Brief Articles

Design, Synthesis, and Biological Evaluation of (2*R*,α*S*)-3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)-phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol as Potent and Orally Active Cholesteryl Ester Transfer Protein Inhibitor

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With the goal of identifying a CETP inhibitor with high in vitro potency and optimal in vivo efficacy, a conformationally constrained molecule was designed based on the highly potent and flexible **13**. The synthetic chemistry efforts led to the discovery of the potent and selective **12**. In high-fat fed hamsters, human CETP transgenic mice, and cynomolgus monkeys, the in vivo efficacy of **12** for raising HDL-C was demonstrated to be comparable to torcetrapib.

Introduction

Cardiovascular disease (CVD[a]) is the most common cause of morbidity and mortality in developed nations.[1] Atherogenic dyslipidemia, characterized by an abnormal circulating lipid profile including low levels of high density lipoprotein cholesterol (HDL-C), elevated levels of small-dense low density lipoprotein cholesterol (LDL-C), or elevated triglycerides (TG), is often found in patients who are obese, have type 2 diabetes, or metabolic syndrome.[2] These individuals are at high risk for premature CVD. Due to the fact that LDL-C is prone to accumulate in the arterial wall leading to the formation of atherosclerotic cholesterol-laden foam cells, studies suggest that for every 1 mg/dL (0.026 mmol/L) decrease in plasma LDL-C, CVD risk is reduced by 0.5%.[3] Despite aggressive lowering of LDL-C with HMG-CoA reductase inhibitors (statins),[4] however, two-thirds of statin-treated patients continued to develop CVD. In addition, several epidemiological studies have established that a low level of HDL-C (<40 mg/dL) is a critical determinant of CVD, independent of LDL-C levels.[5] Analysis of the epidemiological data suggests that for every 1 mg/dL increase in HDL-C, CVD risk is reduced by 2−3%.[6]

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that transfers cholesterol ester (CE) from HDL to LDL and VLDL, thereby lowering antiatherogenic HDL and raising pro-atherogenic LDL and VLDL, and in return, it transfers TG from VLDL (or LDL) to HDL. The resulting TG-enriched HDL are more readily hydrolyzed by hepatic lipase to generate smaller HDL particles, which are more effective in promoting reverse cholesterol transport.[7] While the impact of CETP-mediated lipid transfer on atherogenesis remains controversial,[8] many animal studies support the hypothesis that inhibition of CETP activity is beneficial. For example, expression of CETP in animals lacking CETP can exert marked atherogenesis. On the other hand, inhibition of CETP can reduce the progression of atherosclerosis.[9] In addition, plasma CETP levels are typically increased by 2- to 3-fold in those at risk for CVD when compared to normal subjects (1−3 μg/mL).[10] Therefore, there has been great interest in identifying potent and selective CETP inhibitors[7] since the early reports connecting CETP deficiency to HDL-C elevation in late 1980s. To date, with the discontinuation of development of **1** (torcetrapib, Pfizer, Figure 1)[11] that occurred in December 2006, **2** (dalcetrapib, JTT-705, Roche/Japan Tobacco)[12] and **3** (anacetrapib, MK-0859, Merck)[13] became the two most advanced CETP inhibitors undergoing clinical trials. This paper describes our identification and

