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Article

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Potent Cholesteryl Ester Transfer Protein Inhibitors of Reduced Lipophilicity: 1,1′-Spiro-Substituted Hexahydrofuroquinoline Derivatives

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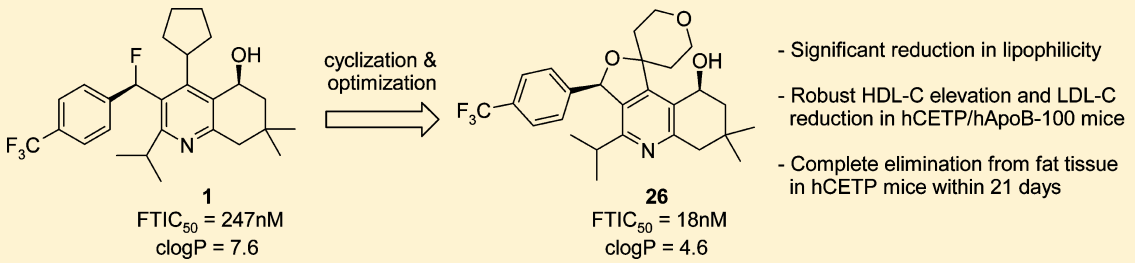
Supporting Information



1
$FTIC_{50}$ = 247nM
clogP = 7.6

26
$FTIC_{50}$ = 18nM
clogP = 4.6

ABSTRACT: A series of 1,1′-spiro-substituted hexahydrofuroquinoline derivatives exhibiting potent cholesteryl ester transfer protein (CETP) inhibition at reduced lipophilicity was identified. A focused structure−activity relationship (SAR) exploration led to the potent and comparatively polar CETP inhibitor **26** showing robust high density lipoprotein-cholesterol (HDL-C) elevation and low density lipoprotein-cholesterol (LDL-C) reduction in transgenic hCETP/hApoB-100 mice. Compound **26** was also shown to positively differentiate from highly lipophilic CETP inhibitors in its complete elimination from fat tissue in hCETP transgenic mice as evident within 21 days after cessation of treatment. In addition, compound **26** showed no significant effects on aldosterone secretion from H295R cells, as well as no significant effects on blood pressure and electrocardiogram parameters in telemetrized cynomolgus monkeys.

INTRODUCTION

Cardiovascular disease is the leading cause of mortality and morbidity in the developed world. Elevated levels of low density lipoprotein-cholesterol (LDL-C) are considered to be a major risk factor for cardiovascular events.[1] The development of the statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors) has helped to reduce LDL-C levels in patients at risk for cardiovascular events by approximately 30%.[2] However, a considerable risk remains.[3] Epidemiological studies have linked increased levels of high density lipoprotein-cholesterol (HDL-C) with a decreased number of cardiovascular events.[4] Inhibition of cholesteryl ester transfer protein (CETP) is considered to be one of the most powerful mechanisms for raising HDL-C levels and could therefore answer the key question whether raising HDL-C translates directly and on top of statins into a reduced risk for cardiovascular events.

CETP is a glycoprotein that mediates the exchange of cholesteryl ester from HDL with triglycerides from the apolipoprotein B (apoB)-containing lipoproteins, primarily very low density lipoprotein (VLDL).[5] The net effects of this exchange are increased LDL-C levels and decreased HDL-C levels. In a clinical phase III study (dal-OUTCOMES), the covalent but weakly binding CETP inhibitor dalcetrapib (Figure 1) showed only modest effects on lipoproteins (negligible LDL-C reduction, HDL-C increase of 30%) and failed to effect a clinically meaningful reduction in CV events.[6] The competitive and more potent CETP inhibitors anacetrapib and evacetrapib (Figure 1) however have been shown to reduce LDL-C levels in humans by more than 30% and to increase HDL-C levels by more than 120%.[7] Consequently a strong motivation to evaluate these agents and CETP inhibitors of comparable efficacy in cardiovascular outcome trials remains.

Since the hydrophobic nature of the CETP binding pocket[8] determines the physicochemical properties of potential inhibitors, it is no surprise that all published CETP inhibitors are highly lipophilic. This includes the structurally related CETP inhibitors torcetrapib, anacetrapib, and evacetrapib (Figure 1) that have reached clinical phase III trials.

High lipophilicity however represents a significant risk in drug development due to its effects on solubility, drug

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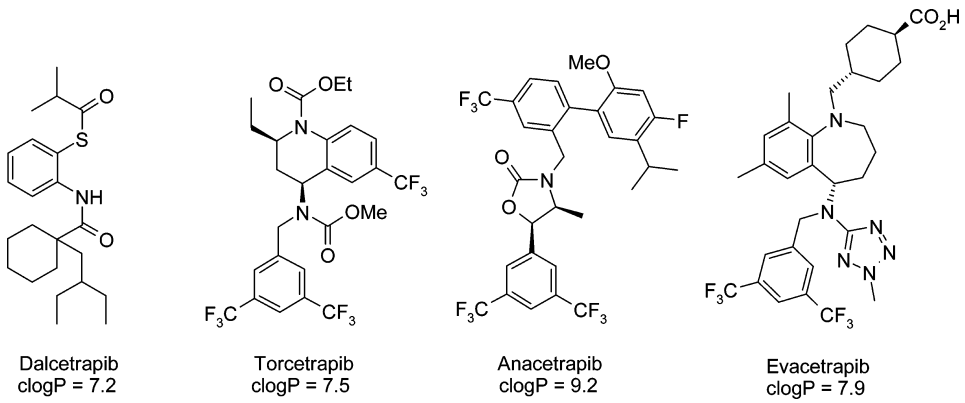


Figure 1. CETP inhibitors that reached phase III clinical trials.

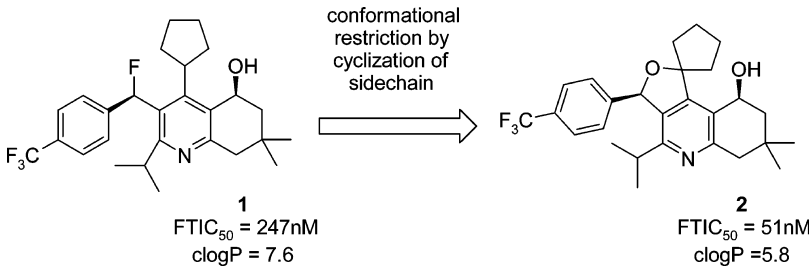
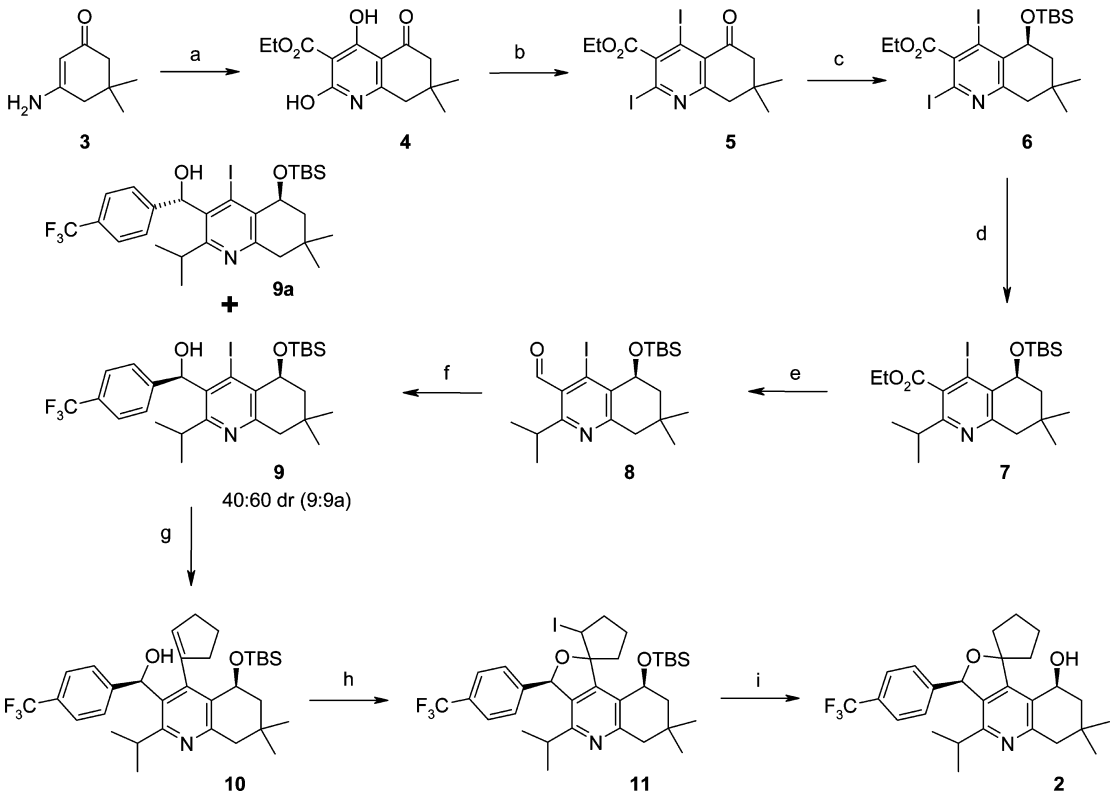


Figure 2. Design of hexahydrofuroquinoline CETP inhibitors.

