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Design and synthesis of potent inhibitors of cholesteryl ester transfer protein (CETP) exploiting a 1,2,3,4-tetrahydroquinoline platform

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ABSTRACT

Tetrahydroquinoline A is a potent inhibitor of the cholesterol ester transfer protein (CETP), a target for the treatment of low HDL-C and atherosclerosis. Low HDL-C has been identified as a key risk factor for cardiovascular disease in addition to high LDL-C, the target of the statin drugs. Tetrahydroquinoline A inhibits partially purified CETP with an IC_{50} of 39 nM. The preparation of a series of potent inhibitors of CETP designed around a 1,2,3,4-tetrahydroquinoline platform will be discussed.

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood by mediating the transfer of cholesteryl esters from the cardioprotective high density lipoprotein cholesterol (HDL-C) to the proatherogenic low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL-C). HDL cholesterol (the 'good' cholesterol) plays a major role in the transfer of excess cholesterol from the peripheral tissues to the liver (reverse cholesterol transport), where it can be cleared from the body. Thus, the movement of cholesteryl esters from HDL-C to LDL-C by CETP has the overall undesirable effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile.[1,2] Currently there are no marketed CETP inhibitors, although there are several compounds currently in clinical trials.[3] Several pharmaceutical companies including Pfizer, Merck, Bristol-Myers Squibb, Japan Tobacco, Array BioPharma, Bayer and formerly Pharmacia, have or have had ongoing programs in this area.[4] Pfizer's torcetrapib[5] is a potent CETP inhibitor which was recently withdrawn from Phase III trials due to risks associated with blood pressure increase, and Japan Tobacco's JTT-705[6] is currently in Phase III trials but is of moderate potency and is an irreversible inhibitor. Further investigation of the Pharmacia compound (Fig. 1) was halted due to unacceptable pharmacokinetic properties. At the time of this writing, the Merck CETP inhibitor has entered into Phase III trials.

We have initiated a drug discovery program directed toward the discovery of CETP inhibitors based on our competitor's platforms as starting templates, in particular, the Pharmacia[7] molecule. The initial starting point of this endeavor would simply involve preparing a conformationally restricted version of the Pharmacia compound. Although this approach appeared to be fairly straightforward, the synthetic construction of such a platform required a number of synthetically challenging manipulations, which will be described in this letter.

The synthetic route commences with the preparation of aryl ketone **4** (Scheme 1). Exposure of 2,6-dibromobenzyl bromide **1** to

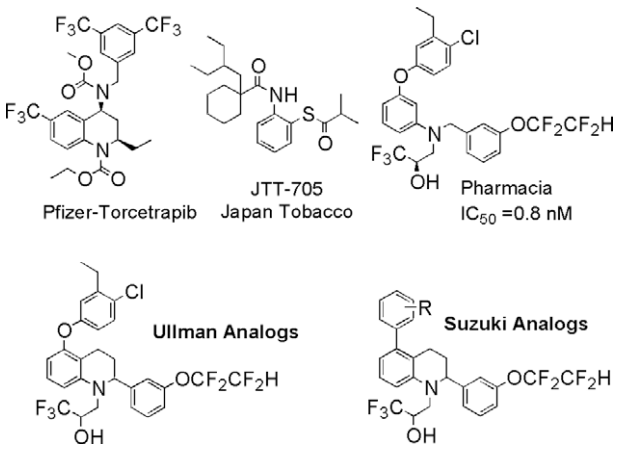

Figure 1. Structures of current CETP inhibitors.

