 1H), 5.85 (tt, 1H), 4.62 (s, 2H), 4.33 (m, 1H), 3.82 (dd, 1H), 3.55 (dd, 1H), 2.47 (q, 2H), 2.35 (bs, 1H), 1.12 (t, 3H). ^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{26}H_{25}F_7NO_3$ 532.1723 $[M + H]^+$, found 532.1713.

1-Nitro-3-[3-(trifluoromethoxy)phenoxy]benzene (15c). To a solution of 1,3-dinitrobenzene (4.5 g, 0.03 mol) and 3-trifluoromethoxyphenol (4.8 g, 0.03 mol) in 54 mL of dimethyl sulfoxide was added cesium carbonate (21.8 g, 0.07 mol). The reaction mixture was heated at 100 °C under nitrogen overnight, then cooled to room temperature. The reaction mixture was diluted with water and extracted with diethyl ether several times. The organic layers were combined, washed with 1 N HCl and water, dried over anhyd $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to afford **15c** (3.0 g, 38%) as a yellow-orange liquid, which was 85% pure by reverse phase HPLC analysis. HRMS calcd for $C_{13}H_8NO_3$ 300.0484 $[M + H]^+$, found 300.0463. This material was carried on below without further purification.

3-[3-(Trifluoromethoxy)phenoxy]aniline (16c). To a solution of **15c** (3.0 g, 0.01 mol) in 100 mL of glacial acetic acid was added zinc metal (6.6 g, 0.1 mol) at room temperature, and the resulting mixture was stirred for 1 h. The reaction mixture was filtered through Celite. The filtrate was neutralized with ammonium hydroxide and extracted with diethyl ether then ethyl acetate. The combined organic layers were dried over anhyd $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to afford **16c** (1.2 g, 44%) as a yellow oil, which was 98% pure by C_{18} reverse phase HPLC analysis. HRMS calc for $C_{13}H_{11}F_3NO_2$ 270.0742 $[M + H]^+$, found 270.0767. Anal. Calcd for $C_{13}H_{10}F_3NO_2$ C, 58.00; H, 3.74; N, 5.20, found C, 57.68; H, 3.57; N, 5.14.

***N*-[3-(1,1,2,2-Tetrafluoroethoxy)benzyl]-3-[(3-trifluoromethoxy)phenoxy]aniline (13c).** To a solution of **16c** (1.0 g, 3.7 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (0.83 g, 3.7 mmol) in 18.5 mL of dichloroethane were added sodium triacetoxyborohydride (1.0 g, 4.7 mmol) and glacial acetic acid (0.25 mL, 4.3 mmol). The reaction mixture was stirred at room-temperature overnight, then quenched with saturated aqueous sodium bicarbonate and extracted with methylene chloride. The organic layer was dried over anhyd $MgSO_4$ and concentrated in vacuo to give **13c** (1.8 g, 100%) as a yellow oil, which was greater than 92% pure by reverse phase HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.33−7.21 (m, 3H), 7.18 (m, 3H), 6.93 (m, 2H), 6.88 (d, 1H), 6.42 (dd, 1H), 6.39 (dd, 1H), 6.28 (s, 1H), 5.89 (t, 1H), 4.34 (s, 2H). ^{19}F NMR ($CDCl_3$) δ −58.2 (s, 3F), −88.4 (m, 2F), −137.1 (dt, 2F). HRMS calcd for $C_{22}H_{17}F_7NO_3$ 476.1097 $[M + H]^+$, found 476.1069.

(2*R*)-3-{[3-(3-Trifluoromethoxyphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)-benzyl]amino}-1,1,1-trifluoro-2-propanol (4c). A solution of **13c** (1.8 g, 3.7 mmol), *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.57 g, 5.2 mmol), and ytterbium(III) trifluoromethanesulfonate (0.24 g, 0.38 mmol) in 2.0 mL of acetonitrile was heated at 40 °C in a sealed glass tube overnight. At this time reverse phase HPLC analysis indicated that the reaction was only 50% complete. Additional ytterbium(III) trifluoromethanesulfonate and *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane (0.26 g, 2.3 mmol) were added to the reaction mixture and again heated at 40 °C in a sealed glass tube for 48 h. The reaction mixture was cooled to room temperature, then diluted with water and methylene chloride and extracted. The organic layer was washed with brine, dried over anhyd $MgSO_4$, and concentrated in vacuo. The crude product was purified by reverse phase HPLC eluting with 30% to 90% acetonitrile in water to afford **4c** (1.25 g, 23%) as yellow-brown oil (92% ee by chiral HPLC analysis). ^{1}H NMR ($CDCl_3$) δ 7.35−7.18 (m, 3H), 7.12 (t, 2H), 7.01 (s, 1H), 6.93 (d, 1H), 6.85 (d, 1H), 6.82 (s, 1H), 6.56 (dd, 1H), 6.47 (dd, 1H), 6.41 (s, 1H), 5.88 (t, 1H), 4.66 (s, 2H), 4.35 (m, 1H), 3.86 (d, 1H), 3.59 (dd, 1H), 2.02 (s, 1H). ^{19}F NMR ($CDCl_3$) δ −58.31 (s,

3F), −79.2 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{20}F_{10}NO_4$ 588.1233 $[M + H]^+$, found 588.1225.

3-(4-Methylphenoxy)nitrobenzene (15d). To a solution of *p*-cresol (5.76 g, 0.053 mol) and 1,3-dinitrophenol (8.97 g, 0.053 mol) in 100 mL of dimethyl sulfoxide was added cesium carbonate (43.4 g, 0.133 mol). The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature, quenched with water, and extracted with diethyl ether. The organic layer was combined, washed with 0.1 N HCl and water, dried over anhyd $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica eluting with 1:4 ethyl acetate:hexane to afford **15d** (8.0 g, (66%) as a yellow oil. ^{1}H NMR ($CDCl_3$) d 7.83 (s, 1H), 7.64 (t, 1H), 7.32 (d, 1H), 7.18 (d, 1H), 7.09 (d, 2H), 6.8 (d, 2H), 2.20 (s, 3H). ESMS *m*/*z* 230 $[M + H]^+$.