Scheme 1. Synthetic Route[a]



[a]Reagents: (a) $HC(CO_2Et)_3$, reflux, 49%; (b) (i) $POCl_3$, 80 °C, 62%, (ii) AcCl, NaI, MeCN, 94%; (c) (i) (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, borane−diethylaniline complex, THF, 0−25 °C, 78%, (ii) TBSOTf, 2,6-lutidine, THF, 0 °C, 99%; (d) iPrZnBr, $Pd(dppf)Cl_2$, THF/PhMe, 85 °C, 31%; (e) (i) iBu_2AlH, DCM, 0 °C, 81%, (ii) Dess−Martin periodinane, DCM, 0 °C, 60%; (f) 4-iodobenzotrifluoride, iPrMgCl, THF, −20 °C, 84%; (g) 2-cyclopent-1-enyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane, CsF, $Pd(dppf)Cl_2$, THF, 50 °C, 74%; (h) ICl, DCM, 25 °C, 50%; (i) (i) H_2, 10 bar, Pd/C, MeOH, 65%, (ii) TBAF, THF, 25 °C, 58%.

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disposition, and promiscuity.[9] Hence the pharmacokinetics of the nonionizable and poorly water-soluble clinical compounds torcetrapib and anacetrapib show significant food effects and require special lipid formulations.[10] In addition, long terminal elimination half-lives of torcetrapib (221 h),[11] anacetrapib (83 h),[12] and evacetrapib (44 h)[13] after single oral dosing in humans have been reported and were associated with their high lipophilicity.

A phase III clinical trial with torcetrapib (ILLUMINATE) was terminated prematurely since increased cardiovascular events were observed in the torcetrapib-treated group versus placebo. Patients in the torcetrapib-treated group showed elevated mean systolic blood pressure, as well as an increase in aldosterone levels. Studies in preclinical species have recapitulated the effects of torcetrapib on aldosterone and blood pressure and have shown that they occur independent of CETP inhibition.[14] Therefore, there is continued interest in the development of potent small-molecule CETP inhibitors without adverse effects on cardiovascular parameters.

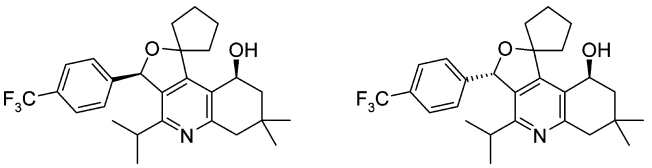
RESULTS AND DISCUSSION

In an effort to reduce the development risk of potential CETP inhibitors, we focused on starting points of reduced lipophilicity. After a careful literature review, we got interested in the published tetrahydroquinoline class of CETP inhibitors. Compound **1**, described in the patent literature,[15] is significantly more polar than anacetrapib. We hypothesized that potency of **1** could be improved by conformational restriction[16] of the fluorobenzylic side chain. While several cyclization efforts did not lead to compounds with improved potency, the hexahydrofuroquinoline derivative **2** showed a significant improvement in the hCETP fluorescence transfer[17] IC_{50} ($FTIC_{50}$). Gratifyingly, the increase in potency versus **1** was accompanied by a significant reduction in lipophilicity (Figure 2).

Developing a robust synthetic route to access various analogues of **2** presented a formidable challenge. However, a sequence employing a Hantzsch-type tetrahydroquinoline synthesis was identified and utilized for the exploration of modifications in different positions (Scheme 1).

Dimedone enamine **3** was submitted to condensation with triethylmethanetricarboxylate to give tetrahydroquinoline **4**. Compound **4** was dichlorinated with phosphorus oxychloride and then transferred into the diiodide **5** using acetyl chloride/sodium iodide. The 5-oxo substituent was reduced enantioselectively[18] using a modified CBS-reagent[19] and then TBS-protected to give 5-(*S*)-trimethylsilylether **6**. The desired 2-substituent was introduced by a regioselective Negishi-type coupling with isopropyl zinc bromide to give 2-isopropyl-tetrahydroquinoline **7**. For elaboration of the substituent in the 3-position, the ester **7** was transferred into aldehyde **8** via reduction with diisobutylaluminum hydride and oxidation using the Dess–Martin periodinane. Addition of 4-(trifluoromethyl)-phenyl magnesium bromide gave a 40:60 mixture[20] of the (3*R*,5*S*)-alcohol **9** and its (3*S*,5*S*)-diastereomer **9a**, which could be separated by flash chromatography. The substituent in the 4-position was introduced via Suzuki coupling to give 4-cyclopentenyl-tetrahydroquinoline **10**. Spirocyclization of the free hydroxyl onto the cyclopentenyl substituent was affected with iodine chloride, yielding iodo-spiro-hexahydrofuroquinoline **11** as a mixture of diastereomers. Finally, removal of the iodine by hydrogenation and cleavage of the TBS-protecting group using tetrabutylammonium fluoride furnished CETP inhibitor **2**.

Using an identical synthetic sequence, we transformed diastereomer **9a** into the diastereomeric CETP inhibitor **2a**, which is over 20-fold less potent than **2** (Figure 3).



2 $FTIC_{50}$ = 51 nM **2a** $FTIC_{50}$ = 1433 nM

Figure 3. Diastereomeric CETP inhibitors **2** and **2a**.

Initial modifications focused on the 3′-4-trifluorophenyl substituent and the 4′-isopropyl substituent of compound **2** (Table 1). While the high potency for lipophilic substituents in the 3′-position is eminent (e.g., compounds **2**, **16**, and **18**), we were gratified to see that subtle introduction of polarity allowed for reduction in lipophilicity without loss of potency (e.g., compounds **15**, **19**, and **20**).

Results from the modification of the 4′-isopropyl substituent showed that a branched substituent seems to be optimal for potency (see reduced potency for compound **21**). Again, it was possible to increase polarity without loss of potency (compound **23**).

Modifications of the 1,1′-spiro-substituent (Table 2) were limited by the requirements of the Suzuki–iodospirocyclization–hydrogenation sequence for its synthesis. However, within these limitations, a more polar and potent tetrahydropyranyl substituent was identified (compound **26**).

The enantiomeric excess of compound **26** was determined to be >95% using a chiral HPLC-method. In addition, the relative and absolute stereochemistry of compound **26** was unambiguously proven by crystal structure analysis. For further comparison, the enantiomer ***ent*-26** was synthesized and shown to be over 30-fold less potent than compound **26** (Figure 4). Compound **26** was also shown to be a potent CETP inhibitor in the presence of 88% human plasma ($FTIC_{50}$ (hplasma) = 151 nM).

Since the *in vivo* pharmacokinetic profile of compound **26** in mice looked promising,[21] it was advanced to evaluation in pharmacodynamic models. Compound **26** dose-dependently inhibited plasma CETP activity in male hCETP transgenic mice.[22] This resulted in a robust dose-dependent increase of HDL-cholesterol after 5 days of treatment of up to +74% for the 10 mg/kg dose (Figure 5). In this experimental setting, the 3 mg/kg dose of **26** showed similar efficacy to a 10 mg/kg dose of anacetrapib.

Compound **26** also dose-dependently elevated HDL-cholesterol up to +37% and reduced LDL-cholesterol down to −60% in hCETP/hApoB-100 transgenic mice[23] at doses of 10 mg/kg (Figure 6).