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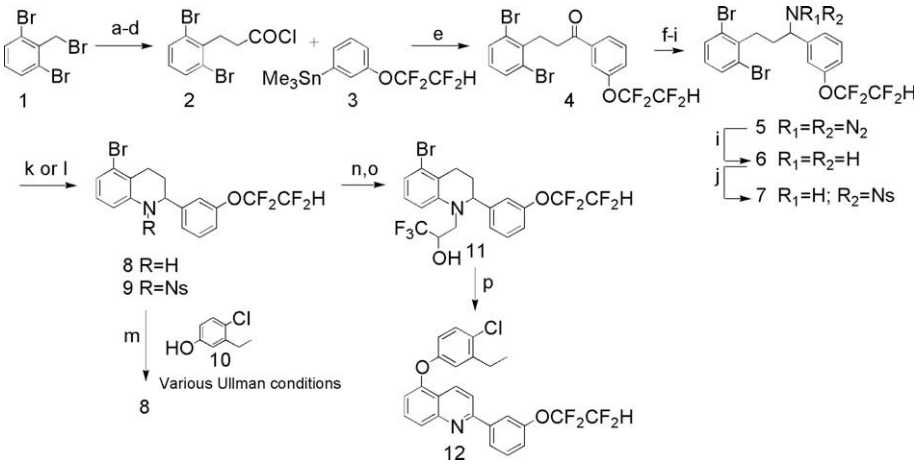
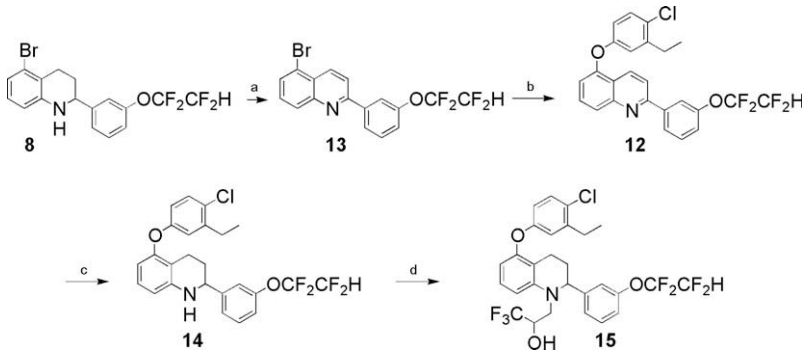


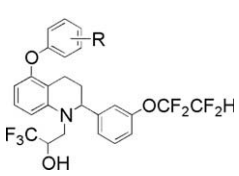
Scheme 1. Reagents and conditions: (a) $(EtO_2C)_2CHNa$, DMF, 50 °C, 75%; (b) NaCl, DMSO, water, 180 °C, quantitative; (c) 3 N NaOH, THF, reflux, quantitative: (d) oxalyl chloride, DCM, quantitative; (e) Pd_2DBA_3, DIEA, THF, 50 °C, 66%; (f) $NaBH_4$, MeOH, 84–94%; (g) MsCl, TEA, DCM, quantitative; (h) NaN_3, DMF, 50 °C, 92–97%; (i) $Me_2S{\cdot}BHCl_2$, DCE, reflux, then HCl, 95%; (j) NsCl, TEA, DCM, 85%; (k) 10% CuI, K_3PO_4, 40% *o*-$(OH)C_6H_4CONEt_2$, ~25%; (l) CuI, Cs_2CO_3, DMSO, 90 °C, 90%; (m) Ullman conditions (n) $HSCH_2CO_2H$, LiOH, DMF, 88%; (o) $Yb(OTf)_3$; 1,1,1-trifluoroepoxypropane; DCE, 50 °C; (p) CuCl, Cs_2CO_3, $(CH_3)_3CCOCH_2COC(CH_3)_3$, phenol **9**, NMP, 120 °C.



Scheme 2. Reagents and conditions: (a) DDQ, THF, reflux, 95%; (b) CuCl, Cs_2CO_3, $(CH_3)_3CCOCH_2COC(CH_3)_3$, phenol **9**, NMP, 120 °C, 70%; (c) pyr·BH_3, AcOH, 90%; (d) $Yb(OTf)_3$; 1,1,1-trifluoroepoxypropane; DCE, 50 °C, 79%.

