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SAR studies on the central phenyl ring of substituted biphenyl oxazolidinone-potent CETP inhibitors

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ABSTRACT

SAR studies of the substitution effect on the central phenyl ring of the biphenyl scaffold were carried out using anacetrapib (**9a**) as the benchmark. The results revealed that the new analogs with substitutions to replace trifluoromethyl (**9a**) had a significant impact on CETP inhibition in vitro. In fact, analogs with some small groups were as potent or more potent than the CF_3 derivative for CETP inhibition. Five of these new analogs raised HDL-C significantly (>20 mg/dL). None of them however was better than anacetrapib in vivo. The synthesis and biological evaluation of these CETP inhibitors are described.

It has long been recognized that in mammals, variations in circulating lipoprotein profiles correlate with the risk of atherosclerosis and coronary heart disease (CHD). The clinical success of HMG-CoA reductase inhibitors,[1–4] especially the statins, in reducing coronary events is based on the reduction of circulating Low Density Lipoprotein cholesterol (LDL-C), levels of which correlate directly with increased risk for atherosclerosis. More recently, epidemiologic studies have demonstrated an inverse relationship between High Density Lipoprotein cholesterol (HDL-C) levels and atherosclerosis, leading to the conclusion that low serum HDL-C levels are associated with an increased risk for CHD. In fact, a substantial number of people who develop atherosclerosis have total plasma cholesterol levels in the 'desirable' range while having abnormally low HDL (<35 mg/dL). Therefore, low HDL levels are not only recognized as a risk factor for the disease, but are also the single best predictor for the eventual development of CHD.[5–8]

Metabolic control of lipoprotein levels is a complex and dynamic process involving many factors. One important metabolic control in man is the cholesteryl ester transfer protein (CETP), a plasma glycoprotein that catalyzes the movement of cholesteryl esters from HDL to the apoB containing lipoproteins, especially VLDL. Under physiological conditions, the net reaction is a hetero-exchange in which CETP carries triglyceride to HDL from the apoB lipoproteins and transports cholesterol ester from HDL to the apoB lipoprotein. It has been established clinically that pharmacological inhibition of CETP will lead to increased HDL-C concentrations. However, there remains uncertainty as to whether a CETP inhibitor can provide clinical benefit to high risk CHD patients. More studies are needed to determine if increasing HDL-C via CETP inhibition will reduce atherosclerosis in patients.[9–11] Several CETP inhibitor scaffolds have been reported from this laboratory and other research organizations, most notably the tetrahydroquinoline core of Pfizer's torcetrapib **1** and the acylaminobenzenethiol core of the Roche/Japan Tobacco inhibitor dalcetrapib **2**, compounds from Pharmacia **3** and Lilly's evacetrapib **4** (Fig. 1).[12–24] Tocetrapib was the first CETP inhibitor that underwent large PhIII trials involving more than 15,000 patients.[25–27] All ongoing clinical trials with torcetrapib were discontinued abruptly in December 2006 when the investigators from one of the trials (ILLUMINATE) reported an increase in all-cause mortality associated with torcetrapib though positive lipid targets were met.[25–27] Discussion surrounding the withdrawal of torcetrapib from development is still ongoing, centered around the question of whether the increased rate of deaths associated with torcetrapib resulted from inhibition of CETP, off-target effects, or a combination of these two factors.[16,28–30]

A chemistry program was initiated at Merck in order to identify a suitable CETP inhibitor for development as a treatment for atherosclerosis, and the program has led to the discovery of anacetrapib.[43] The ability of anacetrapib to inhibit CETP-mediated transfer of both cholesteryl ester and triglycerides and its mechanism of