In a recent analysis of a clinical trial with the clinical CETP inhibitor anacetrapib (DEFINE), drug levels after cessation of active treatment were shown to decrease only to approximately 40% of on-treatment trough levels at 12 weeks after dosing.[24] Significant drug concentrations were still detectable in plasma 2–4 years after the last dosing. The extremely slow elimination of anacetrapib was linked to a delayed clearance from adipose tissue due to its high lipophilicity. To differentiate compound

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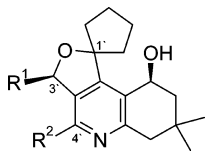
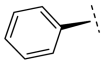
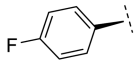
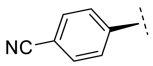
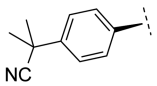
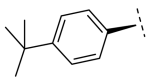
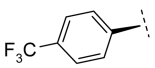
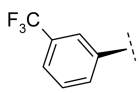
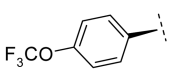
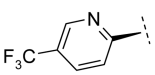
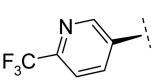
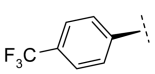
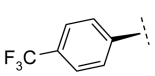
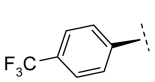
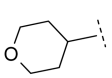
Table 1. Structure−Activity Relationship (SAR) of 3′- and 4′-Substituent



Cpd	R^1	R^2	clogP	FT IC_{50} [nM]	95% CL[a]
12			4.9	4052	3476-4723
13			5.1	796	702-902
14			4.4	1077	836-1388
15			5.1	47	27-84
16			6.8	29	15-54
2			5.8	51	36-71
17			5.8	524	445-617
18			6.0	131	83-206
19			4.5	96	64-143
20			4.5	135	104-174
21			5.4	418	343-509
22			6.5	37	22-62
23			4.6	42	25-71

[a]95% confidence limit.

26 from the extremely long terminal half-life characteristics of the more lipophilic anacetrapib, the elimination of both compounds was followed in the hCETP transgenic mouse model described above. Drug exposure in different tissues was measured at day 3 and day 21 after cessation of treatment for 5 days with doses of similar efficacy on HDL-C of 10 mg/kg for

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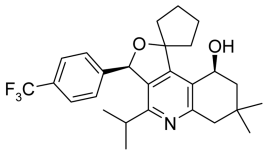
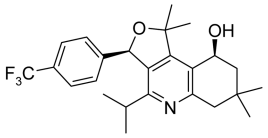
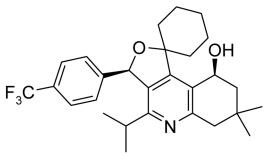
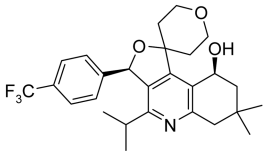
Table 2. SAR of the Spiro-Substituent

Cpd	Structure	clogP	FT IC_{50}	95% CL[a]
2		5.8	51	36-71
24		6.0	548	469-640
25		7.0	45	18-111
26		4.6	18	6-53

[a]95% confidence limit.

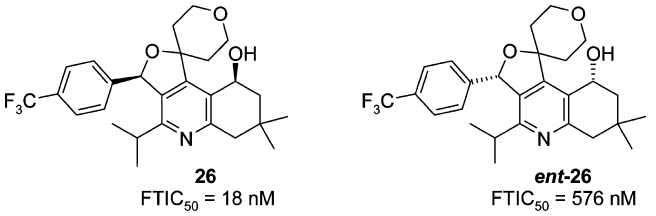
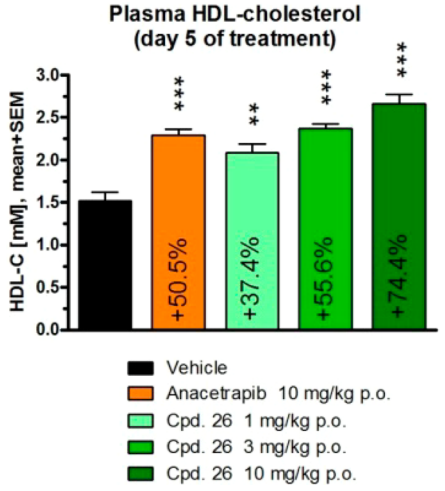


Figure 4. Enantiomeric CETP inhibitors **26** and ***ent*-26**.

anacetrapib and 3 mg/kg for compound **26** (Figure 5). At day 3 after cessation of treatment, both compounds showed high exposure in all tissues investigated (Figure 7). On day 21 after cessation of treatment, high levels of anacetrapib were observed in muscle, kidney, testes, and adipose tissue suggesting an extremely slow elimination from these compartments. In contrast to this, exposure of the less lipophilic CETP inhibitor compound **26** on day 21 after cessation of treatment was below the limit of quantification (LLQ = 30 nM) in all analyzed tissues, suggesting a significantly faster elimination.

Unlike torcetrapib,[14d] compound **26** showed no effects up to 10 μM on aldosterone secretion from the H295R human adrenal carcinoma cell line. To further differentiate from blood pressure effects reported for torcetrapib,[25] compound **26** was evaluated in an acute telemetry study in conscious cynomolgus monkeys. Compound **26** showed no significant effects on blood pressure, left ventricular pressure, myocardial contractility, or heart rate and had no significant effect on the electrocardiogram (ECG) parameters (PR-interval, QRS-complex, QT-interval) up to doses of 100 mg/kg with sustained high exposure (C_{max} > 10 μM, MRT > 20 h).

In summary, a hexahydrofuroquinoline scaffold was identified from conformational restriction of a known literature series. A synthesis was developed and utilized for the introduction of structural modifications. Initial SAR revealed that polar substituents were tolerated in a number of positions. Based on its *in vitro* properties and its PK profile, compound **26** was selected for *in vivo* evaluation. Compound **26** demonstrated dose dependent CETP inhibition and HDL-cholesterol elevation in hCETP transgenic mice. Compound **26** also showed robust HDL-cholesterol elevation and LDL-cholesterol reduction in hCETP/hApoB-100 mice. In contrast to the clinical CETP inhibitor anacetrapib, compound **26** eliminated completely from tissues of hCETP transgenic mice 21 days after cessation of treatment for 5 days at a fully efficacious dose. Compound **26** also showed no significant effects on aldosterone secretion from H295R cells up to 10 μM, as well as no significant effects on blood pressure and ECG parameters in telemetrized cynomolgus monkeys. The studies described herein led to the selection of the CETP inhibitor **26** as a development candidate.



Cpd	Dose [mg/kg]	Cplasma[a] [nM]
anacetrapib	10	507
Cpd. 26	1	96
Cpd. 26	3	206
Cpd. 26	10	671

[a] plasma concentration on day 5, 7h post dose

Figure 5. Effects on HDL-C and plasma exposure of anacetrapib and compound **26** in hCETP transgenic mice.

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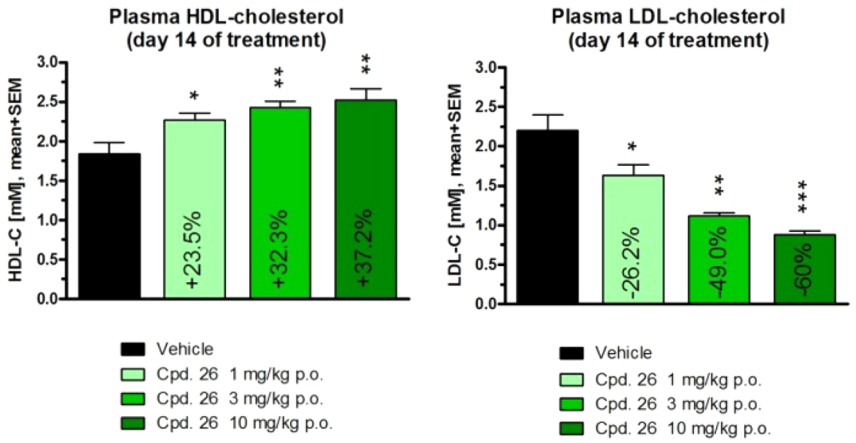

Figure 6. Effects of **26** on HDL-C and LDL-C in hCETP/hApoB-100 transgenic mice.

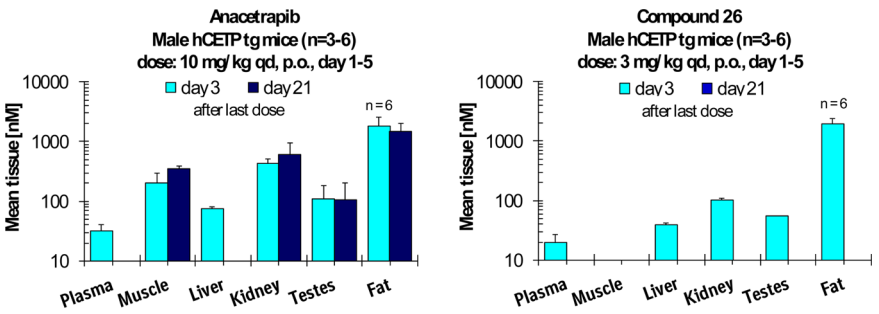

Figure 7. Exposure of anacetrapib and compound **26** in different tissues of male hCETP transgenic mice at day 3 and day 21 after cessation of oral treatment for 5 days with either 10 mg/kg of anacetrapib or 3 mg/kg of compound **26**.