the sodium salt of diethyl malonate[8] provided the geminal diester which was decarbalkoxylated under modified Krapcho[9] conditions to cleanly afford the mono ester in quantitative yield. Saponification of the resultant ethyl ester with NaOH followed by acidification with HCl provided the crude acid, which was smoothly converted to acid chloride **2** in 75% overall yield for the four steps. In the construction of ketone **4**, several synthetic routes were attempted without success. For example, direct alkylation of the lithium, potassium or sodium enolate of *m*-tetrafluoro-ethoxy acetophenone with **1** led to complex mixtures of ketone **4** along with bis-alkylation, starting material and decomposition products. Halogen-metal exchange of *m*-tetrafluoro-ethoxy bromobenzene followed by addition to 3-(2,6-dibromopheny)propionaldehyde provided no desired product. It was subsequently determined that the hydrogen atom of the tetrafluoro-ethoxy moiety was sufficiently acidic to be deprotonated by strong base, resulting in the splitting out of tetrafluoro ethylene and the corresponding phenol. However, the mild conditions afforded by the Stille coupling of aryl stannane **3**[10] with **2** afforded requisite ketone **4** in 66% yield. Sodium borohydride reduction, mesylation of the resultant racemic alcohol and displacement with sodium azide afforded azide **5** in excellent yield. Several attempts at reducing the azide met with difficulty. Fortunately, reduction under Brown's[11] conditions reproducibly provided amine **6** in yield >90%. The stage was now set for the intramolecular cyclization. Investigating a number of Buchwald conditions only provided the desired compound **8** in approximately 25% yield under conditions 'k' in Scheme 1. Application of the Fukuyama[12] conditions (copper iodide and cesium carbonate in hot DMSO) on compound **6** provided no **8** what so ever. However, when amine **6** was first 'activated' as the nosylate **7**, the copper mediated Fukuyama conditions afforded the desired tetrahydroquinoline core template **9** in near quantitative yield. Unfortunately, when **9** was subjected to Ullman coupling conditions, the major product obtained was compound **8**, that which the nosyl group was cleaved from the tetrahydroquinoline nitrogen. To

Table 1
In vitro inhibition of partially purified human CETP by phenolic ether tetrahydroquinoline derivates



Compds	R_f	R=	% Inhibition (μM)	IC_{50} (μM)
15	Higher	4-Chloro-3-ethyl	62	0.600
16	Lower	4-Chloro-3-ethyl	86	0.400
17	Higher	2,3-Dichloro	67	NM*
18	Lower	2,3-Dichloro	86	0.400

* NM, not measured.

Scheme 3. Reagents and conditions: (a) $Pd(Ph_3)_4$, *m*-$CF_3OC_6H_4B(OH)_2$, 2 M K_2CO_3, dioxane, reflux, 91%; (b) $Yb(OTf)_3$, 1,1,1-trifluoroepoxypropane, DCE, 50 °C.

circumvent this problem, the nosylate group was removed followed by alkylation with 1,1,1-trifluoroepoxypropane affording compound **11** in 91% yield as a mixture of racemic diastereomers. Once again, **11** also failed to provide the desired phenolic ether under a wide variety of both Ullman and Buchwald coupling conditions. However, when **11** was subjected to modified Ullman conditions reported by Merck researchers,[13] the phenolic ether **12** was obtained in approximately 45% yield. Interestingly, the product was not the expected tetrahydroquinoline phenolic ether, but the fully aromatized quinoline compound.

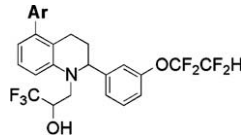
During careful examination of the Merck Ullman conditions by TLC analysis, one could observe the starting tetrahydroquinoline core template **9**, the resultant product **12**, as well as a newly formed highly UV active intermediate which dissipated as the reaction progressed. We postulated that under the reaction conditions reported by the Merck workers, compound **9** was first being transformed into a fully aromatized quinoline with concomitant loss of the nosyl group prior to phenolic either formation. In order to test this hypothesis, compound **8** was aromatized to quinoline **13** in 95% yield by exposure to DDQ in refluxing THF (Scheme 2).