3-(4-Methylphenoxy)aniline (16d). A solution of 3-(4-methylphenoxy)nitrobenzene (8.0 g, 0.035 mol) **15d** in 25 mL of ethanol under nitrogen was charged with 10% palladium on carbon (0.80 g). The resulting mixture was hydrogenated for 4 h at room temperature and 45 psi. The reaction mixture was filtered through Celite and concentrated in vacuo to give 6.7 g (96%) of a yellow oil. ESMS *m*/*z* 200 $[M + H]^+$.

3-(4-Methylphenoxy)-*N*-[3-(1,1,2,2-tetrafluoroethoxy)-benzyl]aniline (13d). To a solution of **16d** (2.5 g, 12.5 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (2.8 g, 12.7 mmol) in 40 mL of dichloroethane were added sodium triacetoxyborohydride (3.1 g, 15.0 mmol) and glacial acetic acid (0.85 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched with water and extracted with diethyl ether. The organic layer was washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to give **13d** (3.5 g, 75%) as a tan oil, which was greater than 94% pure by reverse phase HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.20 (m 2H), 7.10 (m 3H), 6.88 (m, 3H), 6.80 (d, 1H), 6.49 (dd, 1H), 6.46 (dd, 1H), 6.19 (d, 1H), 5.82 (t, 1H), 4.30 (s, 2H), 2.33 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −88.2 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{22}H_{20}F_4NO_2$ 406.1430 $[M + H]^+$, found 406.1420.

(2*R*)-3-{[3-(4-Methylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4d). A solution of **13d** (1.6 g, 4.0 mmol), *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.64 g, 5.7 mmol), and ytterbium(III) ytterbium(III)trifluoromethanesulfonate (0.25 g, 0.4 mmol) in 1.5 mL of CH_3CN was heated at 40 °C in a sealed glass tube for 1 h. The reaction mixture was cooled to room temperature, then diluted with water and diethyl ether and extracted. The ether layer was washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1:8:0.01 of EtOAc:hexane:concentrated NH_4OH to afford **4d** (2.46 g, 48%) as a tan oil (96% ee by chiral HPLC analysis). ^{1}H NMR ($CDCl_3$) δ 7.17−7.01 (m, 5H), 6.92 (d, 2H), 6.82 (d, 2H), 6.65 (d, 1H), 6.34 (d, 1H), 5.92 (m, 1H), 4.48 (tt, 1H), 4.43 (s, 2H), 4.27−4.12 (m, 1H), 3.67 (bs, 1H), 3.11 (dd, 1H), 2.90 (m, 1H), 2.33 (s, 3H). ^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F), −88.6 (m, 2F), −137.2 (dt, 2F). HRMS calcd for $C_{25}H_{23}F_7NO_3$ 518.1566 $[M + H]^+$, found 518.1587.

1-Isopropyl-3-(3-nitrophenoxy)benzene (15e). To a solution of 1,3-dinitrobenzene (5 g, 30 mmol) and 3-isopropyl phenol (4.1 g, 30 mmol) in 72 mL of dimethyl sulfoxide was added cesium carbonate (24 g, 74 mmol). The reaction mixture was heated at 100 °C under nitrogen overnight, cooled to room temperature, and poured into water, and the resulting solution was extracted with diethyl ether. The ether layer was washed with 0.1 N HCl and water. The organic layer was dried over anhyd $MgSO_4$ and concentrated in vacuo. The oil was chromatographed on silica (98:2 hexanes:ethyl acetate) give **15e** (3.7 g, 45%) as light brown oil. ^{1}H NMR ($CDCl_3$) δ 7.95 (dd, 1H), 7.82 (m, 2H), 7.51 (t, 1H), 7.35 (m, 1H), 7.12 (d, 1H), 6.99 (m, 1H), 6.89 (m, 1H) 2.95 (m, 1H), 1.35 (d, 6H). HRMS calcd for $C_{15}H_{15}NO_3.NH_4$ 275.1396 $[M + NH_4]^+$, found 275.1400.

3-(3-Isopropylphenoxy)aniline (16e). To a solution of **15e** (3.5 g, 12.7 mmol) in 145 mL of glacial acetic acid and 1 mL of water was added zinc metal (7.1 g, 108 mmol) at room temperature, and the resultant mixture was stirred for 0.5 h. The filtrate was neutralized with ammonium hydroxide and extracted with diethyl ether. The organic layer was washed with water and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to give **16e** (2.7 g, 94%) as a yellow oil, which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.2d (m, 1H), 7.14 (t 1H), 7.00 (d, 1H), 6.95 (m, 1H), 6.85 (dd, 1H), 6.50 (m, 2H), 6.42 (m, 1H), 2.92 (m, 1H), 1.24 (d, 6H). HRMS calcd for $C_{15}H_{18}NO$ 228.1388 $[M + H]^+$, found 228.1384.