EXPERIMENTAL SECTION

Methods. *CETP Activity Measurement.* The determination of CETP activity ($FTIC_{50}$) was based on the transfer of a neutral fluorescence labeled lipid from donor vesicles to acceptor vesicles by CETP. The manufacturer's protocol of the ROAR CETP RP activity assay kit, 250 assays, was adapted to a 384-well format by reducing the total assay volume to 100 μL. Test compound (2.5 μL) dissolved in DMSO was incubated at 37 °C for 3 h with 97.5 μL of a master mix (containing 2 μL of donor particles, 2 μL of acceptor particles, and 0.8 μL of human recombinant CETP in assay buffer). Typical hCETP concentrations were 0.2−1 mg/mL. The change of fluorescence at 485/535 nm is an indicator of CE-transfer. The inhibition of transfer was measured. IC_{50} values were calculated by nonlinear regression analysis using a four-parameter logistic equation (sigmoidal dose−response model, variable slope).

Animals. Hemizygous human CETP transgenic male mice (B6.SJL-Tg(APOA-CETP)1Dsg N11), as well as hemizygous human CETP/human apolipoprotein B100 (apoB100) transgenic male mice (B6.SJL-Tg(APOA-CETP)1Dsg Tg(APOB)1102Sgy N10), were purchased from Taconic (Laven, Denmark). Mice at an age of 26−30 weeks were housed in a temperature- (22 ± 2 °C) and humidity-controlled (55% ± 10%) environment and were fed ad libitum a standard chow diet with free access to water. All animal studies were performed in accordance with the German law on the protection of animals. Animal experiments were approved by the local animal ethics committee.

Treatment and Blood Sampling for Lipoprotein Analysis. For the treatment studies, anacetrapib and compound **26** were suspended in the vehicle (0.5% aqueous hydroxyethylcellulose). Animals were treated with indicated compound for 5 or 14 consecutive days via oral gavage in the morning. Blood was collected into EDTA coated tubes from animals 7 h post-dosing either in the fed state (5-day treatment) or after a 4 h fast (14-day treatment) via bleeding of the vena facialis under isoflurane anesthesia.

Plasma Lipoprotein Analysis. Plasma was assayed for the HDL and LDL cholesterol fraction, using the Cobas Integra 400 Plus system.[26]

Statistics. The data are presented as mean ± standard error of the mean. Statistical comparisons were conducted by one-way ANOVA followed by Bonferroni post-test (using GraphPad Prism 6 software). A p value <0.05 was considered to show a statistically significant difference.

Tissue Drug Exposure Analysis Using LC/MS/MS Quantification. Samples were prepared for LC/MS/MS measurement by protein precipitation with acetonitrile/methanol (1:1, v:v) using a generic internal standard. Tissue sample aliquots were first diluted with phosphate buffered saline (6:1 PBS/(brain/liver/testis), 12:1 PBS/muscle); fat sample aliquots were diluted with acetonitrile (6:1 ACN/fat), homogenized, and then further processed as plasma samples. The LC/MS/MS system consisted of Agilent 1100 series binary pumps (flow rate 0.4 mL/min), a CTC Analytics HTC PAL autosampler, a YMC ODS AQ C18 column (33 mm × 2.1 mm, 3 μm ID), and an AB Sciex API 4000 triple quadrupole mass spectrometer. The mass spectrometer was operated in a positive turbo ionspray and multiple reaction monitoring mode with parent to product ion transitions of 467.2 to 448.2 for compound **26** and 638.2 to 283.0 for anacetrapib. Calibration standards were freshly prepared, and the linear calibration range for compound **26** and anacetrapib was from 5 to 2500 nM and 12.5 to 2500 nM, respectively. For each compound, quality controls (QCs) at concentrations of 4.0, 50, and 1000 nM and additional QCs in each matrix at concentrations of 10, 100, and 1000 nM were used. Measurements of two sets of QC samples were within ±30% of the target concentrations. All samples were stored at −20 °C.

General Analytics. NMR spectra were recorded on a Bruker 400 MHz instrument. Chemical shifts are given in parts per million (ppm) downfield from internal reference tetramethylsilane in δ units. Selected data are reported in the following manner: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants (J), integration. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60

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F254 plates. All compounds were visualized as single spots using short wave UV light (254 nm). Low resolution mass spectra were obtained using a liquid chromatography mass spectrometer (HPLC-MS) that consisted of an Agilent 1100 series LC coupled to an Agilent 6130 quadrupole mass spectrometer (electrospray positive ionization) and an Agilent G1315C DAD SL detector operating at 254−360 nm (typically 254 nM was used for compound detection). Unless otherwise specified, the purity of all intermediates and final compounds was determined to be >95% by HPLC-MS using the eluents water containing 0.1% formic acid (eluent A), acetonitrile containing 0.1% formic acid (eluent B), water containing 0.1% trifluoro actetic acid (eluent C), acetonitrile containing 0.1% trifluoro actetic acid (eluent D), and methanol (eluent E) and the following conditions: Agilent Zorbax Bonus RP, 50 mm × 2.1 mm, 3.5 μm, 1.2 mL/min, gradient 4.5 min 10% → 99% eluent B in eluent A (method 1); Agilent Zorbax Bonus RP, 50 mm × 2.1 mm, 3.5 μm, 1.2 mL/min, gradient 1.0 min 10% → 75%, 0.3 min 75%, 1.0 min 75% → 99% eluent B in eluent A (method 2); Varian Microsorb 100 C18, 30 mm × 4.6 mm, 3.5 mL/min, gradient 2.0 min 5% → 98% eluent D in eluent C (method 3); Merck Chromolith Flash RP18e, 25 mm × 4.6 mm, 1.6 mL/min, gradient 2.0 min 10% → 90%, 5.00 min 90% eluent B in eluent A (method 4); BEH C18, 50 mm × 2.1 mm, 1.7 μm, 0.85 mL/min, gradient 1.2 min 50% → 90% eluent D in eluent C (method 5); Varian Microsorb 100 C18, 30 mm × 4.6 mm, 3.5 mL/min, gradient 3.95 min 5% → 100% eluent E in eluent C (method 6); Atlantis dC18, 50 mm × 4.6 mm, 5 μm, 1.3 mL/min, gradient 3.5 min 10% → 90% eluent D in eluent C/eluent D 9:1 (method 7); Symmetry Shield RP8, 150 mm × 4.6 mm, 5 μm, 1.0 mL/min, gradient 1.5 min 5%, 10 min 5% → 95% eluent A/eluent B 1:9 in eluent A/eluent B 9:1 (method 8); Symmetry Shield RP8, 150 mm × 4.6 mm, 5 μm, 0.85 mL/min, gradient 1.5 min 30% → 50%, 7.0 min 50% → 100% eluent A/eluent B 1:9 in eluent A/eluent B 9:1 (method 9); Daicel ODH, 250 mm × 4.6 mm, 4 mL/min, gradient 10 min supercritical carbon dioxide containing 10% ispropanol and 2% diethylamine (chiral HPLC).

Synthesis Procedures. *Ethyl 2,4-Dihydroxy-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**4**).* 3-Amino-5,5-dimethyl-2-cyclohexen-1-one [**3** (10 g, 71.8 mmol)] and 2-ethoxycarbonylmalonic acid diethyl ester (25 g, 108 mmol) were combined and heated for 10 min at 210 °C (bath temperature). Thereafter the mixture was cooled to room temperature and triturated with diethyl ether. The crystalline precipitate was collected by filtration and dried in vacuo. Yield: 9.9 g (49% of theory). LCMS (ESI^+) calculated for $C_{14}H_{17}NO_5$ $[M + H]^+$ m/z 280.11, found 280.1. R_f-value: 0.45 (silica gel, dichloromethane/methanol 9:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 12.88 (s, 1H), 12.35 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.73 (s, 2H), 2.49 (s, 2H), 1.23 (t, J = 7.1, 3H), 1.04 (s, 6H).