When **13** was subjected to the Merck conditions, phenolic ether **12** rapidly formed and was isolated in 70% yield. In order to arrive at our intended synthetic target, quinoline **12** was reduced to the tetrahydroquinoline **14** in 90% yield employing borane-pyridine complex. Alkylation of the resultant aniline provided the fully elaborated target CETP inhibitor **15** as a mixture of racemic diastereomers. These diastereomers could be separated via SiO_2 flash chromatography. Several analogs containing the phenolic ether motif were prepared and evaluated for their ability to inhibit partially purified human plasma derived CETP, some of which are illustrated in Table 1.[14] Disappointingly, these conformationally restricted analogs exhibited only modest CETP potency with IC_{50}'s ranging from 400–600 nM as opposed to the acyclic Pharmacia compound which possesses an IC_{50} = 0.77 nM.[7]

In light of the synthetic challenges encountered with the preparation of the phenolic ether derivates such as **15**, as well as their unimpressive potency, our efforts were refocused on preparation of biphenyl analogs of the tetrahydroquinoline core as depicted in Figure 1. The advanced synthetic intermediate **8** would serve as a useful synthon for the construction of the biphenyl moiety. Initial Stille coupling reactions of aryl bromide **8** and a suitable aryl stannane under palladium (0) catalysis provided little cross-coupled biphenyl product. However, standard Suzuki coupling employing a wide variety of readily available aryl boronic acids afforded the desired biphenyl analogs in excellent yields. As illustrated in Scheme 3, exposure of **8** and the requisite aryl boronic acid to $Pd(PPh_3)_4$ and aqueous K_2CO_3 in dioxane heated to reflux efficiently provided the desired Suzuki product. Alkylation of the tetrahydroquinoline nitrogen as before once again afforded a racemic mixture of diastereomer **19** (higher R_f compound) and **20** (lower R_f compound), which were separated by silica gel chromatography.

When this unique set of biphenyl CETP inhibitors were evaluated for inhibition of partially purified human plasma derived CETP (Table 2), the in vitro activities were significantly improved. In this

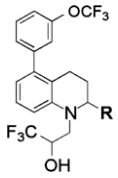
Table 2
In vitro inhibition of partially purified human CETP by biphenyl tetrahydroquinoline derivates



Compound	R_f	Ar=	% Inhibition (μm)	IC_{50}[a] (μm)
19	Higher	3-Trifluoromethoxy phenyl	100	0.033
20	Lower	3-Trifluoromethoxy phenyl	86	0.300
21	Higher	3-Chloro phenyl	67	0.064
22	Lower	3-Chloro phenyl	55	NM
23	Higher	3-Fluoro phenyl	93	0.117
24	Lower	3-Fluoro phenyl	52	NM
25	Higher	3-Trifluoromethyl phenyl	93	0.096
26	Lower	3-Trifluoromethyl phenyl	37	NM
27	Higher	3-Methoxy phenyl	68	0.126
28	Lower	3-Methoxy phenyl	38	NM
29	Higher	3-Cyano phenyl	85	0.235
30	Lower	3-Cyano phenyl	21	NM
31	Higher	4-Trifluoromethoxy phenyl	85	0.500
32	Higher	4-Trifluoromethoxy phenyl	61	NM
33	Higher	3-Chloro-3-methoxy phenyl	96	0.320
34	Higher	3-Pyridyl	47	>3.0
35	Higher	2-Thienyl	63	317
36	Higher	3-Isopropyl phenyl	63	277
37	Higher	3-Isopropoxy phenyl	55	345

NM, not measured.
[a] Compounds processing IC_{50}'s <250 nM were typically assayed at least twice, while those >250 nM only once.

Table 3
In vitro inhibition of partially purified human CETP by biphenyl tetrahydroquinoline derivates

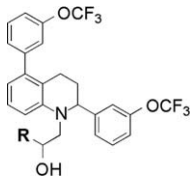


Compound	R_f	R=	% Inhibition (μM)	IC_{50}[a] (μM)
38	Higher	2-Tetrafluoroethoxy phenyl	9	NM
39	Lower	2-Tetrafluoroethoxy phenyl	0	NM
40	Higher	4-Tetrafluoroethoxy phenyl	5	NM
41	Lower	4-Tetrafluoroethoxy phenyl	14	NM
42	Higher	Cyclohexyl	11	NM
43	Lower	Cyclohexyl	2	NM
44	Higher	Ethyl	44	NM
45	Lower	Ethyl	12	NM
46	Higher	Phenyl	21	NM
47	Lower	Phenyl	6	NM
48	Higher	3-Trifluoromethyl phenyl	50	0.143
49	Lower	3-Trifluoromethyl phenyl	37	2.90
50	Higher	2-Thienyl	28	NM
51	Lower	2-Thienyl	12	NM
52	Higher	3-Trifluoromethoxy phenyl	68	0.125
53	Lower	3-Trifluoromethoxy phenyl	34	NM