3-(3-Isopropylphenoxy)-*N*-[3-(1,1,2,2-tetrafluoroethoxy)-benzyl]aniline (13e). To a solution of **16e** (1.0 g, 4.4 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (0.9 g, 4 mmol) in 20 mL of dichloroethane were added sodium triacetoxyborohydride (1.1 g, 5.2 mmol) and glacial acetic acid (0.3 mL, 4.8 mmol). The reaction mixture was stirred at room temperature for 1.5 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give **13e** (1.73 g, 100%) as a brown oil, which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.38 (t, 1H), 7.28 (t, 1H), 7.24 (d, 1H), 7.14 (t, 1H), 7.00 (d, 1H), 6.94 (m, 1H), 6.8 (dd, 2H), 6.42 (d, 1H), 6.34 (s, 1H), 6.10 (t, 1H), 5.92 (t, 1H), 5.74 (t, 1H), 4.38 (s, 2H), 3.78 (s, 1H), 2.90 (m, 1H), 1.22 (d, 6H). ^{19}F NMR ($CDCl_3$) −88.7 (m, 2F), −137.3 (dt, 2F). HRMS calcd for $C_{24}H_{23}F_4NO_2$ 434.1743 $[M + H]^+$, found 434.1736.

(2*R*)-3-{[3-(3-Isopropylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4e). A solution of **13e** (1.0 g, 2.3 mmol), *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.4 g, 3.5 mmol), and ytterbium(III) trifluoromethanesulfonate (0.14 g, 0.23 mmol) in 0.8 mL of CH_3CN was heated at 40 °C in a sealed glass tube for 18 h. The reaction mixture was cooled to room temperature, then diluted with water and diethyl ether and extracted. The ether layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 9:1 hexanes: ethyl acetate to afford **4e** 0.68 g (54%). Tan oil, 683 mg (54%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.2 (m, 4H), 7.1 (m, 1H), 7.0, (d, 1H), 6.9 (s, 1H), 6.8 (d, 1H), 6.5 (m, 4H), 5.9 (tt, 1H), 4.7 (s, 2H), 4.4 (br s, 1H), 3.9 (dd, 1H), 3.6 (br m, 1H), 2.9 (m, 1H), 2.5 (br s, 1H), 1.2 (t, 6H). ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F), −88.4 (m, 2F), −137.1 (dt, 2F). HRMS calcd for $C_{27}H_{27}F_7NO_3$ 546.1879 $[M + H]^+$, found 546.1900.

3-(4-Chloro-3-ethylphenoxy)-*N*-[3-(trifluoromethoxy)-benzyl]aniline (13f). To a solution of **16a** (2.0 g, 8.1 mmol) and 3-(trifluoromethoxy)benzaldehyde (1.4 g, 7.3 mmol) in 30 mL of dichloroethane and acetic acid (0.5 mL, 8.9 mmol) was added solid sodium triacetoxyborohydride (2.0 g, 9.7 mmol). The mixture was stirred at room temperature for 1 h, then quenched with water and extracted with diethyl ether. The ether layer was washed with water and brine, then dried over anhyd $MgSO_4$, and evaporated to give 3.0 g (88%) of **13f** as a brown oil, which was greater than 94% pure by reverse phase HPLC analysis. ^{1}H NMR δ ($CDCl_3$) 7.34(t, 1H), 7.26(d, 1H), 7.21(m, 1H), 7.17 (m, 1H), 7.09 (m, 2H), 6.87(m, 1H), 6.72(dd, 1H), 6.46(dd, 1H), 6.43 (m, 1H), 6.32 (m, 1H), 4.32 (s, 1H), 2.69 (q, 2H), 1.19(t, 3H). ^{19}F NMR ($CDCl_3$) δ −58.4 (s, 3F). HRMS calcd for $C_{22}H_{20}NO_2ClF_3$ 422.1134 $[M + H]^+$, found 422.1135.

(2*R*)-3-{[3-(4-Chloro-3-ethylphenoxy)phenyl][3-(trifluoromethoxy)benzyl]amino}-1,1,1-trifluoro-2-propanol (4f). To a solution of **13f** (1.7 g, 4.0 mmol) and *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.67 g, 6.0 mmol) in 1.5 mL of acetonitrile, ytterbium(III) trifluoromethanesulfonate (0.25 g, 0.4 mmol) was added, and the stirred solution was warmed to 40 °C for 1 h, at which time HPLC analysis indicated that no amine starting material remained. The reaction was quenched with water and extracted with diethyl ether. The ether layer was washed with water and brine, then dried over anhyd $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate/hexane/ammonium hydroxide (1:7:0.01) to give **4f** (1.2 g, 56%) as a yellow oil, (97% ee by chiral HPLC analysis). ^{1}H NMR δ ($CDCl_3$) 7.30 (t, 1H), 7.21 (d, 1H), 7.14 (t, 1H), 7.08 (t, 2H), 7.01 (s, 1H),

6.86 (d, 1H), 6.68 (dd, 1H), 6.46 (dd, 1H), 6.36 (dd, 1H), 6.32 (t, 1H), 4.63 (d, 2H), 4.33 (m, 1H), 3.86 (dd, 1H), 3.84 (dd, 1H), 2.96 (bs, 1H), 2.67 (q, 2H), 1.17 (t, 3H). ^{19}F NMR ($CDCl_3$) δ −58.22 (s, 3F), −79.23 (d, 3F). Anal. Calcd for $C_{25}H_{22}NO_3ClF_6$ C, 56.24; H, 4.15; N, 2.62, found C, 56.50; H, 4.33; N, 2.44. HRMS calcd for $C_{25}H_{23}NO_3ClF_6$ 534.1271 $[M + H]^+$, found 534.1309.

1-Methyl-3-(pentafluoroethyl)benzene. Sodium pentafluoroethylpropionate (8.4 g, 50 mmol) and 3-iodotoluene (5.5 g, 25 mmol) were dissolved in anhydrous DMF (300 mL) under nitrogen. CuI (9.5 g, 50 mmol) was added, and the mixture was heated to 160 °C under nitrogen for 4 h, at which time a 15 mL fraction of a mixture of DMF and 3-pentafluoroethyltoluene was collected by distillation. The distillate was diluted with Et_2O and washed with brine. The ether layer was dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo to give 5.25 g (55%) of the title product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 4H), 2.40 (s, 3H). ^{19}F NMR (300 MHz, $CDCl_3$) δ −85.2 (s, 3F), −115.2 (s, 2F). HRMS calcd for $C_{13}H_{10}F_3NO_2$ 211.0532 $[M + H]^+$, found 211.0546.