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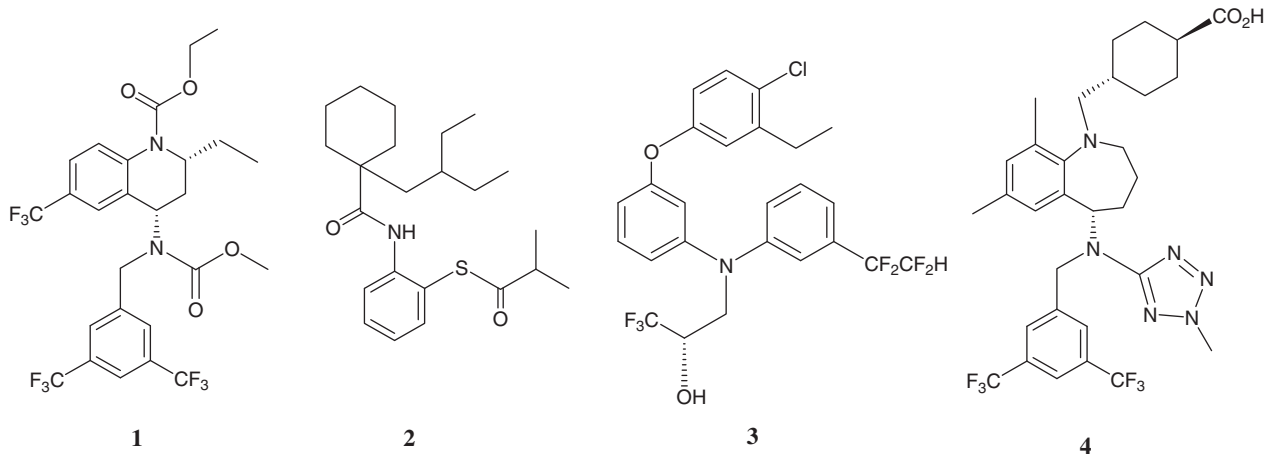
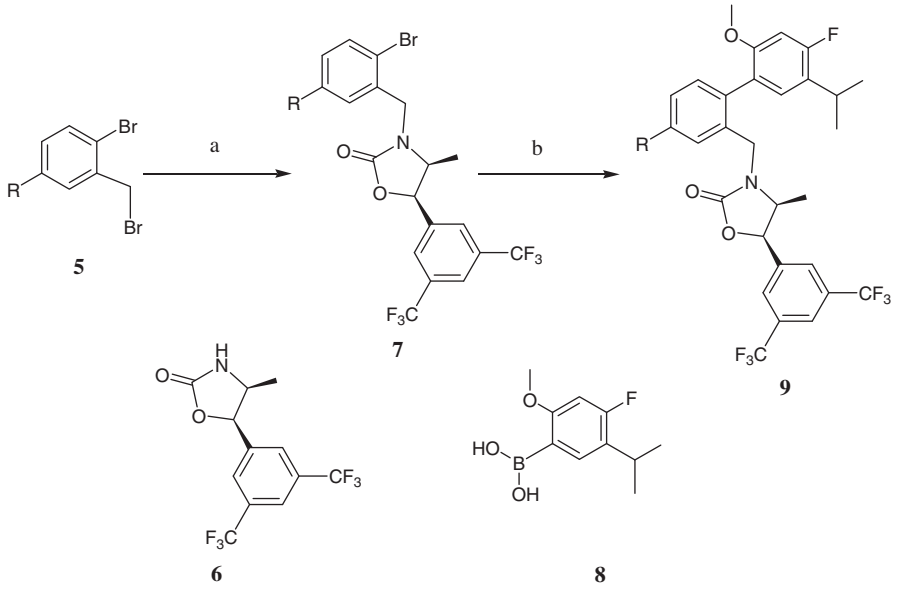


Figure 1. Representative published CETP inhibitors.

action has been characterized.[31] Anacetrapib itself was extensively profiled in phase I and II clinical trials and was shown to cause a dose-dependent increase in HDL-C levels and decrease in LDL-C levels.[32–37] It was also found that HDL isolated from humans treated with anacetrapib had potentially promoted cholesterol efflux and retained anti-inflammatory effects.[38] Preclinical and clinical studies with anacetrapib, including recent results from the phase III safety study DEFINE, have thus far given no evidence of blood pressure or aldosterone increases which were observed with torcetrapib. As such, the development of anacetrapib continues.[39–41] The design of the biphenyl scaffold and the subsequent work that led to the discovery of anacetrapib were published recently from this laboratory.[42,43] We intended to explore the structure–activity relationship (SAR) of the substitution effect on the central phenyl ring of the biphenyl scaffold using anacetrapib (**9a**) as the benchmark. The results revealed that the new analogs with substitutions to replace trifluoromethyl (**9a**) could significantly impact the in vitro CETP inhibition. In fact, analogs with some small groups were as potent as or better than CF_3 group for CETP inhibition. Five of these new analogs raised HDL-C significantly (>20 mg/dL). None of them however was better than anacetrapib in vivo.