Ethyl 2,4-Dichloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate. Compound **4** (9.9 g, 35.5 mmol) was suspended in phosphoroxychloride (50 mL, 545 mmol). After addition of *N*,*N*-dimethylformamide (0.5 mL), the mixture was heated to 80 °C for 12 h. Then the phosphoroxychloride was evaporated in vacuo, and the residue was dissolved in dichloromethane. After washing with water, saturated aqueous sodium bicarbonate solution, and brine, the solution was dried with magnesium sulfate. The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel cyclohexane/ethyl acetate (90:10 to 50:50). Yield: 6.95 g (62% of theory). LCMS (ESI^+) calculated for $C_{14}H_{15}Cl_2NO_3$ $[M + H]^+$ m/z 316.14, found 316.1 (100% intensity), 317.1 (15% intensity), 318.1 (65% intensity), 319.1 (10% intensity), 320.1 (11% intensity), 320.1 (1.8% intensity). R_f-value: 0.44 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 4.43 (q, J = 7.1 Hz, 2H), 3.06 (s, 2H), 2.62 (s, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.04 (s, 6H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 194.6, 165.8, 162.6, 148.1, 141.3, 129.4, 123.2, 62.7, 52.4, 46.0, 31.7, 27.4 (2C), 13.7.

*Ethyl 2,4-Diiodo-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**5**).* Ethyl 2,4-dichloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (6.95 g, 22.0 mmol) was dissolved in acetonitrile (100 mL) and reacted with sodium iodide (10 g, 66.7 mmol) and acetyl chloride (1.6 mL, 22.5 mmol) for 3 h at 50 °C. The mixture was diluted with diethyl ether (100 mL) and then washed with saturated aqueous sodium bicarbonate solution (50 mL), saturated aqueous sodium thiosulfate (50 mL), and brine (50 mL). After drying with magnesium sulfate, the solvents were evaporated in vacuo. Yield: 10.3 g (94% of theory). LCMS (ESI^+) calculated for $C_{14}H_{15}I_2NO_3$ $[M + H]^+$ m/z 500.01, found 500.2. HPLC (method 1): retention time = 3.484 min. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 4.39 (q, J = 7.0 Hz, 2H), 3.04 (s, 2H), 2.63 (s, 2H), 1.36, (t, J = 7.0 Hz, 3H), 1.00 (s, 6H).

(S)-Ethyl 5-Hydroxy-2,4-diiodo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate. (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol (500 mg, 3.35 mmol) was dissolved in tetrahydrofuran (100 mL), and to this solution of a borane−diethylaniline complex (7.3 mL, 41.1 mmol) was added dropwise. After completion of gas evolution, the solution was cooled to 0 °C, and ethyl 2,4-diiodo-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (10.3 g, 20.6 mmol) in tetrahydrofuran (20 mL) was added cautiously over 5 min. The temperature was raised during 28 h to room temperature, methanol (20 mL) was added dropwise, and the mixture was stirred for additional 10 min. The solution was diluted with diethyl ether (100 mL) and washed with 1 N hydrochloric acid (50 mL), saturated aqueous sodium bicarbonate solution (50 mL), and brine (50 mL). After drying with magnesium sulfate, the solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 30:70). Yield: 8.1 g (78% of theory). LCMS (ESI^+) calculated for $C_{14}H_{17}I_2NO_3$ $[M + H]^+$ m/z 502.03, found 502.2. HPLC (method 1): retention time = 3.286 min. R_f-value: 0.21 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 5.15 (d, J = 5.6 Hz, 1H), 4.68 (m, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.73 (d, J = 16.9 Hz, 1H), 2.56 (d, J = 16.9 Hz, 1H), 1.85 (dd, J = 14.0, 5.5, Hz, 1H,), 1.75 (dd, J = 14.0, 4.2 Hz, 1H), 1.35, (t, J = 7.1 Hz, 3H), 1.05 (s, 3H), 0.92 (m, 3H).

*(S)-Ethyl 5-(tert-butyldimethylsilyloxy)-2,4-diiodo-7,7-dimethyl-5,6,7,8-tetrahydro-quinoline-3-carboxylate (**6**).* (*S*)-Ethyl 5-hydroxy-2,4-diiodo-7,7-dimethyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (8.1 g, 16.2 mmol) was dissolved in tetrahydrofuran (70 mL) and cooled to 0 °C, 2,6-lutidine (3.2 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5 mL, 21.8 mmol) were added dropwise, and the mixture was stirred for further 12 h while warming to room temperature. The solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 30:70). Yield: 9.8 g (99% of theory). LCMS (ESI^+) calculated for $C_{20}H_{31}I_2NO_3Si$ $[M + H]^+$ m/z 616.03, found 616.1. HPLC (method 1): retention time = 4.916 min. R_f-value: 0.71 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 5.02 (dd, J = 3.5, 4.6 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 2.88 (d, J = 16.2 Hz, 1H), 2.55 (d, J = 16.2 Hz, 1H), 1.91 (dd, J = 14.5, 3.2, Hz, 1H,), 1.75 (dd, J = 14.5, 4.5 Hz, 1H), 1.35, (t, J = 7.2 Hz, 3H), 1.13 (s, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.89 (m, 3H), 0.89 (m, 9H), 0.20 (s, 3H).

*(S)-Ethyl 5-(tert-butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydro-quinoline-3-carboxylate (**7**).* Under argon, **6** (9.8 g, 15.9 mmol) was dissolved in toluene (25 mL) and tetrahydrofuran (25 mL). 1,1′-Bis(diphenylphosphino)-ferrocene-dichloro-palladium(II) (800 mg, 1.09 mmol) was added, the mixture was heated to 85 °C, and a 0.5 M solution of isopropyl-zinc-bromide in tetrahydrofuran (50 mL, 25.0 mmol) was added dropwise. After completion of the addition, the mixture was heated for 12 h at reflux. The mixture was cooled to room temperature, diluted with diethyl ether (50 mL), and washed with saturated ammonium chloride solution (30 mL) and brine (30 mL). The solvents were evaporated under reduced pressure, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 60:40). Yield: 2.63 g (31% of theory). LCMS (ESI^+) calculated for $C_{23}H_{38}INO_3Si$ $[M + H]^+$ m/z 532.17, found 532.1. R_f-value: 0.85 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 5.03 (dd, J = 3.5, 4.6 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.91 (d, J = 16.1 Hz, 1H), 2.91−2.80 (m, 1H), 2.55 (d, J = 16.1 Hz, 1H), 1.91 (dd, J = 3.3, 14.3 Hz, 1H), 1.74 (dd, J = 4.6, 14.4 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.19 (d, J = 1.7 Hz, 3H), 1.17 (d, J = 1.6 Hz, 3H), 1.15 (s, 3H), 0.87 (s, 3H), 0.85 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 168.1, 160.4, 158.3, 134.1, 133.3, 110.9, 72.6, 61.7, 46.7,

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44.3, 33.5, 30.3, 30.0, 30.0, 26.1 (3C), 22.3, 22.0, 17.9, 13.8, −2.9, −3.9.

(S)-(5-(tert-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydro-quinolin-3-yl)methanol. Compound 7 (2.63 g, 4.95 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C. A 1 M solution of diisobutylaluminumhydride in dichloromethane (16.5 mL, 16.5 mmol) was added dropwise, and the solution was stirred for another 2 h. Then the solution was diluted with dichloromethane, and 1 N hydrochloric acid (1 mL) was added dropwise under vigorous stirring. After 5 min magnesium sulfate was added and stirring was continued for further 5 min. Filtration and evaporation of the solvents in vacuo gives a crude product, which was chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 60:40). Yield: 1.96 g (81% of theory). LCMS (ESI^+) calculated for $C_{21}H_{36}INO_3Si$ $[M + H]^+$ m/z 490.16, found 490.4. HPLC (method 1): retention time = 4.100 min. R_f-value: 0.55 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 4.94−4.90 (m, 1H), 4.89−4.85 (m, 1H), 4.59−4.54 (m, 2H), 3.35−3.26 (m, 1H), 2.73 (d, J = 15.6 Hz, 1H), 2.34 (d, J = 15.6 Hz, 1H), 1.74 (dd, J = 14.3, 3.3 Hz, 1H,), 1.50 (dd, J = 14.3, 4.6 Hz, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.68 (s, 3H), 0.67 (s, 9H), 0.30 (s, 3H), 0.00 (s, 3H).

*(S)-5-(tert-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydro-quinoline-3-carbaldehyde (**8**).* (*S*)-(5-(*tert*-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl) methanol (1.96 g, 4.00 mmol) was dissolved in dichloromethane (60 mL), cooled to 0 °C, and mixed with 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1*H*)-one (Dess−Martin periodinane, 15 g, 5.31 mmol). The mixture was stirred for 12 h while warming to room temperature. Then the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 95:5 to 80:20). Yield: 1.17 g (60% of theory). LCMS (ESI^+) calculated for $C_{21}H_{34}INO_3Si$ $[M + H]^+$ m/z 488.15, found 488.1. HPLC (method 1): retention time = 5.106 min. R_f-value: 0.45 (silica gel, petroleum ether/ethyl acetate 16:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 10.12 (s, 1H), 5.15 (dd, J = 3.6, 4.5 Hz, 1H), 3.48−3.40 (m, 1H), 2.95 (d, J = 16.3 Hz, 1H), 2.58 (d, J = 16.3 Hz, 1H), 1.95 (dd, J = 14.3, 3.3 Hz, 1H,), 1.77 (dd, J = 14.3, 5.0 Hz, 1H), 1.19 (d, J = 6.7 Hz, 3H), 1.17 (s, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.88 (s, 3H), 0.85 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H).