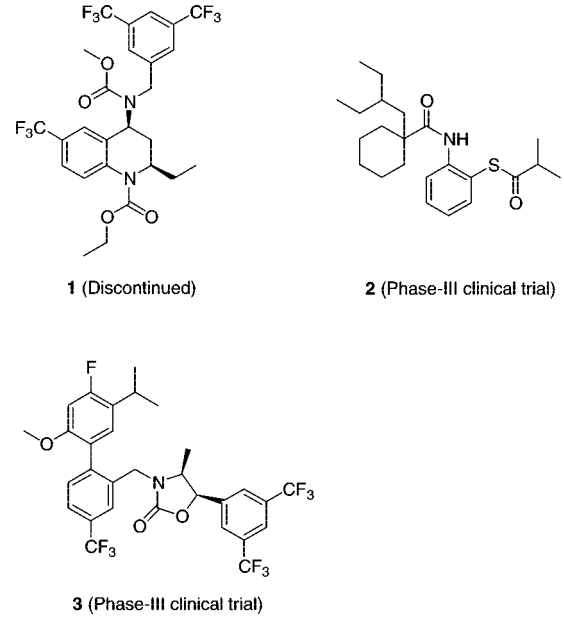

Figure 1. Structures of **1**, **2**, and **3**.

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[a] Abbreviations: CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; CETP, cholesteryl ester transfer protein; CE, cholesteryl ester; VLDL, very low density lipoprotein cholesterol; PLTP, phospholipids transfer protein; MTP, microsomal triglyceride transfer protein; LCAT, lecithin-cholesterol acyltransferase; LPL, lipoprotein lipase; HL, hepatic lipase; EL, endothelial lipase; AUC, area under the curve; CL, systemic clearance; *F*%, oral bioavailability.

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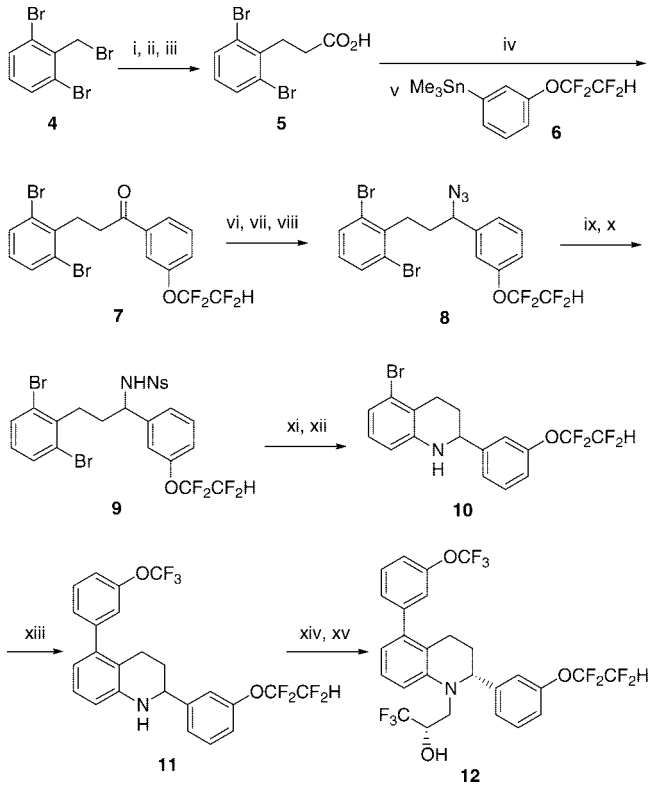
Scheme 1[a]



[a] (i) Sodium diethyl malonate, DMF, 20 °C, 75%; (ii) NaCl, DMSO, H_2O, 180 °C, 100%; (iii) 3 N NaOH, THF, 65 °C, 100%; (iv) oxalyl chloride, CH_2Cl_2, 20 °C; (v) **6**, *N*,*N*-diisopropylethylamine, $Pd_2(dba)_3$, THF, 50 °C, 66%; (vi) $NaBH_4$, EtOH, 95%; (vii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (viii) NaN_3, DMF, 50 °C, 95%; (ix) Me_2S-$BHCl_2$, 1,2-dichloroethane, 20−50 °C, 98%; (x) NsCl, Et_3N, CH_2Cl_2, 20 °C, 95%; (xi) CuI, CsOAc, DMSO, 95 °C, 96%; (xii) thioacetic acid, LiOH, DMF, 20 °C, 88%; (xiii) 3-trifluoromethoxy-phenyl-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 108 °C, 91%; (xiv) chiral HPLC; (xv) (*S*)-1,1,1-trifluoro-2,3-epoxy-propane, $Yb(OTf)_3$, $CH2Cl_2$, 50 °C, 69%.

characterization of (2*R*,α*S*)-3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol as a novel, potent, and orally active CETP inhibitor.

