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Discovery of hydroxyl 1,2-diphenylethanamine analogs as potent cholesterol ester transfer protein inhibitors

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ABSTRACT

Hydroxyl 1,2-diphenylethanamine analogs were identified as potent inhibitors of cholesterol ester transfer protein (CETP), a therapeutic target to raise HDL cholesterol. In an effort to improve the pharmaceutical properties in the previously disclosed DiPhenylPyridineEthanamine (DPPE) series, polar groups were introduced to the N-linked quaternary center. Optimization of analogues for potency, in vitro liability profile and efficacy led to identification of lead compound **16** which demonstrated robust pharmacodynamic effects in human CETP/apo-B100 dual transgenic mice.

Accumulation of cholesterol-rich fatty deposits on the arterial wall can lead to development of atherosclerotic plaque. The consequent restriction of blood flow and loss of oxygen supply ultimately culminate in coronary artery disease (CAD) and results in higher risk of myocardial infarction (MI).[1] Epidemiology studies have demonstrated that abnormal lipoprotein levels contribute significantly to CAD.[2] Higher levels of low density lipoprotein cholesterol (LDLC) are associated with increased risk of cardiovascular disease. Current clinical therapies target lowering LDLC level through inhibition of cholesterol biosynthesis by statins or through limitation of cholesterol absorbance.[3,4] Conversely, there is an inverse associated risk of CAD with the level of high density lipoprotein (HDL).[5,6] It is believed that HDL plays a key role in mediating the reverse cholesterol transport (RCT) pathway, transferring excess cholesterol from the periphery to the liver for removal via biliary secretion.[7] Thus, there are continued efforts focused on biological targets that raise HDLC level.

CETP (cholesterol ester transfer protein) is a plasma glycoprotein secreted predominantly by liver and adipose tissue. It mediates transport of neutral lipids among various lipoproteins. Due to their hydrophobic properties, neutral lipids such as free cholesterol (FC), cholesterol esters (CE) and triglyceride (TG) are transported through the body via association with larger lipoprotein particles: very-low-density lipoprotein (VLDL), low-density lipoprotein and high-density lipoprotein. HDL is enriched with CE and VLDL and LDL are enriched with TG. The net activity of CETP mediation is to transfer CE from HDL to LDL and VLDL in exchange of TG, thereby reducing the HDL cholesterol level and increasing LDL and VLDL cholesterol levels. Inhibition of CETP activity has been clinically proven to increase HDL cholesterol level in plasma.[8a–d] Clinical data from CETP inhibitor Torcetrapib did not demonstrate benefit likely due to blood pressure elevation due to the inhibition of aldosterone synthase. Subsequent evaluation of Evacetrapib for treatment of high-risk vascular disease was discontinued due to lack of efficacy. Data for Anacetrapib phase III trial is expected to be collected through 2017. In this manuscript we describe a series of hydroxyl analogues of the previously disclosed DPPE series which demonstrate good in vitro potency, improved ADME and pharmaceutics properties, and robust pharmacodynamic effects in the human CETP/apo-B100 dual transgenic mouse model.

We have previously described the DPPE series including example analogue (*S*)-*N*-(1-(5-chloropyridin-2-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide (**1**), as a CETP inhibitor (Scintillation Proximity Assay (SPA) IC_{50} = 52 nM and Whole Plasma Assay (WPA) IC_{50} = 7.0 μM).[9,10] This compound showed good SPA activity and metabolic stability, however, low WPA activity and poor solubility (<1.0 μg/mL) were identified as issues. We sought to reduce lipophilicity in compound **1** (Fig. 1) by incorporating polar

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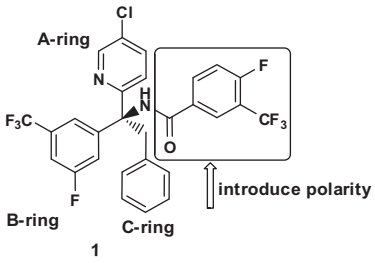


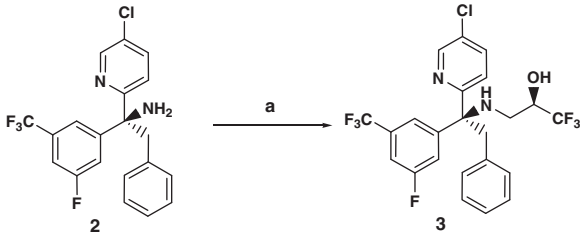
Figure 1. Introduction of polar functionality to improve physical properties.

moieties. Hence. trifluoro-3-amino-2-propanol analogue, **3** was synthesized.[11,12] We were pleased to note that this modification improved SPA and WPA activity by approximately 2 and 4 fold respectively.