*(R)-((S)-5-(tert-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydro-quinolin-3-yl)(4-(trifluoromethyl)phenyl)-methanol (**9**) and (S)-((S)-5-(tert-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl)(4-(trifluoromethyl)phenyl)methanol (**9a**).* 4-Iodobenzotrifluoride (1.1 mL, 7.34 mmol) was dissolved in tetrahydrofuran (60 mL) and cooled to −20 °C. Isopropylmagnesium chloride (3.7 mL of a 2 M solution in tetrahydrofuran, 7.40 mmol) was added dropwise, and the solution was stirred for further 5 h. Then the solution was cooled to −40 °C, and **8** (1.17 g, 2.40 mmol) in tetrahydrofuran (5 mL) was added dropwise. The mixture was stirred for 12 h while warming to room temperature. Then it was cooled to 0 °C, methanol (10 mL) was added, and it was stirred for 30 min. The solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 95:5 to 80:20).

*(R)-((S)-5-(tert-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl)(4-(trifluoromethyl)phenyl)-methanol (**9**).* Yield: 496 mg (33% of theory). LCMS (ESI^+) calculated for $C_{28}H_{39}F_3INO_2Si$ $[M + H]^+$ m/z 634.18, found 634.2. HPLC (method 1): retention time = 5.195 min. R_f-value: 0.62 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.69 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.62 (d, J = 4.13, 1H), 6.51 (br, 1H), 5.24−5.20 (m, 1H), 3.30−3.20 (m, 1H), 2.84 (d, J = 16.3 Hz, 1H), 2.56 (d, J = 16.3 Hz, 1H), 1.96 (dd, J = 14.3, 2.6, 1H), 1.82 (dd, J = 14.2, 4.8 Hz, 1H), 1.16 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.46 (d, J = 6.6 Hz, 3H), 0.28 (s, 3H), 0.25 (s, 3H).

*(S)-((S)-5-(tert-Butyldimethylsilyloxy)-4-iodo-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydro-quinolin-3-yl)(4-(trifluoromethyl)phenyl)-methanol (**9a**).* Yield: 782 mg (51% of theory). LCMS (ESI^+) calculated for $C_{28}H_{39}F_3INO_2Si$ $[M + H]^+$ m/z 634.18, found 634.2. HPLC (method 1): retention time = 5.256 min. R_f-value: 0.56 (silica gel, petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.69 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.69−6.65 (m, 1H), 6.48 (br, 1H), 5.15−5.12 (m, 1H), 3.26−3.18 (m, 1H), 2.95 (d, J = 15.6 Hz, 1H), 2.53 (d, J = 15.6 Hz, 1H), 1.95 (dd, J = 14.3, 3.5, 1H), 1.74 (dd, J = 14.3, 4.7 Hz, 1H), 1.19 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H), 0.93 (s, 3H), 0.93 (s, 9H), 0.46 (d, J = 6.6 Hz, 3H), 0.22 (s, 3H), 0.18 (s, 3H).

*(R)-((S)-5-(tert-Butyldimethylsilyloxy)-4-cyclopentenyl-2-isopropyl-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-3-yl)(4-(trifluoromethyl)-phenyl)methanol (**10**).* Under argon, **9** (490 mg, 0.773 mmol) and 2-cyclopent-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (900 mg, 2.782 mmol) were dissolved in tetrahydrofuran (20 mL). Cesium fluoride (900 mg, 5.93 mmol) was added, and the mixture was purged for 5 min with argon. After the addition of 1,1′-bis-(diphenylphosphino)-ferrocene-dichloro-palladium-(II) (50 mg, 0.068 mmol), the mixture was heated to 50 °C for 36 h. Then the mixture was diluted with diethyl ether (30 mL), washed with saturated aqueous ammonium chloride (20 mL) and brine (20 mL), and dried with magnesium sulfate. The solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 95:5 to 60:40). Yield: 330 mg (74% of theory). LCMS (ESI^+) calculated for $C_{33}H_{46}F_3NO_2Si$ $[M + H]^+$ m/z 574.33, found 574.4. R_f-value: 0.37 (silica gel, petroleum ether/ethyl acetate 8:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.26−6.20 (m, 1H), 5.88−5.83 (m, 1H), 5.67 (br, 1H), 4.89 (br, 1H), 3.03 (d, J = 14.3 Hz, 1H), 2.65−2.60 (m, 1H), 2.55−2.43 (m, 2H), 2.01−1.91 (m, 2H), 1.54−1.42 (m, 1H), 1.25−1.22 (m, 2H), 1.12−1.07 (m, 2H), 1.23 (s, 3H), 1.10 (d, J = 6.0 Hz, 3H), 0.84 (s, 9H), 0.79 (s, 3H), 0.48 (d, J = 6.0 Hz, 3H), 0.13 (s, 3H), −0.02 (s, 3H).

*(3′R,9′S)-9′-(tert-Butyldimethylsilyloxy)-2-iodo-4′-isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinoline] (**11**).* Compound **10** (105 mg, 0.183 mmol) was dissolved in dichloromethane (4 mL), mixed with iodinechloride (500 μL of a 1 M solution in dichloromethane, 0.500 mmol), and stirred for 24 h. Then the solution was diluted with diethyl ether (30 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL), saturated aqueous sodium thiosulfate solution (20 mL), and brine (20 mL). After drying with magnesium sulfate, the solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 98:2 to 80:20). Yield: 64 mg (50% of theory). LCMS (ESI^+) calculated for $C_{33}H_{45}F_3INO_2Si$ $[M + H]^+$ m/z 700.23, found 700.2. R_f-value: 0.57 (silica gel, petroleum ether/ethyl acetate 8:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 6.20 (s, 1H), 5.16−5.13 (m, 1H), 4.44−4.38 (m, 1H), 3.15 (d, J = 13.7 Hz, 1H), 2.56 (d, J = 13.7 Hz, 1H), 2.49−2.42 (m, 1H), 2.23−2.12 (m, 4H), 2.06−2.00 (m, 2H), 1.83−1.72 (m, 2H), 1.23 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 0.82 (s, 9H), 0.73 (s, 3H), 0.64 (d, J = 6.0 Hz, 3H), 0.22 (s, 3H), 0.76 (s, 3H).

(3′R,9′S)-9′-(tert-Butyldimethylsilyloxy)-4′-isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinoline]. To a solution of **11** (60 mg, 0.086 mmol) in methanol (5 mL) was added triethylamine (25 μL, 0.179 mmol) and palladium (10% on charcoal, 90 mg, 0.085 mmol). The mixture was hydrogenated at 10 bar for 12 h. After filtration, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 98:2 to 80:20). Yield: 32 mg (65% of theory). LCMS (ESI^+) calculated for $C_{33}H_{46}F_3NO_2Si$ $[M + H]^+$ m/z 574.33, found 574.4. HPLC (method 2): retention time = 2.797 min. R_f-value: 0.52 (silica gel, petroleum ether/ethyl acetate 8:1). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 6.23 (s, 1H), 5.19−5.16 (m, 1H), 3.12 (d, J = 13.7 Hz, 1H), 2.68−2.65 (m, 1H), 2.53 (d, J = 13.7 Hz, 1H), 2.48−2.42 (m, 1H), 2.33−2.31 (m, 1H), 2.05−1.95 (m, 3H), 1.87−1.76 (m, 4H), 1.64 (dd, J = 14.3, 4.8 Hz, 1H), 1.23 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.86 (s, 9H), 0.69 (s, 3H), 0.56 (d, J = 6.6 Hz, 3H) 0.20 (s, 3H), 0.09 (s, 3H).