Chemistry

Displacement of the benzylic bromide of the readily available 1,3-dibromo-2-bromomethyl-benzene **4**[14] with sodium diethyl malonate gave the malonic acid diethyl ester adduct (Scheme 1). Removal of one of the carboxylic acid ester with NaCl in DMSO/H_2O, followed by base hydrolysis, provided the carboxylic acid **5**. Conversion of **5** to the corresponding acid chloride, followed by the palladium-catalyzed acylation with organo-stannane **6**, afforded the ketone **7**. The organo-stannane **6** was easily prepared from the bromo-precursor. The conversion of **7** to the azide **8** was accomplished in three steps: reduction of **7** with $NaBH_4$ to give the alcohol, conversion of the alcohol to the mesylate, and followed by the reaction of the mesylate with NaN_3 to give the azide **8**. Reduction of **8** with Me_2S-$BHCl_2$ gave the primary amine that was subsequently converted to the sulfonamide **9** by reaction with NsCl (Ns is *o*-nitrobenzenesulfonyl).[15] A copper-mediated intramolecular amination[16] of sulfonamide **9**, followed by deprotection with thioacetic acid, gave **10** in good yield. A palladium-catalyzed Suzuki coupling reaction of **10** with 3-trifluoromethoxy-phenylboronic acid afforded **11**. Using chiral HPLC to separate (2*R*)-**11** from racemate **11**, followed by *N*-alkylation with (*S*)-1,1,1-trifluoro-2,3-epoxypropane,[17] gave the target **12**.[18]

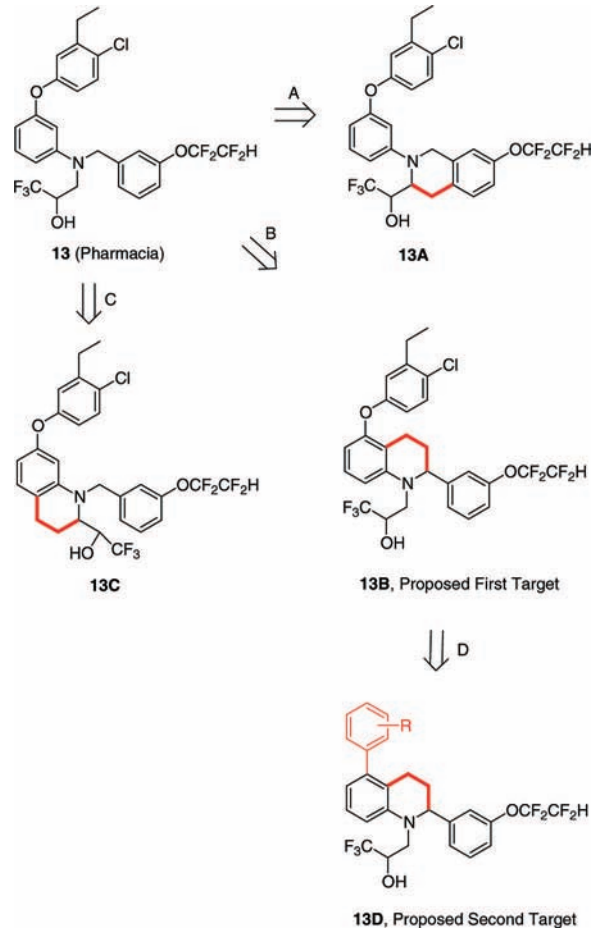


Figure 2. Design of the lead molecules.