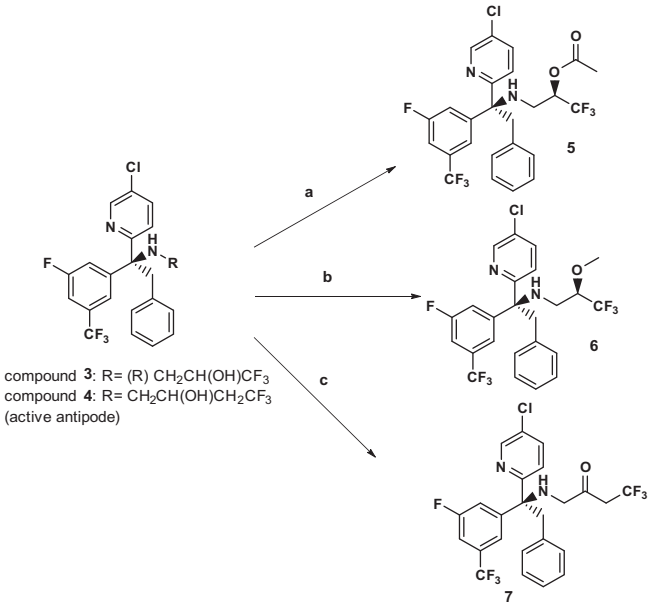
A general synthetic route for amino hydroxyl analogues is shown in Scheme 1. Enantiomerically pure epoxides (*S*)-2-(trifluoromethyl)oxirane, (*R*)-2-(trifluoromethyl)oxirane, (*S*)-2-(2,2,2-trifluoroethyl)oxirane and (*R*)-2-(2,2,2-trifluoroethyl)oxirane were synthesized following Jacobsen's[13,14] or Brown's procedures[15] and the advanced intermediate **2**, was synthesized as previously reported.[16] Treatment of the amine and single epoxide antipode with ytterbium triflate catalyst under microwave irradiation yielded the desired chirally pure hydroxyl amine compound **3** in 64% yield. Racemic epoxide was used for the synthesis of compound **4**. The resulting diastereoisomers were separated using chiral PrepHPLC (OD column, Isopropyl Alcohol/Heptane solvent system, 50 mL/min flow rate). Compound **4** was the more active antipode.

To further extend SAR at this position, compounds **5** and **6** were synthesized following the same methodology. The hydroxyl group was converted to the acylate using acetic anhydride and pyridine in DCM, yielding compound **5** in 76% yield. Selective O-methylation using MeI and NaH in DMF, afforded compound **6** in 62% yield. Compound **4** was oxidized using Swern oxidation conditions to give ketone **7** in 27% yield (Scheme 2).

Using the general routes shown in Schemes 1 and 2, compounds **3**–**11** were prepared. Table 1 lists the SPA and the WPA CETP potency for compounds with various hydroxyalkyl substitutions. Introduction of hydroxy trifluoromethyl ethanamine (compound **3**) improved potency (SPA IC_{50} = 22 nM and WPA IC_{50} = 1.6 μM) and maintained good metabolic stability (Human, Mouse, Rat, % remaining at 10 min was 100%, 95%, 88% respectively) compared to **1** (93%, 100%, 97%).[17] Homologation of the propyl group to a butyl group in compound **4** retained both potency and in vitro metabolic stability (Human, Mouse, Rat, % remaining at 10 min was 93%, 73%, 69% respectively). When the hydroxyl group was either methylated, acetylated or oxidized, the compounds were significantly less potent (compounds **5**–**7**). The terminal trifluoromethyl group was critical for potency and replacing the CF_3 group with a methyl group led to a significant loss in potency (compounds **8** and **9**). Despite additional polarity, the aqueous solubility for these analogs still remained low (compounds **3**–**9** <1 μg/mL). However, introduction of a diol side chain significantly improved solubility (Amorphous compounds **10** and **11**, 44 μg/mL and 37 μg/mL respectively). Unfortunately, this improvement in solubility came with a decrease in CETP potency.

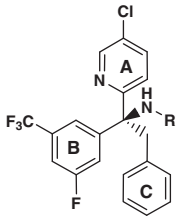


Scheme 1. Reagents and conditions: (a) $Yb(OSO_2CF_3)_3$, (*R*)-2-(trifluoromethyl) oxirane, acetonitrile, microwave irradiation 140 °C, 20 min, 64%.



Scheme 2. Reagents and conditions: (a) Ac_2O, pyridine, DCM, 76%; (b) MeI, NaH, DMF, 62% (c) DMSO, oxalyl chloride, TEA, DCM, 27%.

Table 1
SAR of DPPE amino hydroxyl analogs



Compounds	R	SPA IC_{50} (nM)	WPA IC_{50} (μM)
1		52	7.0
3	(*R*) $CH_2CH(OH)CF_3$	22	1.6
4	$CH_2CH(OH)CH_2CF_3$ (active antipode)	9	1.2
5	(*R*)$CH_2CH(OCOCH_3)CF_3$	826	100
6	(*R*)$CH_2CH(OCH_3)CF_3$	253	48
7	$CH_2COCH_2CF_3$	641	30
8	(*S*) $CH_2CH(OH)CH_3$	334	20
9	(*R*) $CH_2CH(OH)CH_3$	520	32
10	(*R*)$CH_2CH(OH)CH_2OH$	8532	
11	(*S*)$CH_2CH(OH)CH_2OH$	3097	98

As we continued to develop SAR in the closely related DPPE amide series, we showed that 3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl was the optimal substitution on the B ring for CETP WPA potency.[10] We therefore prepared the 3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl B-ring analogs of both compound **3** (compound **12**) and compound **4** (compound **13**) (Table 2). Compound **13** was synthesized following the same procedure described for compound **4**. Compound **12** showed SPA IC_{50} = 14 nM and WPA IC_{50} = 0.9 μM and had excellent metabolic stability (Human, Mouse, Rat, % remaining at 10 min was 100%, 88%, 84%