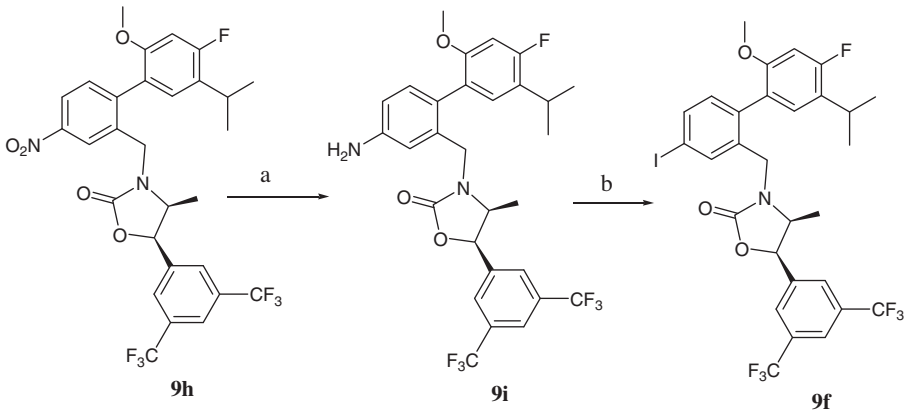
The general approach to prepare these compounds is exemplified by the synthesis of analog **9** as shown in Scheme 1. Thus, previous disclosed compound **6**[43] was treated with NaH at 0 °C in THF followed by addition of the commercially available 4-substituted benzyl bromide **5** afforded compound **7** in good to excellent yields. Suzuki coupling of compound **7** with previously described boronic acid **8**[43] and $Pd(PPh_3)_4$ gave compound **9** in good yield (Scheme 1).

Several compounds were prepared from **9h** by functional group manipulations. Hydrogenation of **9h** with Pd/C in methanol at 40 psi gave the aniline **9i** in excellent yield. Treatment of **9i** with *n*-amyl nitrite and iodine in chloroform under reflux afforded iodide **9f** (Scheme 2). **9g** was obtained by treatment of **9f** with copper cyanide in DMF at 100 °C. Suzuki coupling reaction resulted in compounds **9j**, **9k**, **9q**, and **9t** in respectable yields (Scheme 3). All other analogs were prepared in a similar fashion.



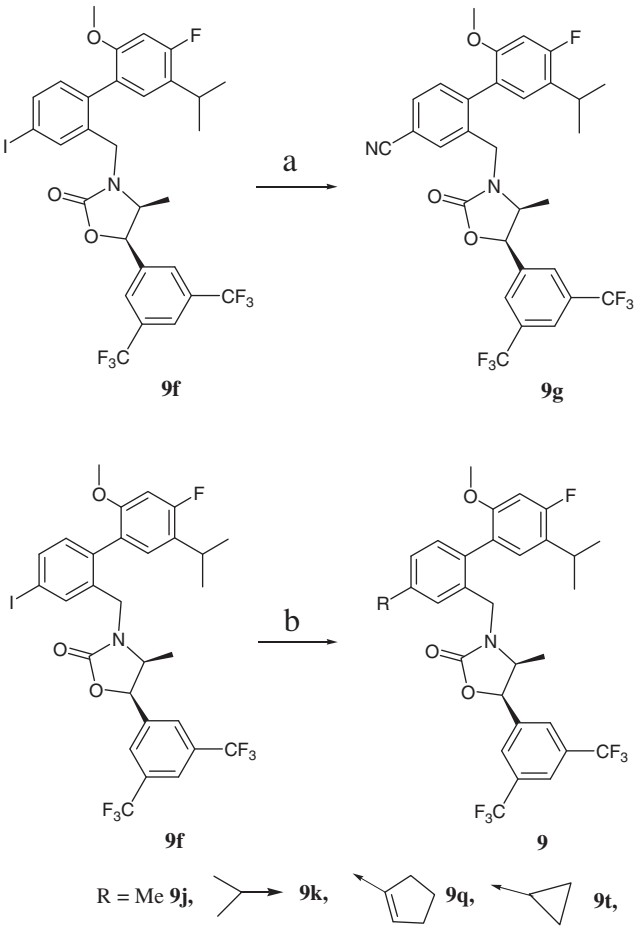
R = H, F, Cl, NO_2, t-Bu, MeS, PrS, i-PrS, CF_3S

Scheme 1. Synthesis of the biphenyl analogs. Reagents and conditions: (a) (1) NaH, **6**, 0 °C, THF; (2) **5**, 0 °C to rt, 70–95% (b) $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O (4:2:1), reflux, 80–90%.



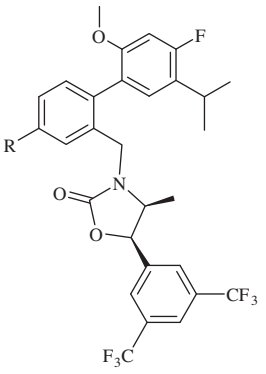
Scheme 2. Synthesis of the substituted biphenyl analogs. Reagents and conditions: (a) H_2, Pd/C, 40 psi, MeOH, 95% (b) *n*-amyl nitrite, I_2, $CHCl_3$, reflux, 76%.