Results and Discussion

Lead Generation. The primary goal of this project was the identification of a potent and selective CETP inhibitor with optimal in vivo efficacy and maximal safety margin. High-throughput screening of internal compound libraries resulted in the discovery of only a few hits with micromolar potencies. However, subsequent studies of the structure−activity relationship (SAR) of these hits did not yield compounds with submicromolar inhibitory potencies. At that time, Pharmacia[19] disclosed **13** (Figure 2) as a highly potent CETP inhibitor (IC_{50} = 3 nM in buffer, and IC_{50} = 59 nM in human serum), although it had relatively modest oral exposure and in vivo efficacy. While examining the structure of **13**, we felt the molecule was quite flexible (with 12 rotatable bonds), and this high flexibility might be the basis for poor absorption in vivo.[20] Therefore, a conformationally constrained analogue would reduce the flexibility and may potentially increase absorption and improve oral exposure and in vivo efficacy. While there were several ways to design the conformationally constrained molecules, we found that one of the cyclized molecules (**13B**, proposed first target, Figure 2) superimposed nicely to **1**. Therefore, we synthesized this target compound first. Interestingly, it displayed good potency (IC_{50} = 400 nM) although not as potent as **13** (IC_{50} = 3 nM). Meanwhile, because bromo-tetrahydroquinoline **10** (Scheme 1) was the intermediate for the synthesis of the biphenyl-ether molecule, we envisioned that the palladium-catalyzed Suzuki coupling reaction of **10** with various phenyl-

boronic acids might generate diverse biphenyl molecules (**13D**, proposed second target, Figure 2). Indeed, many biphenyl analogues were prepared in a short period of time. Most excitingly, the trifluoromethoxy-substituted biphenyl analogue gave ~10-fold increase in potency (IC_{50} = 45 nM, racemic **12**, Scheme 1). Later, the optically active **12** was synthesized and proved to be the most potent CETP inhibitor in this series, with IC_{50} = 39 nM in a CETP SPA assay and IC_{50} = 0.2 μM in a human plasma ^{3}H-CE HDL assay. The in vitro CETP inhibitory potency of **12** in a plasma CETP Roar assay with samples from different species were also measured. For example, **12** was more potent in species with relatively low plasma CETP activity (hamster plasma, IC_{50} = 0.1 μM) and less potent in species with relatively high plasma CETP activity (rabbit plasma, IC_{50} = 3.5 μM). Meanwhile, **12** displayed moderate potencies in species that express moderate plasma CETP activity (human plasma, IC_{50} = 1.2 μM; monkey plasma, IC_{50} = 1.4 μM). We next explored the selectivity of **12** against other lipid transfer proteins or proteins that modify lipoproteins,[21] including phospholipid transfer protein (PLTP), microsomal triglyceride transfer protein (MTP), lecithin-cholesterol acyltransferase (LCAT), lipoprotein lipase (LPL), hepatic lipase (HL), and endothelial lipase (EL). In summary, **12** exhibited little or no inhibition in any of these cellular assays, similar to that of **1**.[21] Compound **12** was also screened in a panel of 50 GPCR or ion channel binding assays, and no significant inhibitions were observed. Compound **12** was highly stable in human liver microsomes with $t_{1/2}$ >128 min. The pharmacokinetic studies of **12** in rat, dog, and monkey were conducted. Compound **12** displayed acceptable oral bioavailability in rat (F% = 31%), with slow oral absorption (T_{max} = 6 h), significant plasma drug exposure (AUC = 31.3 μg·h/mL), and long plasma duration ($t_{1/2}$ = 28 h). It also exhibited low systemic clearance (CL = 1.8 mL/min·kg) and low volume of distribution (Vdss = 0.36 L/kg). Because the target (CETP) is present in plasma, the low volume of distribution of **12** is optimal for its pharmacodynamic actions and potential for reduced nonspecific actions in vivo. Compound **12** displayed low oral bioavailability (F% = 5%) in dogs, but oral bioavailability in monkeys (F% = 27%) was comparable to that in rats (F% = 31%).