1-(Bromomethyl)-3-(pentafluoroethyl)benzene. *N*-Bromosuccinimide (2.5 g, 13.8 mmol) and 1-methyl-3-pentafluoroethylbenzene (2.9 g, 13.8 mmol) were dissolved in CCl_4 (25 mL). AIBN (50 mg, 0.3 mmol) was added, and the mixture was refluxed for 3.5 h under N_2. The reaction mixture was cooled to room temperature and diluted with water. The layers were separated, and the organic layer was washed with brine, dried with anhyd $MgSO_4$, filtered, and concentrated in vacuo to give 3.4 g (87%) of the title crude product as a colorless oil. The ^{1}H NMR spectrum indicated that this crude product contained the desired 1-bromomethyl-3-pentafluoroethylbenzene product (70%), along with the corresponding 3-pentafluoroethylbenzyldibromide (10%) and unreacted 1-methyl-3-pentafluoroethylbenzene (20%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.50 (m, 2H), 4.50 (s, 2H). ^{19}F NMR (300 MHz, $CDCl_3$) δ −85.1 (s, 3F), −115.4 (s, 2F). This crude product was carried forward in the next step without further purification.

3-(4-Chloro-3-ethylphenoxy)-*N*-[3-(pentafluoroethyl)benzyl]aniline (13g). A solution of 3-(4-chloro-3-ethylphenoxy)aniline (**16a**) (1.7 g, 6.9 mmol) was prepared in cyclohexane (13 mL), and a solution of crude 1-bromomethyl-3-pentafluoroethylbenzene (1 g, 3.5 mmol) in cyclohexane (10 mL) was added dropwise under nitrogen over 3 min. The reaction mixture was refluxed under N_2 for 24 h and then was cooled to room temperature. The mixture was diluted with diethyl ether and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with hexanes in ethyl acetate (95:5) to give **13g** (0.56 g, 35%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 4H), 7.27 (d, 1H), 7.15 (t, 1H), 6.93 (d, 1H), 6.77 (dd, 1H), 6.41 (tt, 2H), 6.30 (t, 1H), 4.41 (s, 2H), 2.73 (q, 2H), 1.23 (t, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.6, 156.1, 143.4, 141.3, 140.2, 131.3, 130.7, 130.4, 129.4, 128.1, 120.4, 117.8, 108.8, 103.9, 48.5, 27.5, 14.1. ^{19}F NMR (300 MHz, $CDCl_3$) δ −85.1 (s, 3F), −115.2 (s, 2F). HRMS calcd for $C_{23}H_{20}ClF_5NO$ 456.1154 $[M + H]^+$, found 456.1164.

(2*R*)-3-{[3-(4-Chloro-3-ethylphenoxy)phenyl][3-(pentafluoroethyl)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4g). A solution of **13g** (0.4 g, 0.88 mmol) dissolved in anhydrous acetonitrile (1.5 mL) was combined with *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.22 g, 1.94 mmol), $Yb(OTf)_3$ (22 mg, 0.035 mmol) was added, and the reaction mixture was stirred under N_2 at 45 °C in a sealed glass tube for 15 h. The reaction mixture was then cooled to room temperature and diluted with Et_2O and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O. The ether layers were combined, washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The viscous oil was adsorbed onto silica gel and purified by column chromatography eluting with hexane/ethyl acetate (95:5) yielding **4g** (0.32 g, 64%) as a viscous, colorless oil (98% ee by chiral HPLC analysis). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 4H), 7.23 (m, 3H), 6.90 (d, 1H), 6.72 (dd, 1H), 6.52 (d, 1H), 6.42 (m, 2H), 4.73 (s, 2H), 4.39 (m, 1H), 3.91 (dd, 1H), 3.58 (m, 2H), 2.73 (q, 2H), 2.57 (s, 1H), 1.22 (t, 3H). ^{19}F NMR (300 MHz, $CDCl_3$) δ −79.2 (s, 3F), −84.9 (s, 3F), −115.2 (s, 2F). HRMS calcd for $C_{26}H_{23}ClF_8NO_2$ 568.1290 $[M + H]^+$, found 568.1296.

3-(4-Chloro-3-ethylphenoxy)-*N*-[2-fluoro-5-(trifluoromethyl)benzyl]aniline (13h). 2-Fluoro-5-trifluoromethylbenzaldehyde (0.5 g, 2.6 mmol) and **16a** (0.71 g, 2.96 mmol) were dissolved in dichloroethane (15 mL). $NaBH(OAc)_3$ (0.92 g, 4.3 mmol) and glacial acetic acid (0.18 mL, 3.12 mmol) were added, and the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous anhyd $MgSO_4$, and concentrated in vacuo to give 0.844 g (77%) of **13h** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7 (d, 1H), 7.6 (m, 1H), 7.2 (d, 1H), 7.1 (m, 2H), 6.8 (s, 1H), 6.7 (dd, 1H), 6.44 (d, 1H), 6.40 (d, 1H), 6.25 (s, 1H), 4.41 (s, 2H), 2.76 (q, 2H), 1.23 (t, 3H). ^{19}F NMR (400 MHz, $CDCl_3$) δ −62.4 (s, 3F), −114.6 (m, 1F). HRMS Calcd for $C_{22}H_{19}ClF_4NO$ 424.1091 $[M + H]^+$, found 424.1065.