The final compounds were evaluated in a fluorescence-based assay measuring the compound's ability to inhibit CETP-mediated neutral lipid transfer.[45] The results are reported as IC_{50}s. As can be seen in Table 1, the binding activity was significantly affected by the choice of phenyl substitution. Compared with **9a**, the unsubstituted analog **9b** was two fold less active. Halogen substitutions generally gave potent CETP inhibition and Cl was the most potent substituent (**9d**) with activity slightly better than CF_3 (**9a**). Electron withdrawing groups, including CN and NO_2, were tolerated and NO_2 group was more potent than CF_3 (**9h** vs **9a**). A hydrogen donor led to the loss of potency (**9i** and **9s**). For the alkyl substitutions, smaller group like Me was more potent than CF_3 (**9j** vs **9a**). Moreover, as the size grew, the potency decreased. Cyclopetene analog was the least active among **9j**, **9k**, **9l**, **9t** and **9q**. Alkyl sulfides presented a similar trend. MeS was the most active group and more



Scheme 3. Synthesis of the substituted biphenyl analogs. (a) CuCN, DMF, 100 °C, 84%. (b) $RB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O (4:2:1), reflux, 60 to 80%.

Table 1
SAR of the substituted top phenyl analogs



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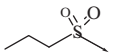
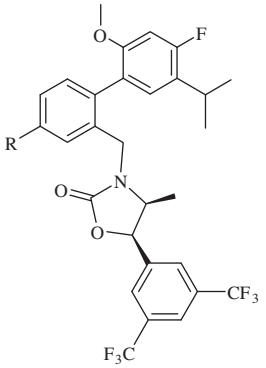
Entry	R	IC_{50} (nM)	Entry	R	IC_{50} (nM)
9a	CF_3	17.2	**9m**	MeS	16.2
9b	H	31.21	**9n**	PrS	1229
9c	F	25	**9o**	*i*PrS	689.1
9d	Cl	16.5	**9p**	CF_3S	19.6
9e	Br	19.8	**9q**		254.2
9f	I	23.5	**9p**		18
9g	CN	23.3	**9s**		71.8
9h	NO_2	13.3	**9t**		24.8
9i	NH_2	296.4	**9u**		33.5
9j	Me	16.7	**9v**		6935
9k	*i*Pr	54.1	**9w**		2599
9l	*t*-Bu	24.9	**9x**		27.1

Table 2
The effects of HDL increase for compound **9** with different substitutions on the transgenic mouse



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	R	+HDL (mg/dL)		R	+HDL (mg/dL)		R	+HDL (mg/dL)
9a	CF_3	28.0	**9l**		21.0	**9j**	Me	13.8
9r		23.2	**9t**		20.6	**9d**	Cl	12.7
9e	Br	23.0	**9m**	MeS	16.4	**9p**	CF_3S	12.4
9h	NO_2	21.5	**9g**	CN	14.8	**9c**	F	8.0

Dose: 10 mpk; $n = 5$.

bulky PrS group caused the activity to decrease drastically (**9m**, **9n**, **9o** and **9p**, respectively). The sulfones were less potent compared to the corresponding sulfides. The fluorinated isopropyl **9r** was more active than isopropyl **9k**, indicating a general trend that the target CETP favored the fluorine substitution at this position. To summarize, small and neutral groups were well tolerated at this position to give potent CETP inhibitors as shown in Table 1.

In light of these in vitro SAR studies, 11 compounds were tested in the transgenic mouse pharmacodynamic assay,[44] using anacetrpib **9a** as benchmark. These compounds were evaluated for their ability to raise HDL utilizing a BID dosing regimen. Thus, the animals were given a first dose of these compounds individually at the beginning of study, an equivalent dose seven hours later and blood was collected 24 h post the first dose. The difference in HDL-C levels between $t = 24$ and $t = 0$ hours was then determined. All of these 11 compounds showed an increase in HDL-C levels at 10 mpk. Five compounds raised HDL-C significantly (>20 mg/dL, **9r**, **9e**, **9h**, **9i** and **9t**). It is worth noting that anacetrapib **9a** is better than any other analogs in the series in vivo (Table 2).

In summary, we have described a class of CETP inhibitors that are potent in both in vitro and in vivo assays. SAR studies of the substitution effect on the central phenyl ring of the biphenyl scaffold were carried out using anacetrapib (**9a**) as the benchmark. The results revealed that the new analogs with substitutions to replace trifluoromethyl (**9a**) had a significant impact on the CETP inhibition in vitro. In fact, analogs with some small groups were as potent as or better than CF_3 group for CETP inhibition. Five of these new analogs raised HDL-C significantly (>20 mg/dL). None of them however was better than anacetrapib in raising HDL-C in vivo.

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