In Vivo Studies. Because mice, rats, and dogs do not express CETP, hamsters, human CETP transgenic mice, and monkeys were used to evaluate the in vivo efficacy of CETP inhibitor **12**. High-fat fed hamsters were orally gavaged with vehicle (10% solutol, 5% ethanol, 85% D5W), **12**, or **1** for 5 days. The lipid parameters measured from the plasma are shown in Figure 3. Compound **12** produced a dose related increase in HDL-C levels. At the 10 and 30 mg/kg doses of **12**, the HDL-C was increased 36% and 40%, respectively. Meanwhile, a 30 mg/kg dose of **1** increased HDL-C by 44%. There were no significant changes in LDL-C and triglyceride levels with either compound. Overall, increasing doses of **12** produced a less atherogenic lipid profile as indicated by the increase in the HDL-C/LDL-C ratio (from 2.9 to 4.6).

Human CETP transgenic mice fed a normal chow diet were orally treated with vehicle, **12**, or **1** for 5 days. As shown in Figure 4, there was a dose related increase in HDL-C with **12** treatment. At 3 mg/kg, **12** already produced a significant increase in HDL-C compared to the vehicle group. At 10 and 30 mg/kg, **12** increased HDL-C by 36% and 25%, respectively. In comparison, HDL-C was increased by 28% at 30 mg/kg dose of **1**.

Male cynomolgus monkeys fed a normal chow diet were dosed orally with vehicle (10% Imwitor 742/20% cremophor RH40/70% water), **12**, or **1** for 5 days. Compound **12** produced a dose-dependent inhibition of CETP and an increase in plasma HDL-C levels (Figure 5). At the 3, 10, and 30 mg/kg doses of **12**, CETP was inhibited by 11%, 51%, and 67%, respectively. Concurrently, plasma HDL-C was increased 4%, 16%, and 32% at the 3, 10, and 30 mg/kg doses, respectively. In comparison, when dosed with **1** at the same three doses (3, 10, and 30 mg/kg), CETP was inhibited by 35%, 66%, and 85%, respectively, and the plasma HDL-C was increased 24%, 41%, and 44%, respectively. Moreover, these changes were observed with fairly equivalent plasma concentrations of compound (0.4, 2.7, and 5.9 μM of **12** and 0.3, 1.3, and 2.9 μM of **1** at the respective dose levels of 3, 10, and 30 mg/kg). Overall, **12** displayed in vivo efficacy comparable to **1** in monkeys.

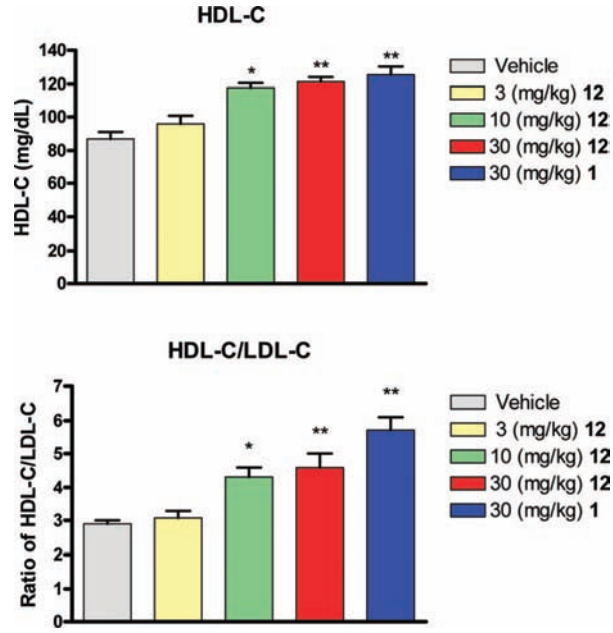


Figure 3. Effects of **12** and **1** on HDL-C and HDL-C/LDL-C in the high-fat-diet hamster model (5 days oral dosing). Bars represent means ± SD (n = 8 per group; *p < 0.05, **p < 0.01 relative to HF vehicle).