NM, not measured.
[a] Compounds processing IC_{50}'s <250 nM were typically assayed at least twice, while those >250 nM only once.

series, the higher R_f diastereomer consistently displayed more potent activity than the lower R_f diastereomer. Substitution at the 3-position of the aryl ring was much preferred over substitution at the 4-position (compare **19**, **32** and **25**, **31**). Compound **19**, possessing a trifluoromethoxy group at the 3 position, displayed the best potency overall. Electron withdrawing groups (**21, 23, 25, 29**) as well as methoxy (**27**) were most preferred. However, fairly bulky alkyl substituents (**36**) and larger alkoxy (**37**) were not well tolerated. Heterocyclic biphenyls analogs resulted in a significant drop in activity as illustrated by the 3-pyridyl derivative **34** and the 2-thienyl derivative **35**.

Table 4
In vitro inhibition of partially purified human CETP by biphenyl tetrahydroquinoline derivates



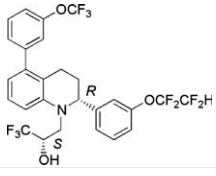
Compound	R_f	R=	% Inhibition (μM)	IC_{50}[a] (μM)
54	Higher	CH_2F	70	0.331
55	Lower	CH_2F	13	NM
56	Higher	CH_2Cl	56	0.744
57	Lower	CH_2Cl	0	NM
58	Higher	$CH(CH_3)_2$	79	0.326
59	Lower	$CH(CH_3)_2$	22	NM
60	Higher	$CH_2OCH_3(S,R)$[b]	13	NM
61	Lower	$CH_2OCH_3(S,S)$[b]	0	NM
62	Higher	$CH_3(R,R)$[c]	68	0.125
63	Lower	$CH_3(S,R)$[c]	13	NM

NM, not measured.
[a] Compounds processing IC_{50}'s <250 nM were typically assayed at least twice, while those >250 nM only once.
[b] Derived from S-(+)-glycidyl methyl ether.
[c] Derived from chiral R epoxypropane.

Next, the aryl moiety appended onto the tetrahydroquinoline ring was examined (Table 3). Migration of the tetrafluoroethoxyl moiety from the meta position on the aryl ring (as in compounds **19**/**20**) to either the ortho position (compounds **38**/**39**) or para position (compounds **40**/**41**) once again resulted in a dramatic loss of potency. Carbocycles such as cyclohexyl or aliphatic hydrocarbons such as ethyl were not tolerated, nor were heterocyclic rings (**42, 44, 50**). The fact that substitution on the aryl ring is imperative is exemplified by the poor activity of the plain phenyl analog **46**. The 3-trifluoromethyl phenyl **48** and 3-trifluoromethoxy phenyl **52** analogs did possess interesting potency, with IC_{50}s equal to 143 nM and 125 nM respectively. Several analogs of these compounds were prepared, but none were as potent as compound **19**.

Rounding out of the SAR of our CETP inhibitors would not be complete without a cursory examination of the ligands attached to the tetrahydroquinoline nitrogen. Alkylation of the aniline moiety with a variety of substrates was thus initiated. We chose to employ compound **52** as our benchmark compound in this study because of the potency (IC_{50} = 125 nM) as well as the availability of the penultimate intermediate of compound **52**. Table 4

Table 5
Stereospecificity of CETP inhibition



Compound	R_f	Configuration	% Inhibition (μM)	IC_{50}[a] (μM)
Tetrahydroquinoline A	Higher	*R,S*	85	0.039
Tetrahydroquinoline B	Lower	*R,R*	62	>3
Tetrahydroquinoline C	Higher	*S,R*	46	NM
Tetrahydroquinoline D	Lower	*S,S*	20	NM

NM, not measured.
[a] Compounds processing IC50's <250 nM were typically assayed at least twice, while those >250 nM only once.