(2*R*)-3-{[3-(4-Chloro-3-ethylphenoxy)phenyl][2-fluoro-5-(trifluoromethyl)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4h). To a solution of **13h** (0.7 g, 1.65 mmol) in anhydrous acetonitrile (1.0 mL) were added *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.41 g, 3.63 mmol) and $Yb(OTf)_3$ (100 mg, 0.16 mmol), and the reaction mixture was stirred under N_2 at 45 °C in a sealed glass tube for 12 h. The reaction mixture was then cooled to room temperature and diluted with Et_2O and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O. The ether layers were combined, washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting viscous oil was adsorbed onto silica gel and purified by column chromatography eluting with hexane/ethyl acetate (95:5) yielding **4h** (0.679 g, 77%) as a viscous, colorless oil (99% ee by chiral HPLC analysis). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (m, 1H), 7.4 (d, 1H), 7.3−7.1 (m, 4H), 6.9 (d, 1H), 6.7 (dd, 1H), 6.48 (dd, 1H), 6.43 (d, 1H), 6.28 (m, 1H), 4.69 (s, 2H), 4.38 (br m, 1H), 3.89 (dd, 1H), 3.62 (dd, 1H), 2.79 (q, 2H), 2.6 (d, 1H), 1.22 (t, 3H). ^{19}F NMR (400 MHz) δ −62.0 (s, 3F), −79.2 (s, 3F), −114.5 (m, 1F),. HRMS Calcd for $C_{25}H_{22}ClF_7NO_2$ 536.1227 $[M + H]^+$, found 536.1252.

3-(4-Chloro-3-ethylphenoxy)-*N*-[2-fluoro-4-(trifluoromethyl)benzyl]aniline (13i). 2-Fluoro-4-trifluoromethylbenzaldehyde (0.5 g, 2.6 mmol) and **16a** (0.71 g, 2.86 mmol) were dissolved in dichloroethane (15 mL). $NaBH(OAc)_3$ (0.72 g, 3.4 mmol) and glacial acetic acid (0.18 mL, 3.12 mmol) were added, and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and was extracted with Et_2O. The organic layers were combined, washed with brine, dried over anhydrous anhyd $MgSO_4$ and concentrated in vacuo. The resulting oil was adsorbed onto silica gel and purified by column chromatography eluting with hexane/ethyl acetate (95:5) yielding 0.71 g (65%) of **13i** as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (m, 1H), 7.4 (m, 2H), 7.2 (t, 1H), 6.9 (d, 1H), 6.8 (dd, 1H), 6.4 (m, 2H), 6.3 (t, 2H), 4.4 (s, 2H), 2.7 (q, 2H), 1.2 (t, 3H). ^{19}F NMR (300 MHz) δ −63.1 (s, 3F), −116.3 (s, 1F). HRMS Calcd for $C_{22}H_{19}ClF_4NO$ 424.1091 $[M + H]^+$, found 424.1084.

(2*R*)-3-{[3-(4-Chloro-3-ethylphenoxy)phenyl][2-fluoro-4-(trifluoromethyl)benzyl]amino}-1,1,1-trifluoropropan-2-ol (4i). To a solution of **13i** (0.6 g, 1.42 mmol) in anhydrous acetonitrile (1.5 mL) were added *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane[29] (0.55 g, 4.9 mmol) and $Yb(OTf)_3$ (75 mg, 0.12 mmol), and the reaction mixture was stirred under N_2 at 45 °C in a sealed glass tube for 15 h. The reaction mixture was then cooled to room temperature and diluted with Et_2O and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O. The ether layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting viscous oil was adsorbed onto silica gel and purified by column

chromatography eluting hexanes/ethyl acetate (95:5) to give 0.25 g (32%) of **4i** as a viscous, colorless oil (99% ee by chiral HPLC analysis). ^{1}H NMR ($CDCl_3$) δ 7.4 (d, 2H), 7.3−7.2 (m, 3H), 6.9 (d, 1H), 6.7 (dd, 1H), 6.5 (dd, 2H), 6.4 (s, 1H), 4.8 (s, 2H), 4.4 (br m, 1H), 3.9 (dd, 1H), 3.6 (dd, 1H), 2.8 (q, 2H), 2.6 (br s, 1H), 1.2 (t, 3H). ^{19}F NMR (400 MHz, $CDCl_3$) δ −116.5 (m, 1F), −79.3 (s, 3F), −63.2 (s, 3F). HRMS Calcd for $C_{25}H_{22}ClF_7NO_2$ 536.1228 $[M + H]^+$, found 536.1241.

CETP Inhibition. The buffer, the human plasma, and the time-dependent CETP inactivation assays were carried out as previously described.[27]

Determination of Lipoprotein Integrity by Agarose Electrophoresis.[27] A paragon Lipoprotein Electrophoresis Kit (Beckman, Fullerton, CA) was used for the electophoretic separation of lipoproteins, according to the manufacturer's instructions. Inhibitors were incubated with LDL or HDL at concentration 1000-fold above the buffer assay IC_{50} value for 2 h at 37 °C. Cholesteryl sulfate was the positive control. After electrophorisis, the lipoproteins in the gel were immobilized in fixative. The gel was dried and the film stained to visualize lipoproteins.

Inhibition of Cholesteryl Ester Binding to CETP.[27] Samples containing [^{3}H]-CE-HDL alone, [^{3}H]-CE-HDL plus CETP, and [^{3}H]-CE-HDL plus CETP and inhibitor were incubated for 2 h at 37 °C and then fractionated by Superose 12 size exclusion chromatography to separate CETP from HDL. The fractions were assayed for [^{3}H]-CE bound to CETP by liquid scintillation counting.