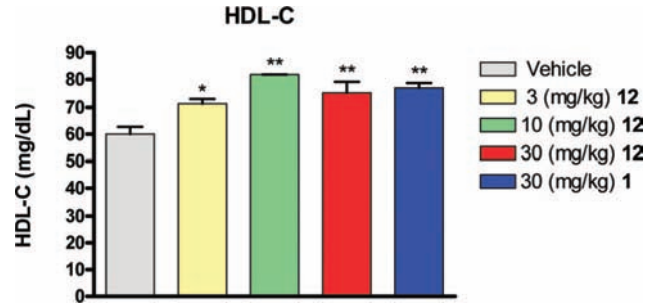


Figure 4. Effects of **12** and **1** on HDL-C in the hCETP transgenic mice model (5 days oral dosing). Bars represent means ± SD (n = 8 per group; *p < 0.05, **p < 0.01 relative to vehicle group).

Conclusions

With the goal of identifying a CETP inhibitor with high in vitro potency and optimal in vivo efficacy, a conformationally constrained molecule was designed based on the highly potent and flexible **13** (IC_{50} = 3 nM). The synthetic efforts led to the discovery of **12** (IC_{50} = 39 nM) that proved to be very selective over other lipid transfer proteins and a large panel of GPCRs and ion channels. Compound **12** had in vivo efficacy (HDL-C raising) comparable to that of **1** in high-fat fed hamsters, human

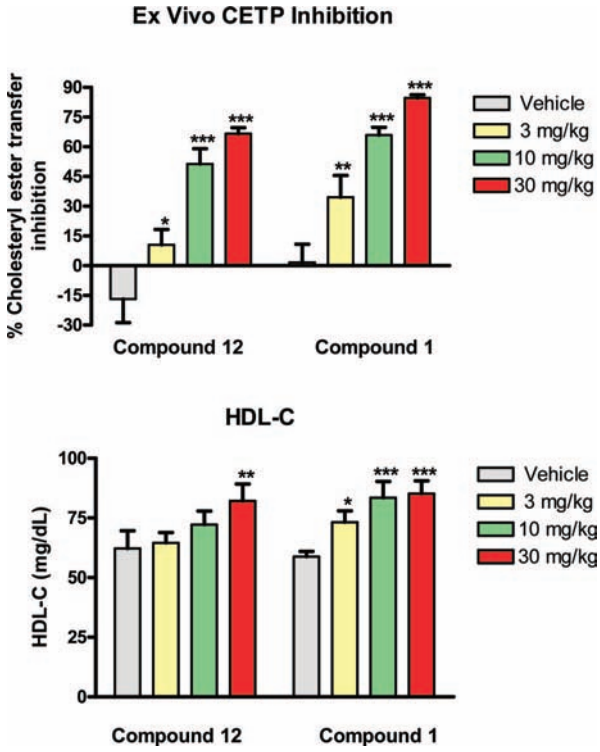


Figure 5. Effects of **12** and **1** on CETP inhibition and HDL-C in the cynomolgus monkey (5 days oral dosing). Bars represent means ± SD ($n = 6$ per group; $^*p < 0.05$ relative to prebleed control).

CETP transgenic mice, and monkeys. Taken together, the potency, selectivity, stability, and in vivo HDL raising efficacy in three animal modes support the utility of **12** for HDL raising through CETP inhibition, with the potential for having a positive impact on atherosclerosis without the off-target cardiovascular liability.

Experimental Section

Chemistry. ^{1}H NMR spectra were measured on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Elemental analyses were obtained by Quantitative Technologies Inc. (Whitehouse, NJ). Electrospray mass spectra (MS-ES) were recorded on a Hewlett-Packard 59987A spectrometer. Synthesis of **5**−**8** are included in Supporting Information.