Table 6
%F = Dose(IV) * AUC(PO)/ Dose(PO) * AUC(IV)

Compound	Species (n = 4)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (ng·h/mL)	%F	Clp (mL/min/kg)	Vss (L/kg)
Tetrahydroquinoline A (p.o.)	Rat (10 mpk)	950	6	28	31,300	31	—	—
Tetrahydroquinoline A (i.v.)	Rat (2 mpk)	31,400	—	17.4	18,900	—	1.8	0.36

establishes the fact that almost all attempts to improve the potency of compound **52** fell short of the mark, except for compound **62** (IC_{50} = 125 nM), which differed from compound **52** only by the replacement of the trifluoromethyl with a methyl group. Again, several analogs of these compounds were prepared, but none were as potent as compound **19**. Since compound **19** proved to be very potent in our binding assay, even as a racemic mixture, we decided to resolve a small amount of the penultimate intermediate of **19** (unalkylated aniline, not shown) via chiral HPLC, followed by alkylation with 1,1,1-trifluoroepoxypropane. Separation of the resultant diastereomers by SiO_2 chromatography afforded enantiomerically pure Tetrahydroquinoline A (once again, the 'higher R_f' compound).

Concomitantly, an asymmetric synthesis of compound **19** was also established in order to determine the absolute stereochemical configuration of the chiral centers.[15] These results, which are illustrated in Table 5, determined that the *R,S* stereochemical configuration (Tetrahydroquinoline A) possessed the best potency of the 4 possible diastereomers, displaying an IC_{50} = 39 nM. This compound was selected for further study.

The pharmacokinetic profile of Tetrahydroquinoline A was determined in Sprague–Dawley rats dosed at 10 mg/kg, using sesame oil as the vehicle for the po route. For the iv arm dosed at 2 mg/kg, values of plasma clearance (Clp) volume of distribution, (Vss) and plasma half-life ($T_{1/2}$) were calculated using Tetrahydroquinoline A formulated in 10% EtOH:10% solutol:80% D5W. Mean pharmacokinetic parameters of Tetrahydroquinoline A (illustrated in Table 6) indicate the average oral bioavailability to be 31%.

Tetrahydroquinoline A exhibited a high permeability (4.7×10^{-6} cm/s) in Caco2 cells. The metabolic stability of Tetrahydroquinoline A in human, rat, monkey, mouse and dog liver microsomal preparations was also determined. The $t_{½}$ of Tetrahydroquinoline A in pooled microsomes from each species was calculated and found to be acceptable, with the compound demonstrating a $t_{½}$ of >128 min in human liver microsomes. Tetrahydroquinoline A was also tested for inhibition of Cytochrome P450 isozymes CYP2C9, CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP1A2, and CYP3A4 in human liver microsomes, and was shown to have no significant inhibitory effect on most P450 isozymes tested.

In conclusion, we have demonstrated that the 1,2,3,4-tetrahydroquinoline moiety can provide a versatile platform for designing a diverse array of potent CETP inhibitors, resulting in the preparation of the bi-phenyl analog Tetrahydroquinoline A. Although Tetrahydroquinoline A is highly permeable (4.7×10^{-6} cm/sec), absorption was delayed (mean $T_{max} \sim 6$ h) after oral administration in sesame oil. Following iv administration of Tetrahydroquinoline A to rats, clearance was about 3% of hepatic blood flow. Elimination $t_{½}$ was long (~28 h) and the compound showed little distribution beyond the central compartment. Low clearance values and a long $t_{½}$ in microsomes suggest that cytochrome P-450-mediated metabolism is not a major elimination pathway. Overall, Tetrahydroquinoline A demonstrates favorable ADME characteristics.[16] Further studies on Tetrahydroquinoline A are ongoing and will be reported in due course.

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