Pharmacokinetics and Bioavailability. Studies were performed in C57Bl mice and Syrian golden hamsters after a single dose administration of the compound to male mice and hamsters. Inhibitor **4a** was formulated in the following manner: mouse IV formulation was 10% Ethanol, 20% water, 70% propylene glycol; mouse IG formulation was 10% ethanol, 90% 0.5% methylcellulose. The hamster iv formulation was 10% ethanol, 90% PEG-300 and the hamster IG formulation was either 90% 0.5%methylcellulose, 0.5% Tween 80, 10% water. The inhibitor was administered at the dose levels of 30 mg/kg in both species. Blood samples were collected from individual animals via cardiac heart stick with animals/time point/dose level (n = 6). Blood samples were withdrawn in chilled heparinized tubes at 2.5, 5, 7, 8, 15, 30 and 60 min after mouse iv dosing; 2, 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 6 h after hamster iv dosing and at 30 min and 1, 4, 7, 15 and 24 h after oral dosing for both species. The samples were centrifuged and the separated plasma stored at −20 °C until analysis. Aliquots (100 μL) were extracted for **4a** by SPE using a C-18 ODS column (100 mg). Columns were washed with Milli-Q water (600 μL) and samples eluted with of acetonitrile (600 μL). The eluant was dried under nitrogen and reconstituted in acetonitrile/0.1% heptafluorobutyric acid in water (70:30 v/v, 50 μL). This solution (25 μL) was analyzed with a Perkin-Elmer SCIEX API 150EX LC/MS. The Column was a Nucleosil C18 (2.1 × 150 mm, 5 μm particle size) heated to 35 °C; the mobile phase was 0.1% heptafluorobutyric acid in acetonitrile/0.1% heptafluorobutyric acid in water (70:30 v/v) (flow rate 0.4 mL/min); and MS detection was with TurboIonspray interface, using positive ion mode. The retention time of **4a** was 7.8 min (LLOQ 0.02 μg/mL, ULOQ: 25 μg/mL). AUC calculations were performed using the linear trapezoidal rule. Bioavailability of **4a** was calculated as the ratio of dose-normalized oral to iv AUCs for the same time frame.

Inhibition of CETP ex Vivo. Inhibition of CETP activity with **4a** was determined by administering a single oral dose of 30 mg/kg or 60 mg/kg to hCETP mice (n = 6). Plasma concentrations of hCETP ranged from 2 to 20 μg/mL. Alternatively, a similar experiment was carried out with golden Syrian hamsters using single doses of 2, 4, 10 and 30 mg/kg. The amount of transfer of [^{3}H]-CE from HDL to VLDL and LDL particles was measured, and this was compared to the amount of transfer observed in control animals. Full details of these experiments have been described.[26]

Effect of 4a on VLDLc, LDLc, and HDLc in Vivo. The hCETP mice were made hypercholesterolemic by feeding cholesterol and fat-supplemented chow for a minimum of two weeks.[26] Test compound **4a** (30 mg/kg qd) was administered for 5 d in selected aqueous- or oil-based vehicles. Similarly, male golden Syrian hamsters, maintained on high cholesterol diet for at least 2 weeks, were given **4a** (3 or 30 mg/kg qd) for 5 d in selected aqueous- or oil-based vehicles. The animals were sacrificed, and the serum was analyzed by size exclusion chromatography using two Superose 6 columns and TSE buffer as eluant for the relative abundance of VLDLc, LDLc, and HDLc. The elution positions of VLDLc, LDLc, HDLc, and albumin were determined by chromatographing standards[26] under the same conditions.

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References

(1) Bruce, C.; Chouinard, R. A., Jr.; Tall, A. R. Plasma Lipid Transfer Proteins, High-Density Lipoproteins, and Reverse Cholesterol Transport. *Annu. Rev. Nutr.* **1998**, *18*, 297−330.

(2) (a) Sikorski, J. A.; Connolly, D. T. The discovery of new cholesteryl ester transfer protein inhibitors. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 602−613. (b) Sikorski, J. A.; Glenn, K. C. Cholesteryl Ester Transfer Protein as a Potential Therapeutic Target to Improve the HDL to LDL Cholesterol Ratio. *Annu. Rep. Med. Chem.* **2000**, *35*, 251−260.

(3) Hirano, K.-I.; Yamashita, S.; Matsuzawa, Y. Pros and cons of inhibiting cholesteryl ester transfer protein. *Curr. Opin. Lipidol.* **2000**, *11*, 589−596.

(4) Inazo, A.; Koizumi, J.; Mabuchi, H. Cholesteryl ester transfer protein and atherosclerosis. *Curr. Opin. Lipidol.* **2000**, *11*, 389−396.

(5) Lagrost, L. Relationship of the Cholesteryl Ester Transfer Protein (CETP) to Athero-sclerosis. *Adv. Vasc. Biol.* **1999**, *5* (Plasma Lipids and Their Role in Disease), 217−231.

(6) Bruce, C.; Chouinard, R. A., Jr.; Tall, A. R. Plasma Lipid Transfer Proteins, High-Density Lipoproteins, and Reverse Cholesterol Transport. *Annu. Rev. Nutr.* **1998**, *18*, 297−330.

(7) Yamashita, S.; Maruyama, T.; Hirano, K.-I.; Sakai, N.; Nakajima, N.; Matsuzawa, Y. Impairment of reverse cholesterol transport system and atherosclerosis. In *Lipoprotein Metab. Atherog.*; Kita, T.; Yokode, M., Eds. Springer-Verlag: Tokyo, Japan, 2000; pp 115−123.

(8) Krause, B. R.; Auerbach, B. J. Reverse cholesterol transport and future pharmacological approaches to the treatment of atherosclerosis. *Curr. Opin. Invest. Drugs* **2001**, *2*, 375−381.

(9) Tall, A. R.; Wang, N.; Mucksavage, P. Is it time to modify the reverse cholesterol transport model? *J. Clin. Invest.* **2001**, *108*, 1273−1275.