***N*-{3-(2,6-Dibromo-phenyl)-1-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-propyl}-2-nitro-benzenesulfonamide (9).** To a solution of **8** (2.90 g, 5.67 mmol) in 1,2-dichloroethane (38 mL) under N_2 was added $Me_2S\cdot BHCl_2$ (1.64 mL, 14.2 mmol) dropwise. The solution was stirred at 20 °C for 0.5 h and then heated at 50 °C for 1.5 h. The reaction was cooled to 0 °C, and then 6 N HCl (10 mL) was added and heated at reflux for 1 h. Upon cooling to 0 °C, the solution was basified with 3 N NaOH, worked up with H_2O, and purified by column chromatography (100% EtOAc) to provide 2.69 g (98%) of 3-(2,6-dibromo-phenyl)-1-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-propylamine as an oil; MS (ES) *m*/*z*: 486 (M + H^+). To a solution of the amine (2.67 g, 5.50 mmol) and Et_3N (1.53 mL, 11.0 mmol) in CH_2Cl_2 (27 mL) was added NsCl (1.34 g, 6.05 mmol) under N_2. The reaction mixture was stirred at 20 °C for 1 h and then poured into EtOAc/Et_2O, worked up with H_2O, and purified by column chromatography (5%−10%−15%−20% EtOAc/hex) to afford 3.54 g (95%) of **9** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J = 8.0$ Hz, 1 H), 7.66 (d, $J = 7.9$ Hz, 1 H), 7.33−7.56 (m, 4 H), 7.08−7.13 (m, 2 H), 7.01 (s, 1 H), 6.88−6.95 (m, 2 H), 5.96 (d, $J = 8.9$ Hz, 1 H), 5.86 (tt, $J = 53.1$, 2.8 Hz, 1 H), 4.69 (dd, $J = 16.0$, 7.8 Hz, 1 H), 3.11−3.19 (m, 1 H), 2.80−2.88 (m, 1 H), 1.94−2.14 (m, 2 H). MS (ES) *m*/*z*: 693 (M + Na^+).

5-Bromo-2-[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-1,2,3,4-tetrahydro-quinoline (10). A mixture of **9** (3.54 g, 5.26 mmol), CuI (2.00 g, 10.5 mmol), and CsOAc (5.04 g, 26.3 mmol) in DMSO (52 mL) under N_2 was heated at 95 °C for 24 h. After cooling to 20 °C, the reaction mixture was worked up with EtOAc/H_2O and purified by column chromatography (25% EtOAc/hex) to afford 2.99 g (96%) of 5-bromo-1-(2-nitro-benzenesulfonyl)-2-[3-(1,1,2,2-tetrafluro-ethoxy)-phenyl]-1,2,3,4-tetrahydro-quinoline as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.1$ Hz, 1 H), 7.69−7.73 (m, 1 H), 7.50−7.63 (m, 3 H), 7.43 (d, $J = 8.0$ Hz, 1 H), 7.09−7.39 (m, 5 H), 5.88 (tt, $J = 53.1$, 2.9 Hz, 1 H), 5.62 (t, $J = 6.9$ Hz, 1 H), 2.66−2.74 (m, 1 H), 2.39−2.47 (m, 1 H), 2.27−2.35 (m, 1 H), 1.96−2.05 (m, 1 H). MS (ES) *m*/*z*: 589 (M). To a solution of protected-quinoline (2.99 g, 5.06 mmol) in DMF (25 mL) was added thioacetic acid (0.707 mL, 10.1 mmol) and powdered LiOH (485 mg, 20.2 mmol). The reaction mixture was stirred at 20 °C for 6 h and then worked up with EtOAc/H_2O and purified by column chromatography (25% EtOAc/hex) to afford 1.80 g (88%) of **10** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, $J = 7.8$ Hz, 1 H), 7.21−7.30 (m, 2 H), 7.15 (d, $J = 7.9$ Hz, 1 H), 6.71−6.95 (m, 2 H), 6.51 (d, $J = 7.8$ Hz, 1 H), 5.90 (tt, $J = 53.1$, 2.8 Hz, 1 H), 4.40 (dd, $J = 9.3$, 3.1 Hz, 1 H), 4.13 (brs, 1 H), 2.79−2.88 (m, 2 H), 2.11−2.21 (m, 1 H), 1.90−2.05 (m, 1 H). MS (ES) *m*/*z*: 406 (M + 2).