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(3′R,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)-phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**2**). To a solution of (3′*R*,9′*S*)-9′-(*tert*-butyldimethylsilyloxy)-4′-isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)-phenyl)-6′,7′,8′,9′-tetrahydro-3′*H*-spiro[cyclopentane-1,1′-furo[3,4-*c*]-quinoline] (30 mg, 0.051 mmol) in tetrahydrofuran (2 mL) was added tetrabutylammonium fluoride (150 μL of a 1 M solution in tetrahydrofuran, 0.150 mmol). The solution was stirred for 12 h at room temperature, then the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 to 50:50). Yield: 14 mg (58% of theory). HRMS (ESI$^+$) calculated for $C_{27}H_{32}F_3NO_2$ [M + H]$^+$ *m*/*z* 460.2463, found 460.2464. HPLC (method 1): retention time = 2.800 min. R_f-value: 0.50 (silica gel, petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.19 (s, 1H), 5.01 (d, *J* = 5.3 Hz, 1H), 4.93 (dd, *J* = 11.0, 5.5 Hz, 1H), 2.93−2.84 (m, 1H), 2.84 (d, *J* = 16.4 Hz, 1H), 2.59 (d, *J* = 16.4 Hz, 1H), 2.51−2.42 (m, 1H), 2.17−2.07 (m, 1H), 1.87−1.64 (m, 8H), 1.14 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 3H), 0.61 (d, *J* = 6.6 Hz, 3H).

Synthesis of Compounds **2a** *and* **12**−**26**. By an analogous synthetic sequence to that for the synthesis of compound **2**, the compounds **2a** and **12**−**26** were obtained.

(3′S,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)-phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**2a**). Obtained starting from diasteromer **9a**. HRMS (ESI$^+$) calculated for $C_{27}H_{32}F_3NO_2$ [M + H]$^+$ *m*/*z* 460.2463, found 460.2464. HPLC (method 1): retention time = 2.792 min. R_f-value: 0.29 (silica gel, petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 6.16 (s, 1H), 5.04−4.95 (m, 1H), 4.96 (d, *J* = 6.0 Hz, 1H), 2.78 (d, *J* = 16.7 Hz, 1H), 2.65−2.38 (m, 3H), 2.56 (d, *J* = 16.7 Hz, 1H,) 1.93−1.64 (m, 8H), 1.10 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 3H), 0.50 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 158.2, 155.9, 152.2, 146.9, 133.1, 129.1 (2C), 128.6 (d, *J* = 20 Hz), 125.2 (2C), 124.7, 124.1 (d, *J* = 185 Hz), 96.9, 79.6, 63.3, 46.9, 45.7, 39.0, 36.7, 30.2, 31.2, 29.8, 27.5, 25.0, 24.4, 21.7, 20.6.

(3′R,9′S)-7′,7′-Dimethyl-3′-phenyl-4′-(propan-2-yl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinoline]-9′-ol (**12**). HRMS (ESI$^+$) calculated for $C_{26}H_{33}NO_2$ [M + H]$^+$ *m*/*z* 392.2590, found 392.2592. HPLC (method 4): retention time = 2.52 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.41−7.31 (m, 3H), 7.26 (dd, *J* = 7.8, 1.6 Hz, 2H), 6.20 (s, 1H), 4.96 (dd, *J* = 6.4, 5.3 Hz, 1H), 2.95 (d, *J* = 17.0 Hz, 1H), 2.94−2.84 (m, 1H), 2.74 (d, *J* = 17.0 Hz, 1H), 2.68−2.59 (m, 1H), 2.20−2.09 (m, 1H), 1.92−1.65 (m, 8H), 1.17 (s, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 3H), 0.69 (d, *J* = 6.7 Hz, 3H); OH not visible.

(3′R,9′S)-3′-(4-Fluorophenyl)-4′-isopropyl-7′,7′-dimethyl-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]-quinolin]-9′-ol (**13**). HRMS (ESI$^+$) calculated for $C_{26}H_{32}FNO_2$ [M + H]$^+$ *m*/*z* 410.2495, found 410.2499. HPLC (method 3): retention time = 1.41 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.29 (d, *J* = 8.3 Hz, 2H), 0.7.18 (d, *J* = 8.3 Hz, 2H), 6.10 (s, 1H), 4.97 (d, *J* = 5.1, 1H), 4.95−4.87 (m, 1H), 3.28 (s, 1H), 2.93−2.83 (m, 1H), 2.84 (d, *J* = 16.3 Hz, 1H), 2.58 (d, *J* = 16.3 Hz, 1H), 2.53−2.45 (m, 1H), 2.12−2.02 (m, 1H), 1.87−1.66 (m, 7H), 1.15 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 3H), 0.31 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 161.6 (d, *J* = 244 Hz), 158.3, 156.5, 152.1, 138.9, 132.5, 130.1 (2C), 124.9, 115.1 (d, *J* = 21 Hz, 2C), 96.5, 80.5, 63.1, 46.7, 45.4, 40.8, 38.9, 31.4, 30.6, 30.0, 28.8, 25.0 (2C), 21.5, 20.9.

4-((3′R,9′S)-9′-Hydroxy-4′-isopropyl-7′,7′-dimethyl-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinoline]-3′-yl)-benzonitrile (**14**). HRMS (ESI$^+$) calculated for $C_{27}H_{32}N_2O_2$ [M + H]$^+$ *m*/*z* 417.2542, found 417.2544. HPLC (method 5): retention time = 1.09 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.06 (s, 1H), 5.09 (m, 1H), 2.98 (m, 1H), 2.82−2.66 (m, 2H), 2.46 (m, 1H), 2.15−1.72 (m, 10H), 1.25−1.23 (m, 3H), 1.00 (s, 3H), 0.91−0.84 (m, 6H).

2-(4-((3′R,9′S)-9′-Hydroxy-4′-isopropyl-7′,7′-dimethyl-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinoline]-3′-yl)-phenyl)-2-methylpropanenitrile (**15**). LCMS (ESI$^+$) calculated for $C_{30}H_{38}N_2O_2$ [M + H]$^+$ *m*/*z* 459.30, found 459.4. HPLC (method 1): retention time = 2.440 min. R_f-value: 0.47 (silica gel, petroleum ether/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.50 (d, *J* = 82 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.08 (s, 1H), 4.98 (d, *J* = 5.1 Hz, 1H), 4.95−4.90 (m, 1H), 3.28−3.26 (m, 1H), 2.92−2.85 (m, 1H), 2.84 (d, *J* = 16.2 Hz, 1H), 2.50−2.45 (m, 1H), 2.58 (d, *J* = 16.2 Hz, 1H), 2.07 (m, 1H), 1.86−1.65 (m, 7H), 1.67 (s, 6H), 1.15 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 3H), 0.60 (d, *J* = 6.8 Hz, 3H).

(3′R,9′S)-3′-(4-tert-Butylphenyl)-4′-isopropyl-7′,7′-dimethyl-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]-quinolin]-9′-ol (**16**). HRMS (ESI$^+$) calculated for $C_{30}H_{41}NO_2$ [M + H]$^+$ *m*/*z* 448.3216, found 448.3220. HPLC (method 6): retention time = 3.45 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.40 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.20 (s, 1H), 5.00−4.95 (m, 1H), 2.99 (d, *J* = 16.7 Hz, 1H), 2.94−2.85 (m, 1H), 2.80 (d, *J* = 16.7 Hz, 1H), 2.73−2.63 (m, 1H), 2.21−2.11 (m, 1H), 1.94−1.66 (m, 8H), 1.27 (s, 9H), 1.18 (m, 6H), 0.93 (s, 3H), 0.70 (d, *J* = 7.0 Hz, 3H), OH not visible.

(3′R,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(3-(trifluoromethyl)-phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**17**). HRMS (ESI$^+$) calculated for $C_{27}H_{32}F_3NO_2$ [M + H]$^+$ *m*/*z* 460.2463, found 460.2469. HPLC (method 1): retention time = 2.800 min. HPLC (method 4): retention time = 2.46 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.62−7.57 (m, 2H), 6.29 (s, 1H), 4.95 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.92−2.85 (m, 1H), 2.91 (d, *J* = 16.1 Hz, 1H), 2.72−2.63 (m, 1H), 2.58−2.51 (m, 1H), 2.20−2.10 (m, 1H), 1.90−1.66 (m, 8H), 1.16 (s, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 3H), 0.64 (d, *J* = 6.9 Hz, 3H), OH not visible.

(3′R,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethoxy)-phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**18**). LCMS (ESI$^+$) calculated for $C_{27}H_{32}F_3NO_3$ [M + H]$^+$ *m*/*z* 476.24, found 476.4. HPLC (method 6): retention time = 3.18 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.39 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.14 (s, 1H), 4.99 (d, *J* = 5.1 Hz, 1H), 4.95−4.90 (m, 1H), 2.95−2.87 (m, 1H), 2.84 (d, *J* = 16.4 Hz, 1H), 2.58 (d, *J* = 16.4 Hz, 1H), 2.51−2.45 (m, 1H), 2.13−2.04 (m, 1H), 1.86−1.67 (m, 8H), 1.14 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 3H), 0.59 (d, *J* = 6.6 Hz, 3H).