(10) Zhang, Z.; Yamashita, S.; Hirano, K.; Nakagawa-Toyama, Y.; Matsuyama, A.; Nishida, M.; Sakai, N.; Fukasawa, M.; Arai, H.; Miyagawa, J.; Matsuzawa, Y. Expression of cholesteryl ester transfer protein in human atherosclerotic lesions and its implication in reverse cholesterol transport. *Atherosclerosis* **2001**, *159*, 67−75.

(11) Castelli, W. P.; Garrison, R. J.; Wilson, P. W.; Abbott, R. D.; Kalousdian, S.; Kannel, W. B. Incidence of Coronary Heart Disease and Lipoprotein Cholesterol Levels. The Framingham Study. *J. Am. Med. Assoc.* **1986**, *256*, 2835−2838.

(12) Kannel, W. B. Range of Serum Cholesterol Values in the Population Developing Coronary Artery Disease. *Am. J. Cardiol.* **1995**, *76*, 69c-77c.

(13) Evans, G. F.; Bensch, W. R.; Apelgren, L. D.; Bailey, D.; Kauffman, R. F.; Bumol, T. F.; Zuckerman, S. H. Inhibition of Cholesteryl Ester Transfer Protein in Normocholesterol-emic and Hypercholesterolemic Hamsters: Effects on HDL Subspecies, Quantity, and Apolipoprotein Distribution. *J. Lipid Res.* **1994**, *35*, 1634−1645.

(14) Sugano, M.; Makino, N.; Sawada, S.; Otsuka, S.; Watanabe, M.; Okamoto, H.; Kamada, M.; Mizushima, A. Effect of antisense oligonucleotides against cholesteryl ester transfer protein on the development of atherosclerosis in cholesterol-fed rabbits. *J. Biol. Chem.* **1998**, *273*, 5033−5036.

(15) (a) H, Yonemori, F.; Wakitani, K.; Minowa, T.; Maeda, K.; Shinkai, H. A Cholesteryl Ester Transfer Protein Attenuates Atherosclerosis in Rabbits. *Nature* **2000**, *406*, 203−207. (b)

Shinkai, H.; Maeda, K.; Yamasaki, T.; Okamoto, H.; Uchida, I. Bis[2-(acylamino)phenyl] disulfides, 2-(acylamino)benzenethiols, and *S*-[2-(acylamino)phenyl] alkanethioates as novel inhibitors of cholesteryl ester transfer protein. *J. Med. Chem*. **2000**, *43*, 3566−3572.

(16) Kobayashi, J.; Okamoto, Hiroshi; O. M.; Bujo, H.; Saito, Y. Effect of HDL, from Japanese white rabbit administered a new cholesteryl ester transfer protein inhibitor JTT-705, on cholesteryl ester accumulation induced by acetylated low-density lipoprotein in J774 macrophage. *Atherosclerosis* **2002**, *162*, 131−135.

(17) Koizumi, J.; Inazu, A.; Yagi, K.; Koizumi, I.; Uno, Y.; Kajinami, K.; Miyamoto, S.; Moulin, P.; Tall, A. R.; Mabuchi, H. Serum Lipoprotein Lipid Concentration and Composition in Homozygous and Heterozygous Patients with Cholesteryl Ester Transfer Protein Deficiency. *Atherosclerosis* **1991**, *90*, 189−196.

(18) Ordovas, J. M.; Cupples, L. A.; Corella, D.; Otvos, J. D.; Osgood, D.; Martinez, A.; Lahoz, C.; Coltell, O.; Wilson, P. W. F.; Schaefer, E. J.Polymorphism With Variations in Lipoprotein Subclasses and Coronary Heart Disease Risk. The Framingham Study. *Arterioscler. Thromb. Vasc. Biol*. **2000**, *20*, 1323−1329.

(19) De Grooth, J. G.; Kuivenhoven, J. A.; Stalenhoef, A. F. H.; de Graaf, J.; Zwinderman, A. H.; Posma, J. L.; van Tol, A.; Kastelein, J. J. P. Efficacy and Safety of a Novel Cholesteryl Ester Transfer Protein Inhibitor, JTT-705, in Humans. *Circulation* **2002**, *104*, 2159−2165.

(20) Liu, S.; Schmitz, C.; Stampfer, M. J.; Sacks, F.; Hennekens, C. H.; Lindpaintner, K.; Ridker, P. M. A prospective study of TaqIB polymorphism in the gene coding for cholesteryl ester transfer protein and risk of myocardial infarction in middle-aged men. *Atherosclerosis* **2002**, *161*, 469−474.

(21) Bruce, C.; Sharp, D. S.; Tall, A. R. Relationship of HDL and Coronary Heart Desease to a Common Amino Acid Polymorphism in the Cholesteryl Ester Transfer Protein in Men with and without Hyperalphalipoproteinemia. *J Lipid. Res*. **1998**, *39*, 1071−1078.

(22) Agerholm-Larsen, B.; Tybjaerg-Hansen, A.; Schnohr, P.; Steffensen, R.; Nordestgaard, B. G. Common cholesteryl transfer protein mutations, decreased HDL cholesterol, and possible decreased risk of ischemic heart disease: The Copenhagen City Heart Study. *Circulation* **2000**, *102*, 2197−2203.

(23) Garber, K. Boosting "Good" Cholesterol. *Mod. Drug Discovery* **1999**, *2*, 67−75.

(24) (a) Paulsen, H.; Antons, S.; Brandes, A.; Logers, M.; Muller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuss, J. Stereoselective Mukaiyama-Michael/Michael/Aldol Domino Cyclization as the Key Step in the Synthesis of Pentasubstituted Arenes: An Efficient Access to Highly Active Inhibitors of Cholesteryl Ester Transfer Protein (CETP). *Angew. Chem., Int. Ed*. **1999**, *38*, 3373−3375. (b) Brandes, A.; Logers, M.; Stoltefuss, J.; Schmidt, G.; Bremm, K.-D.; Bischoff, H.; Schmidt, D.; Antons, S.; Paulsen, H.; Muller, S. N.; Naab, P.; Schmeck, C. Substituted Tetrahydronaphthalenes as Cholesteryl Ester Transfer Protein Inhibitors. WO9914174, March 25, 1999.