2-[3-(1,1,2,2-Tetrafluoro-ethoxy)-phenyl]-5-(3-trifluoromethoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (11). A mixture of bromide **10** (30 mg, 0.074 mmol), 3-trifluoromethoxy-phenyl-boronic acid (30 mg, 0.148 mmol), $Pd(PPh_3)_4$ (9 mg, 0.0074 mmol), and 2 N K_2CO_3 (0.11 mL, 0.22 mmol) in 1,4-dioxane (0.75 mL) was heated at reflux for 2 h. After cooling to 20 °C, the mixture was worked up with EtOAc/H_2O and purified by column chromatography to give 33 mg (91%) of **11** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.42 (m, 4 H), 7.25 (m, 1 H), 7.08−7.21 (m, 4 H), 6.62 (s, 1 H), 6.60 (s, 1 H), 5.90 (tt, $J = 53.1$, 2.8 Hz, 1 H), 4.51 (dd, $J = 8.9$, 3.3 Hz, 1 H), 4.20 (brs, 1 H), 2.71−2.81 (m, 1 H), 2.53 (dt, $J = 16.6$, 4.8 Hz, 1 H), 2.02−2.10 (m, 1 H), 1.82−1.92 (m, 1 H). MS (ES) *m*/*z*: 486 (M + H^+).

(2*R*,α*S*)-3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)-phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol (12). Using chiral HPLC (OJ column, using 95% heptane, 5% ethanol as the eluent, 80 mL/min as the flow rate, retention time 4.7 min, wavelength 220 nm) to separate (2*R*)-1,2,3,4-tetrahydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)-phenyl]quinoline (2*R*)-**11** as a clear oil (45%): $[\alpha]_D^{20} = -12.9°$ (C = 1, $CHCl_3$). To a solution of (2*R*)-**11** (33 mg, 0.068 mmol) and (*S*)-1,1,1-trifluoro-2,3-epoxy-propane (38 mg, 0.34 mmol) in CH_2Cl_2 (0.45 mL) under N_2 was added $Yb(OTf)_3$ (10.5 mg, 0.0169 mmol). The reaction mixture was heated at 50 °C for 48 h and then cooled to 20 °C, worked up with EtOAc/H_2O, and purified by column chromatography to get 28 mg (69%) of **12** as an oil: $[\alpha]_D^{20} = -117.3°$ (C = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.40 (m, 2 H), 7.10−7.28 (m, 6 H), 7.04 (s, 1 H), 6.73 (d, $J = 8.3$ Hz, 1 H), 6.67 (d, $J = 7.4$ Hz, 1 H), 5.89 (tt, $J = 53.1$, 2.8 Hz, 1 H), 4.89 (t, $J = 4.4$ Hz, 1 H), 4.42 (m, 1 H), 3.91 (d, $J = 15.5$ Hz, 1 H), 3.30 (dd, $J = 15.6$, 9.7 Hz, 1 H), 2.48 (dt, $J = 16.3$, 4.4 Hz, 1 H), 2.31−2.42 (m, 2 H), 2.09−2.19 (m, 1 H), 1.92−2.00 (m, 1 H). MS (ES) *m*/*z*: 598 (M + H^+). Anal. ($C_{27}H_{21}F_{10}NO_3$) C, H, N.

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Supporting Information Available: Elemental analysis data of target molecule, experimental procedures for **5**−**8**, biological assays, and PK assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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