(3′S,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(5-(trifluoromethyl)-pyridin-2-yl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**19**). HRMS (ESI$^+$) calculated for $C_{26}H_{31}F_3N_2O_3$ [M + H]$^+$ *m*/*z* 461.2416, found 461.2420. HPLC (method 7): retention time = 3.46 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.93 (m, 1H), 8.24 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.64 (d, *J* = 8.3 HZ, 1H), 6.25 (s, 1H), 5.01 (d, *J* = 5.6 Hz, 1H), 4.93 (m, 1H), 2.89−2.83 (m, 1H), 2.82 (d, *J* = 16.4 Hz, 1H), 2.63 (m, 1H), 2.61−2.52 (m, 3 H), 2.36 (m, 1H), 2.21−2.15 (m, 2H), 1.89−1.65 (m, 4H), 1.13 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 3H), 0.57 (d, *J* = 6.8 Hz, 3H).

(3′R,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(6-(trifluoromethyl)-pyridin-3-yl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**20**). HRMS (ESI$^+$) calculated for $C_{26}H_{31}F_3N_2O_3$ [M + H]$^+$ *m*/*z* 461.2418, found 461.2420. HPLC (method 8): retention time = 5.83 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.73 (d, *J* = 8,5 Hz, 1H), 7.64 (d, *J* = 8,5 Hz, 1H) 6.16 (s, 1H), 5.10 (m, 1H), 3.04 (d, *J* = 16.4 Hz, 1H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.77 (m, 1H), 2.50 (m, 1H), 2.12 (m, 1H), 2.04−1.92 (m, 2H), 1.93−1.79 (m, 7H), 1.25 (s, 3H), 1.22 (d, *J* = 6,6 Hz, 3H), 1.01 (s, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

(3′R,9′S)-4′-Ethyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]-quinolin]-9′-ol (**21**). LCMS (ESI$^+$) calculated for $C_{26}H_{30}F_3NO_2$ [M + H]$^+$ *m*/*z* 446.23, found 446.5. HPLC (method 3): retention time = 1.58 min. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 6.16 (s, 1H), 5.02 (d, *J* = 5.1 Hz, 1H), 4.96−4.90 (m, 1H), 2.94−2.84 (m, 1H), 2.83 (d, *J* = 16.2 Hz, 1H), 2.58 (d, *J* = 16.2 Hz, 1H,) 2.32−2.21 (m, 1H), 2.21−2.04 (m, 2H), 1.88−1.66 (m, 8H), 1.14 (s, 3H), 0.87 (s, 3H), 0.79 (t, *J* = 7.5 Hz, 3H).

(3′R,9′S)-4′-Cyclopentyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)-phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-

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*c]quinolin]-9′-ol (**22**).* HRMS (ESI$^+$) calculated for $C_{29}H_{34}F_3NO_2$ [M + H]$^+$ *m/z* 486.2620, found 486.2620. HPLC (method 5): retention time = 1.22 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 6.08 (s, 1H), 5.09 (m, 1H), 2.96 (d, *J* = 16.6 Hz, 1H), 2.77−2.65 (m, 2H), 2.57 (m, 1H), 2.16−1.61 (m, 12H), 1.57−1.41 (m, 1H), 1.39−1.26 (m, 2H), 1.24 (s, 3H), 1.05 (m, 1H), 0.95 (s, 3H), 0.94−0.76 (m, 2H).

*(3′R,9′S)-7′,7′-Dimethyl-4′-(tetrahydro-2H-pyran-4-yl)-3′-(4-(trifluoromethyl)phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro-[cyclopentane-1,1′-furo[3,4-c]quinolin]-9′-ol (**23**).* LCMS (ESI$^+$) calculated for $C_{29}H_{34}F_3NO_2$ [M + H]$^+$ *m/z* 502.26, found 502.6. HPLC (method 1): retention time = 2.891 min. R_f-value: 0,25 (silica gel, petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 6.23 (s, 1H), 5.02 (d, *J* = 5.2 Hz, 1H), 4.93 (dd, *J* = 11.9, 5.4 Hz, 1H), 3.85 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.57 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.25−3.16 (m, 1H), 2.97−2.88 (m, 1H), 2.85 (d, *J* = 16.7 Hz, 1H), 2.80−2.71 (m, 1H), 2.45−2.34 (m, 1H), 2.58 (d, *J* = 16.7 Hz, 1H), 2.07 (m, 1H), 1.95−1.68 (m, 9H), 1.55−1.40 (m, 2H), 1.15 (s, 3H), 0.87 (s, 3H), 0.43−0.36 (m, 1H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 156.8, 156.0, 152.2, 147.2, 132.8, 129.0 (2C), 128.6, 125.3 (2C), 125.2, 124.1, 97.0, 80.5, 66.9, 66.5, 63.1, 46.6, 45.5, 40.7, 39.1, 38.9, 30.9, 30.6, 30.4, 30.0, 28.9, 24.9 (2C).

*(3R,9S)-4-Isopropyl-1,1,7,7-tetramethyl-3-(4-(trifluoromethyl)-phenyl)-1,3,6,7,8,9-hexahydrofuro[3,4-c]quinolin-9-ol (**24**).* LCMS (ESI$^+$) calculated for $C_{25}H_{30}F_3NO_2$ [M + H]$^+$ *m/z* 434.23, found 434.2. HPLC (method 1): retention time = 2.551 min. R_f-value: 0,46 (silica gel, petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 4.98 (dd, *J* = 11.7, 5.6 Hz, 1H), 3.17, (d, 5.2 Hz, 1H), 2.83 (d, *J* = 16.2 Hz, 1H), 2.60 (d, *J* = 16.2 Hz, 1H), 2.50−2.42 (m, 1H), 1.83 (dd, *J* = 13.5, 5.4 Hz, 1H), 1.75 (dd, *J* = 13.5, 5.5 Hz, 1H), 1.67 (s, 3H), 1.54 (s, 3H), 1.14 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 3H), 0.68 (d, *J* = 6.7 Hz, 3H).

*(3′R,9′S)-4′-Isopropyl-7′,7′-dimethyl-3′-(4-(trifluoromethyl)-phenyl)-6′,7′,8′,9′-tetrahydro-3′H-spiro[cyclohexane-1,1′-furo[3,4-c]quinolin]-9′-ol (**25**).* LCMS (ESI$^+$) calculated for $C_{28}H_{34}F_3NO_2$ [M + H]$^+$ *m/z* 474.26, found 474.3. HPLC (method 1): retention time = 3.040 min. R_f-value: 0,52 (silica gel, petrol ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 6.23 (s, 1H), 5.09−5.02 (m, 1H), 4.97(d, *J* = 5.0 Hz, 1H), 2.87 (d, *J* = 16.2 Hz, 1H), 2.58 (d, *J* = 16.2 Hz, 1H), 2.59−2.51 (m, 1H), 2.52−2.44 (m, 1H), 2.03−1.92 (m, 1H), 1.83−1.55 (m, 6H), 1.49−1.40 (m, 2H), 1.34−1.20 (m, 2H), 1.16 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 3H), 0.63 (d, *J* = 6.8 Hz, 3H).

*(3R,9S)-4-Isopropyl-7,7-dimethyl-3-(4-(trifluoromethyl)phenyl)-2′,3′,5′,6,6′,7,8,9-octahydro-3H-spiro[furo[3,4-c]quinoline-1,4′-pyran]-9-ol (**26**).* HRMS (ESI$^+$) calculated for $C_{27}H_{32}F_3NO_2$ [M + H]$^+$ *m/z* 476.2413, found 476. 2416. HPLC (method 9): retention time = 4.96 min. Chiral HPLC: retention time = 2.45 min for **26** and 2.17 min for **ent-26**. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 6.30 (s, 1H), 5.11 (d, *J* = 4.6 Hz, 1H), 5.04 (dd, *J* = 10.1, 5.2 Hz, 1H), 3.80 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.76−3.70 (m, 1H), 3.68 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.55−3.46 (m, 1H), 2.98 (dt, *J* = 13.4, 5.2 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.60 (d, *J* = 16.4 Hz, 1H), 2.52−2.43 (m, 1H), 2.31 (dt, *J* = 12.8, 5.6 Hz, 1H), 1.86−1.76 (m, 2H), 1.60−1.46 (m, 2H), 1.16 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 3H), 0.64 (d, *J* = 6.8 Hz, 3H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Determination of absolute stereochemistry and crystal data of compound **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

hApoB, human apolipoprotein B; CBS reduction, Corey−Bakshi−Shibata reduction; CL, confidence limit; Cpd, compound; hCETP, human cholesteryl ester transfer protein; LLQ, lower limit of quantification; tg, transgenic

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