(25) (a) Deninno, M. P.; Mangus-Aryitey, G. T.; Ruggeri, R. B.; Wester, R. T. Preparation of N-(1-Alkoxycarbonyl-1,2,3,4-Tetrahydroquinolin-4-yl)Carbamates as Cholesteryl Ester Transfer Protein Inhibitors. WO0017164, March 30, 2000. (b) Deninno, M. P.; Mangus-Aryitey, G. T.; Ruggeri, R. B.; Wester, R. T. Preparation of 4-Amino Substituted 2-Substituted 1,2,3,4-Tetrahydroquinolines as CETP Inhibitors. WO0017165, March 30, 2000. (c) Allen, D. J. M.; Appleton, T. A.; Brostrom, L. R.; Tickner, D. L. Preparation of (2R,4S)-4-[(3,5-bistri-fluoromethylbenzyl)methoxycarbonylamino]-2-ethyl-6-trifluoromethyl-3,4-di-hydro-2H-quinoline-1-carboxylic acid ethyl ester as CETP inhibitor. WO0140190, June 7, 2001. (d) Damon, D. B. and Dugger, R. W. Method for making 4-carboxyamino-2-substituted 1,2,3,4-tetrahydroquinolines. US6313142, November, 6, 2001.

(26) (a) Durley, R. C.; Grapperhaus, M. L.; Massa, M. A.; Mischke, D. A.; Parnas, B. L.; Fobian, Y. M.; Rath, N. P.; Honda, D. D.; Zeng, M.; Connolly, D. T.; Heuvelman, D. M.; Witherbee, B. J.; Glenn, K. C.; Krul, E. S.; Smith, M. E.; Sikorski, J. A. Discovery of Chiral *N*,*N*-Disubstiuted Trifluoro-3-amino-2-propanols as Potent Inhibitors of Cholesteryl Ester Transfer Protein. *J. Med. Chem*. **2000**, *43*, 4575−4578. (b) Durley, R. C.; Grapperhaus, M. L.; Hickory, B. S.; Massa, M. A.; Wang, J. L.; Spangler, D. P.; Mischke, D. A.; Parnas, B. L.; Fobian, Y. M.; Rath, N. P.; Honda, D. D.; Zeng, M.; Connolly, D. T.; Heuvelman, D. M.; Witherbee, B. J.; Glenn, K. C.; Krul, E. S.; Smith, M. E.; Sikorski, J. A.Chiral *N*,*N*-Disubstiuted Trifluoro-3-amino-2-propanols are Potent Inhibitors of Cholesteryl Ester Transfer Protein. *J. Med. Chem*. **2002**, *45*, 3891−3904.

(27) Connolly, D. T.; Witherbee, B. J.; Melton, M. A.; Durley, R. C.; Grapperhaus, M. L.; McKinnis, B. R.; Vernier, W. F.; Babler, M. A.; Shieh, J.-J.; Smith, M. E.; Sikorski, J. A. Stereospecific Inhibition of CETP Activity by Chiral *N*,*N*-Disubstituted Trifluoro-3-Amino-2-propanols. *Biochemistry* **2000**, *39*, 13870−13879.

(28) Hartwig, J. F. Carbon-Heteroatom Bond-Forming Reductive Elimination of Amines, Ethers and Sulfides. *Acc. Chem. Res*. **1998**, *31*, 852−860.

(29) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. A General Copper-Catalyzed Synthesis of Diaryl Ethers. *J. Am. Chem. Soc*. **1997**, *119*, 10539−10540.

(30) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. Preparation of Diaryl Ethers and Related Compounds by Condensation reactions Using Transition metal Complex Catalysts. WO9918057, April 15, 1999.

(31) Ramachandran, P. V.; Gong, B.; Brown, H. C. Chiral Synthesis via Organoboranes. 40. Selective Reductions. 55. A Simple One-Pot Synthesis of the Enantiomers of Trifluoro-methyloxirane. A General Synthesis in High Optical Purities of α-Trifluoromethyl Secondary Alcohols via the Ring-Cleavage Reactions of the Epoxide. *J. Org. Chem*. **1995**, *60*, 41−46.

(32) The ability of compounds to inhibit CETP activity was assessed using a reconstituted buffered in vitro assay that measures the rate of CETP-mediated transfer of radiolabeled cholesteryl ester ([^{3}H]CE) from HDL donor particles to LDL acceptor particles with recombinant human CETP. Alternatively the transfer activity from ([^{3}H]CE)-HDL donor particles could be measured in the presence of human serum, which provided the source of the LDL, VLDL, and human CETP as described in detail in ref 27.

(33) Massa, M. A.; Spangler, D. P.; Durley, R. C.; Hickory, B. S.; Connolly, D. T.; Witherbee, B. J.; Smith, M. E.; Sikorski, J. A. Novel Heteroaryl Replacements of Aromatic 3-Tetrafluoroethoxy Substituents in Trifluoro-3-(tertiaryamino)-2-propanols as Potent Inhibitors of Cholesteryl Ester Transfer Protein. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1625−1628.

(34) Hope, H. R.; Heuvelman, D.; Duffin, K.; Smith, C.; Zablocki, J.; Schilling, R.; Hegde, S.; Lee, L.; Witherbee, B.; Baganoff, M.; Bruce, C.; Tall, A. R.; Krul, E.; Glenn, K.; Connolly, D. T. Inhibition of cholesteryl ester transfer protein by substituted dithiobis-nicotinic acid dimethyl ester: involvement of a critical cysteine. *J. Lipid Res*. **2000**, *41*, 1604−1614.

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